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Evidence-based management of ANCA vasculitis

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The vasculitides associated with antineutrophil cytoplasmic antibodies (ANCAs) present to and are managed by a wide spectrum of physicians, reflecting the multi-organ nature of the conditions. Treatment strategies for these primary inflammatory vascular diseases have varied based on the outcomes of different clinical trials and practice reviews. The individual drugs used and their route of administration, dose, and duration of therapy have varied and have been the source of much debate. Advances in our understanding of disease immunopathogenesis, clinical assessment and outcome have formed the basis for several recent good-quality clinical trials. Now, with the results of these large-scale multicentre collaborative studies, there is a firmer evidence base to guide management decisions for individual patients. This evidence base, reviewed here, has led to the publication of treatment guidelines which importantly encompass many of the broader aspects of disease management.

Cyclophosphamide (Cyc), in combination with steroids, has long been accepted as the gold standard for the management of patients with systemic necrotizing vasculitis (SNV). Lieb's publication in 1979 showed that in a mixed group of patients with SNV receiving no specific therapy the 5-year mortality was 90%. The addition of steroids improved the outcome to 50% survival at 5 years, but it was with the addition of a range of immunosuppressive therapies, which included azathioprine (Aza) and Cyc, to the steroids that the 5-year prognosis improved to 80% [1]. In 1992 the National Institutes of Health (NIH) published a review of 158 patients with Wegener's granulomatosis (WG) in which continuous oral Cyc

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was advocated for treatment of this condition [2]. The treatment regimen consisted of continuous oral Cyc at a dose of 2 mg/kg/day until remission, followed by a further 12 months of treatment. Oral prednisolone in a dose tapering over 1 year was an important part of the treatment regimen. Several other case series supported this approach [3–5]. However, these earlier studies were limited by being uncontrolled and often retrospective reviews of a heterogeneous group of patients with varying diagnoses where the toxicity from Cyc and steroids was high. There were also poorly defined outcome definitions for remission and relapse, making interpretation and comparison between studies difficult.

Since these early studies the concept for treatment has changed from one drug for all patients to a phased approach to therapy modified for the individual patient. This change in practice has come about for many reasons, including the development of criteria for classification [6,7] and nomenclature [8] that allow the differentiation of one form of vasculitis from another, an important factor given the different outcomes of the specific vasculitides. In addition there are now validated clinical tools for the assessment of disease activity (Birmingham Vasculitis Activity Score, BVAS) [9] and organ damage (Vasculitis Damage Index, VDI) [10] which have been modified and improved since their first introduction and are now widely used in clinical studies of vasculitis [11]. Far more is also understood about the immunopathogenesis and in particular the role of antineutrophil cytoplasmic antibodies (ANCAs) [12]. All these factors have contributed to effective collaboration between interested clinicians across Europe and America. This unified approach has allowed development and completion of several treatment studies on ANCA-associated vasculitis (AAV), particularly under the auspices of the European Vasculitis Study Group (EUVAS), which now allow an evidence-based approach to the therapy of this group of conditions.

This review will synthesize the evidence from large-cohort studies and randomized clinical trials in AAV and provide the clinician with a practical, evidence-based approach towards management of this difficult group of patients.

EUVAS collaborative studies

The EUVAS studies have examined the therapeutic approach to patients with AAV based on their disease stage and severity. NORAM compared Cyc against methotrexate (Mtx) for induction of remission in early systemic AAV [13]. CYCLOPS examined the role of pulse versus continuous oral Cyc for induction of remission in AAV [14]. MEPEX studied the role of plasma exchange in patients presenting with rapidly progressive renal failure [15], and CYCAZERAM compared Cyc with Aza for maintenance therapy of AAV [16]. Table 1 summarizes the diagnoses and numbers of patients entered into these studies, illustrating that a collaborative approach between centres (built on sound disease and assessment definitions) can lead to successful large-scale studies even in rare diseases.

Table 1
European Vasculitis Study Group (EUVAS) trials summaries.

Trial	Number of patients	Diagnosis	Stage	Presentation
CYCAZERAM	155	WG (95) MPA (60)	Generalized	New
NORAM	100	WG (94) MPA (6)	Limited	New
CYCLOPS	160	WG (61) MPA (99)	Generalized	New
MEPEX	137	WG (42) MPA (95)	Severe renal impairment	New
TOTAL	552	WG (292) MPA (260)		

Generalized refers to patients presenting with AAV and active renal vasculitis and/or other immediate vital organ threatening disease activity. Limited refers to patients presenting with AAV and one or more involved organ systems plus constitutional symptoms with no immediately vital-organ-threatening disease activity. Severe renal impairment indicates evidence of biopsy-proven necrotizing/crescentic glomerulonephritis and a creatinine of >500 μmol/L or significant oliguria at presentation. WG, Wegener's granulomatosis; MPA, microscopic polyangiitis.