Autoimmunity Reviews xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

# Long-term follow-up of a randomized trial on 118 patients with polyarteritis nodosa or microscopic polyangiitis without poor-prognosis factors

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ARTICLE INFO

*Article history:*
Received 25 September 2013
Accepted 7 October 2013
Available online xxxx

*Keywords:*
Polyarteritis nodosa
Microscopic polyangiitis
ANCA
Relapses
Sequelae
Long-term follow-up

ABSTRACT

The purpose of this study was to assess the long-term outcomes of patients with polyarteritis nodosa (PAN) or microscopic polyangiitis (MPA) without Five-Factor Score (FFS)-defined poor-prognosis factors (FFS = 0) and enrolled in a prospective clinical trial. Patients were followed (2005–2012) under routine clinical care in an extended study and data were recorded prospectively. Long-term survival, disease-free survival (DFS), relapses, therapeutic responses and sequelae were analyzed. Mean ± SD follow-up was 98.2 ± 41.9 months. After having initially received glucocorticoids (GC) alone, according to the study protocol, 82% (97/118) patients achieved remission but 18% (21/118) required ≥1 immunosuppressant(s) (IS) before 19/21 achieved remission. Two patients died before entering remission. After remission, 53% (61/116) patients relapsed 25.6 ± 27.9 months after starting treatment. The 5- and 8-year overall survival rates were 93% and 86%, respectively, with no difference between PAN and MPA, and between relapsers and nonrelapsers. DFS was shorter for MPA than PAN patients ($P = 0.02$). Throughout follow-up, 47% of patients required ≥1 IS. At the last follow-up visit, 44% were still taking GC and 15% IS. The mean vasculitis damage index score was 1.9 ± 1.9; the most frequent sequelae were peripheral neuropathy, hypertension and osteoporosis. For PAN or MPA patients without poor-prognosis factors at diagnosis and treated initially with GC alone, long-term survival was excellent. However, relapses remained frequent, requiring IS introduction for nearly half of the patients. To lower the frequencies of relapses and sequelae remains a challenge for FFS = 0 PAN and MPA patients.



**Contents**



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1568-9972/$ – see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.autrev.2013.10.001

## 1. Introduction

Polyarteritis nodosa (PAN) and microscopic polyangiitis (MPA) are 2 vasculitides characterized by necrotizing inflammation of the vessel wall. They share several clinical features and may be treated the same way, with the exception of hepatitis B virus-associated PAN (HBV–PAN) [1,2] which requires a specific antiviral approach. PAN is a necrotizing arteritis of medium- and small-sized arteries not associated with anti-neutrophil cytoplasm antibodies (ANCA) [3,4]. In contrast, MPA is an ANCA-associated small-vessel vasculitis, mainly anti-myeloperoxidase (MPO) [3,5–7], in which glomerulonephritis and pulmonary capillaritis often occur. More than the type of vasculitis, we hypothesized that its severity should determine the therapeutic strategy. The Five-Factor Score (FFS), in its original version [8] and revisited in 2011 [9], can predict patient mortality depending on the presence of poor-prognosis factors.

To date, only the 1996 version of the FFS had been validated in prospective trials to guide the treatment of vasculitides. Nonsevere PAN and MPA manifestations, as defined by the 1996 FFS = 0 (1996 version), responded to glucocorticoids (GC) alone in 79% of the patients [2]. GC failure or relapse requiring immunosuppressants (IS) occurred in 40% after a mean follow-up of 5 years [2].

Data on the long-term follow-up of these patients treated initially with GC alone are lacking. In this study, we took advantage of the FVSG patient cohort, followed prospectively and homogeneously treated, to describe the long-term outcomes of PAN or MPA patients: survival, disease-free survival (DFS), causes of death, relapses, clinical and laboratory findings, therapeutic responses and sequelae.

## 2. Patients and methods

### 2.1. Patient population

Patients had been included between November 1993 and January 2005, and treated in France and the UK in a prospective randomized controlled trial [2]. Each participant gave signed informed consent. Once the diagnosis of PAN or MPA was confirmed, patients were stratified according to the presence or absence of 1996 FFS-defined poor-prognosis factors [8]: serum creatinine >140 μmol/l, proteinuria >1 g/day, severe gastrointestinal tract involvement, cardiomyopathy and/or central nervous system (CNS) involvement, with each item present accorded 1 point.

Only FFS = 0 patients at baseline were included in this study. They were prescribed GC alone and received IS only when steroids failed to achieve or maintain remission, as previously reported [2].

Short-term results were reported previously [2]. Briefly, data from 118 patients with FFS = 0 PAN or MPA were analyzed in the extended follow-up study. Ninety (76%) patients fulfilled ≥3 of the 1990 ACR classification criteria for PAN [10]. Because patients without HBV or severe renal involvement were selected, 2 criteria were nonapplicable. The remaining 28 patients, despite having <3 ACR criteria, had other clinical features characteristic of PAN or MPA: ANCA anti-MPO antibody-positive or biopsy-proven necrotizing vasculitis. Although the same first-line treatment was given for MPA and PAN patients, the 2 diseases were separated retrospectively based on the biopsy reports, angiography results, ANCA-testing and outcomes, in accordance with the 2012 revised Chapel Hill Nomenclature [3].

### 2.2. Treatment regimen

All patients initially received GC (prednisone) alone, as previously described [2]. Patients with persistent clinical manifestations of active vasculitis because of either the initial GC failure or the impossibility to taper GC doses under 20 mg/day, those with major relapses, and those with minor relapses that were recurrent or refractory to transient GC intensification, were randomized to receive either 6 months of oral azathioprine (AZA) (2 mg/kg) or 6 intravenous (IV) cyclophosphamide (CYC) pulses (600 mg/m$^2$), as previously described [2].

### 2.3. Data collection

Clinical reports, recorded on standardized case-report forms and filled in by the treating physician, were obtained prospectively. Pathologists provided histologic reports and slides were reviewed when necessary. All data were entered into a computerized databank. After the first results were reported [2], patients were routinely monitored prospectively in an extended follow-up study (from 2005 through May 2012), with documented data on relapses, treatments, sequelae and vital status. Each of their organ systems was assessed with the validated 2003 Birmingham Vasculitis Activity Score (BVAS) [11,12] and the vasculitis damage index (VDI) [13].

Every patient's serum was tested for ANCA-positivity on ethanol-fixed neutrophils by indirect immunofluorescence, according to EUVAS recommendations [14]. When ANCA were detected, enzyme-linked immunosorbent assay (ELISA) determination of their specificity (anti-MPO or proteinase-3 [PR3]) was sought. Some routine biologic analyses (complete blood counts, serum creatinine, C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], proteinuria, hematuria) and chest X-ray were performed at entry and regularly, as specified by the protocol. When indicated by clinical manifestations, the treating physician could order specific investigations.

### 2.4. Definitions

Remission was defined as the absence of disease activity attributable to PAN or MPA manifestations for ≥3 consecutive months, corresponding to BVAS = 0, not requiring being off or on a specified GC dose [15]. Failure was defined as the absence of clinical remission, occurrence of new vasculitis manifestation(s) or death before remission was obtained [15]. Relapses were predefined as the recurrence, worsening or appearance of new clinical PAN or MPA manifestation(s), following a ≥3-month period of remission [15]. Major and minor relapses were distinguished. The former corresponded to the recurrence or new appearance of major organ involvement, e.g. the following, if attributable to active vasculitis: 1) 30% increase of serum creatinine level or 25% decrease of glomerular filtration rate within 3 months or histologic evidence of focal necrotizing glomerulonephritis; 2) clinical, radiologic or bronchoscopic evidence of pulmonary hemorrhage (pulmonary infiltrates were not considered a severe manifestation); 3) threatened loss of vision related to retinal vasculitis; 4) new multifocal neurologic lesions or mononeuritis multiplex; 5) acute vasculitis-related limb ischemia or gangrene; 6) gastrointestinal hemorrhage or perforation; and 7) other manifestations included in the 1996 FFS: proteinuria >1 g/day, cardiomyopathy and/or CNS involvement [8,15,16].



Please cite this article as: Samson M, et al, Long-term follow-up of a randomized trial on 118 patients with polyarteritis nodosa or microscopic polyangiitis without..., Autoimmun Rev (2013), http://dx.doi.org/10.1016/j.autrev.2013.10.001