Overall survival, renal survival and relapse in patients with microscopic polyangiitis: a systematic review of current evidence

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Abstract

Objective. There are limited data on the long-term prognosis of microscopic polyangiitis (MPA). A systematic review was performed to estimate the survival, renal survival and relapse rates in patients with MPA.

Methods. Articles included in MEDLINE and EMBASE databases were reviewed. Randomized or non-randomized trials, cohort, case-control and cases-series studies of patients with MPA diagnosed according to Chapel Hill Consensus Conference definitions, a high rate of biopsy-confirmed diagnosis, follow-up >1 year and follow-up losses <10%. Two independent authors using a predefined questionnaire for evaluating the quality and risk of bias for each study extracted data.

Results. Eighteen studies for MPA prognosis (n = 940) and six for MPA outcomes after transplantation (n = 65) were included. Survival rates were 77–100% at 1 year, 46–80% at 5 years and 60–80% at 10 years. Higher mortality density occurred within the first months after diagnosis. Vasculitis was the cause of death in 32–50% of patients. Relapses were detected in 19–39% of cases (median time to relapse 15–43 months). Renal graft survival was 85–94% at 1 year and 51–87% at 5 years. Age, renal involvement and immunosuppressive treatment were related to mortality. Lower relapse rate was achieved with 12 vs 6 CYC pulses.

Conclusion. Evidence regarding MPA prognosis is weak. MPA mortality is mainly concentrated in the first months after diagnosis. Fewer than 50% of deaths are related to MPA activity. MPA long-term prognosis is less severe, although relapses are frequent. End-stage renal failure is a frequent complication of MPA, and renal transplantation could be an effective therapy in these patients. Early diagnosis, early initiation of a tailored therapy according to risk factors and a longer follow-up of the patients are needed.

Key words: Microscopic polyangiitis, Anti-neutrophil cytoplasmic antibody-associated vasculitis, Systemic vasculitis, Review, Systematic.

Introduction

Microscopic polyangiitis (MPA) is a primary systemic vasculitis characterized by inflammation of the small-calibre blood vessels and the presence of circulating ANCAs [1]. MPA is an aggressive disease with significant renal and pulmonary manifestations. The use of glucocorticoids (GCs), CYC and other immunosuppressive agents has changed favourably the prognosis of MPA and the remainder of ANCA-associated vasculitis. Moreover, it has been recently shown that AZA or pulse CYC is fairly effective for treating MPA patients with GC-resistant disease or major relapses [2]. However, regardless of the treatment, MPA may progress to end-stage renal disease [3]. In a retrospective cohort study of our group, 50% of patients with MPA developed end-stage renal disease after a median of 9 months [4]. Moreover, a successful response to initial therapy does not ensure the long-term control of disease activity, the course of which is characterized by frequent relapses (from 8% at 18 months to
41% at 32 months) [5]. Therefore, an accurate assessment of the long-term outcome in terms of disease-related mortality, remission, relapse, renal prognosis and factors affecting prognosis is critical to help clinicians to determine the benefits, risks and harms of interventions in order to tailor therapy to individual characteristics of the patient.

Two systematic reviews conducted to assess the prognosis of ANCA-associated vasculitis have shown survival rates for MPA of 82-92% at 1 year and 45-75% at 5 years, with overall remission rates of 75-89% and relapses of 8% at 18 months and 41% at 32 months [5, 6]. However, data of long-term prognosis (beyond 5 years), renal survival and outcome after renal transplantation (RT) or factors affecting survival in MPA patients are lacking. The small number of studies in the past in which MPA outcome has been assessed independently is one of the reasons for the paucity of data. PAN and MPA were usually considered together until proposals made at the Chapel Hill Consensus Conference (CHCC) on the nomenclature of systemic vasculitis in 1994 [7]. Different factors contributed to the distinction of the two entities, including a better understanding of the pathophysiological mechanisms, the availability of ANCA assay and the differences shown in disease outcome. In this respect, a study of the French Vasculitis Group [8] showed a percentage of relapse of 7.9% in PAN as compared with 34.5% in MPA. Thereafter, MPA and ANCA-associated vasculitis especially WG have been commonly included in the same diagnostic category, assuming that these conditions have the same prognosis as they are associated with the presence of ANCA and show similar histological features and treatment approaches. However, it has been recently shown that MPA has a higher mortality [9, 10], but a lower relapse rate than WG [11].

To further contribute to the knowledge of MPA as a separate clinical entity, a systematic review of relevant clinical studies on the prognosis of patients with MPA was performed. The objective of the study was to clarify the long-term prognosis of this condition according to the best evidence available. By adding data from cohort studies and longitudinal studies data to the results of clinical trials, we gather long-term prognosis data, including renal survival and survival after RT as well as factors affecting survival in a more real-life scenario.

**Materials and methods**

The primary objective was to estimate long-term prognosis in terms of survival rate at 1, 5 and 10 years, renal survival rate (RSR) at 1, 5 and 10 years and relapse rate in patients with MPA. The secondary objective was to determine the survival rate, the allograft survival rate and the relapse rate after a renal allograft in patients with end-stage renal failure (ESRF) secondary to MPA activity. Factors associated with a higher mortality rate, causes of death, period of time with a higher mortality density and differences between MPA and WG were also examined. The review was conducted according to guidelines of preferred reporting items for systematic reviews and meta-analyses (PRISMA) (see checklist available as supplementary data at Rheumatology Online) [12, 13].

**Eligibility criteria**

Randomized and non-randomized clinical trials, cohort studies, case-control studies and longitudinal studies of patients with MPA with a follow-up of at least 1 year were selected. Diagnosis of MPA had to be established according to the CHCC criteria [7] and had to be biopsy proven. Moreover, patients had to be followed up since diagnosis. Studies in which inclusion criteria were limited by severity of disease or MPA system involvement were excluded from the review, except for renal patients, as the majority of MPA patients have renal involvement. These studies are described separately. Primary outcome measures included survival rate or mortality at 1, 5 or 10 years, RSR at 1, 5 or 10 years and relapse rate. Other outcomes such as the cause of death were also registered.

**Information sources**

Studies were identified by searching MEDLINE database via PubMed (from 1966 to 2009) and EMBASE database via Ovid (from 1980 to 2009). No limits were placed for language of publication. Limits for year of publication were not used in order to retrieve publications of microscopic PAN (PANm). The last search was performed on 5 May 2009. The MeSH term MPA was introduced in 2010. The MEDLINE search strategy was developed by two of the authors (L.C.-G. and M.B.-C.-B.) and the EMBASE search was carried out by the Medical Information Department of Lilly, Madrid, Spain. Additional studies were identified through the Cochrane library, checking the reference lists of the articles selected for full-text analysis, and through citation search of the selected studies through the cited reference search of the Institute for Scientific Information (ISI) Web of Knowledge (Thomson Reuters).

**Search**

To retrieve articles on MPA and prognostic studies, a combination of MeSH terms (incidence, mortality, follow-up studies and prognosis) and free terms (MPA, microscopic polyarteritis, PANm, microscopic periarteritis nodosa, disease course, predict and outcome), with the search field tags All Fields and Text Word was used according to published search strategies [14, 15]. In order to make the search as comprehensive as possible, the truncated terms prognos and predict were used to retrieve other terms with the same word root (e.g. prognosis and prognostic, prediction, predicting and predictive). The full electronic search strategies for MEDLINE and EMBASE databases are described in Appendix 1 (available as supplementary data at Rheumatology Online).

**Study selection**

The retrieved records were screened by reading the title and the abstract by two independent reviewers (L.C.-G. and M.B.-C.-B.). Case reports, letters to the editor, editorials, guidelines, prevalences studies and reviews were...
excluded. Also records not focused on MPA, paediatric reports or animal studies were excluded. In a second step, the full texts of the selected articles were examined by the same reviewers independently. The focus of the study selection process was to assess the risk of bias. The major concern was to characterize the sample selection process to avoid selection bias (MPA diagnosis was well characterized, all patients included in the study at diagnosis, there were no restrictions according to severity or MPA system involvement). Also performance bias was tested (treatment schemes and percentage of patients treated with immunosuppressant drugs). The risk of bias of the individual studies was assessed with a checklist developed by our group according to the guidelines of the evidence-based medicine (EBM) group [16] and published recommendations [17, 18] adding specific items. Seven major methodological characteristics of the studies were assessed by answering 18 items as shown in Appendix 2 (available as supplementary data at Rheumatology Online). The reliability of the checklist was examined in a pilot phase with the first 10 studies.

Studies were excluded if they had a high risk of bias (MPA diagnosis was not well characterized, the sample was not representative, patients not entered at diagnosis, the follow-up was inadequate or there was no adjustment for prognosis factors). When the study included other ANCA-associated vasculitis, MPA results had to be reported separately.

The selected studies were graded into two categories according to overall quality and risk of bias. Category 1 included studies meeting all criteria with a low risk of bias. Category 2 included fair studies in which all the criteria were not fulfilled with a moderate risk of bias (e.g. poor analysis or adjustment for prognostics factors and lack of homogeneous treatment schemes). If the two reviewers agreed, then the study was selected. In the case of disagreement, a third reviewer (J.L.L.-M. or J.dP.-M.) resolved whether or not the study should be included. A list of excluded studies detailing the reason for exclusion is shown in Appendix 3 (available as supplementary data at Rheumatology Online).

For studies from the same study group (e.g. French Vasculitis Study Group) with overlapping time frames, only one article with the largest sample size was selected for the assessment of each outcome variable (survival, relapse, renal survival and outcome of MPA after RT) and the remaining concurrent studies were excluded.

Data collection process

A data extraction sheet was developed for the purpose of the study. The reliability of the sheet was examined in a pilot phase with the first 10 studies. One reviewer (L.C.-G.) extracted the data and the second reviewer checked the data (M.B.-C.-B.). Disagreements were resolved by discussion. Details of the checklist included in the data extraction sheet are provided in Appendix 4 (available as supplementary data at Rheumatology Online).

Data items

For each study, the following data were collected: patient-related information (inclusion and exclusion criteria, sample selection, MPA diagnosis, age, gender and stage); follow-up (duration and percentage of patients lost to follow-up); outcome measure (including survival rate at 1, 5 and 10 years, relapse rate, time to relapse and RSR), prognostic factors and adjustment for prognosis factors, particularly for type of treatment; intervention (treatment scheme); and study characteristics (authors, country and period in which the study was conducted, and study design). The variable cause of death was added after the review had been started.

Levels of evidence

Articles were graded according to their level of evidence [19]. Randomized controlled trials and prognostic prospective cohort studies with >80% follow-up were graded as Level 1b, retrospective cohort studies as Level 2b. A minus sign was added when results had a wide 95% CI. Case-control studies and series of cases were graded as Level 4.

Statistical analysis

Descriptive statistics are presented. Survival rates at 1, 5 and 10 years as well as the percentage of relapses and the 95% CI are graphically presented. The method used to calculate the 95% CI for survival and relapse rates was the Wilson score method without continuity correction [20]. Due to the variety of study designs and differences in treatment regimens used across the studies, meta-analysis techniques were not performed.

Results

A total of 18 studies were identified for inclusion in this review [3, 8, 9, 10, 21–36]. One clinical trial, 4 cohort studies and 13 longitudinal studies were included. Another six studies with data of renal transplanted MPA patients were analyzed separately [37–42]. A list with the details of the studies included in the review is shown in Appendix 5 (available as supplementary data at Rheumatology Online). The study selection process is summarized in a flow diagram (Fig. 1). The characteristics of the different studies were heterogeneous. Results of quality assessment are shown in Fig. 2. A table with the assessment of the risk of bias of the studies included in the review is shown in Appendix 6 (available as supplementary data at Rheumatology Online). All studies included adult patients with a diagnosis of MPA or ANCA-associated systemic vasculitis. The sample size varied between 10 and 153 patients and the mean follow-up period varied between 22 and 92 months. Seven studies were multicentric (four were authored by the French Vasculitis Study Group) and the remaining studies described clinical series of patients diagnosed and treated at university-affiliated or tertiary hospitals. Details of the studies included in the review are shown in Appendix 5, risk of bias for each individual study in Appendix 6 and results of individual studies in...
Appendix 7 (available as supplementary data at Rheumatology Online).

Survival

A total of 13 studies provided data on mortality in MPA patients (n = 616) [3, 8, 10, 21–24, 26, 27, 29, 30, 32]. The overall mortality rate ranged between 13 and 67% [3, 9, 21–23, 27, 30]. In two studies, the mortality rate within the first 3 months was 13% [9, 22] and in four studies, the mortality rate within the first 6 months varied between 9.4 and 17% [3, 9, 21, 22]. The 1-year survival rate was estimated in seven studies with 347 patients [3, 9, 10, 24, 26, 29, 32] ranging between 77 and 100%. The 5-year survival rate was reported in six studies (214 patients) and varied between 46 and 85% [9, 10, 21, 26, 29, 32]. The 10-year survival rate was reported in only two studies (68 patients), ranging between 60 and 80% [8, 32] (Fig. 3).

The cause of death was reported in three studies (224 patients) [9, 22, 24]. Vasculitis was the cause of death in 38–50% of patients in two studies. In the study of Bourgarit et al. [24], vasculitis-related causes were only documented in 8% of the cases. In 17–62% of patients, deaths were related to the immunosuppressive treatment.

Factors affecting survival are summarized in Appendix 8 (available as supplementary data at Rheumatology Online).
Fig. 2 Results of quality assessment of studies included in the review (n = 18) excluding those with separate analysis of MPA renal transplanted patients (n = 6).

Inclusion and exclusion criteria shown
Sample selection explained
Sample representative
Included all of the eligible patients
MPA diagnosis according to CHCC definitions
Biopsy-proven MPA in all patients
Clinical and demographic variables specified
All patients entry at diagnosis on the study
Lost to follow-up rates shown
All patients with outcomes
All patients with available prognostic factors
Analysis adjusted by prognosis factors
All patients treated in the same way or randomized
All patients treated with immunosuppressants
Overall risk of bias
Low
Moderate
Level of evidence
1b
2a
4
Study design
Cohort
Longitudinal study

Fig. 3 Survival rates of MPA patients at 1, 5 and 10 years after diagnosis.

One year survival rate

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients Survived</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu et al. [3]</td>
<td>49</td>
<td>64</td>
</tr>
<tr>
<td>Pavone et al. [26]</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Lane et al. [9]</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>Little et al. [99]</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>Bakoush et al. [10]</td>
<td>42</td>
<td>48</td>
</tr>
<tr>
<td>Bourjau et al. [24]</td>
<td>141</td>
<td>153</td>
</tr>
<tr>
<td>Rihová et al. [32]</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Five year survival rate

<table>
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<th>Study</th>
<th>Number of patients Survived</th>
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<tbody>
<tr>
<td>Lane et al. [9]</td>
<td>11</td>
<td>24</td>
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<tr>
<td>Pavone et al. [26]</td>
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<tr>
<td>Bakoush et al. [10]</td>
<td>30</td>
<td>48</td>
</tr>
<tr>
<td>Guillevin et al. [21]</td>
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<td>85</td>
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<tr>
<td>Little et al. [99]</td>
<td>25</td>
<td>33</td>
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<tr>
<td>Rihová et al. [32]</td>
<td>8</td>
<td>10</td>
</tr>
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</table>

Ten year survival rate

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<th>Study</th>
<th>Number of patients Survived</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gayraud et al. [8]</td>
<td>35</td>
<td>58</td>
</tr>
<tr>
<td>Rihová et al. [32]</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>
Online). Most studies have identified prognostic factors associated with ANCA-associated vasculitis. The main factors affecting survival were age, renal involvement and treatment. Also higher five factors score (FFS) and BVAS were associated with higher mortality rates. Three studies showed lower survival rates in patients with MPA than in those with WG [9, 10, 36], with an odds ratio of 4.9 [10] and a risk ratio of 1.9 [36] (level of evidence 1b-). In another study, no differences in survival between the two conditions were observed [28].

Relapse

The percentage of relapses for MPA was described in seven studies (340 patients) [3, 21–23, 25, 26, 34], affecting nearly one-third of the patients (from 19 to 39%) with a median period to relapse of 15–43 months (Fig. 4). Predictors of relapse are shown in Appendix 9 (available as supplementary data at Rheumatology Online). The probability of relapse was lower with more prolonged treatment schemes (12 vs 6 pulses of CYC, hazard ratio 0.44) [22] (level of evidence 1b). The presence of ANCAs, FFS, BVAS and time to diagnosis were not predictors of relapse [22, 23]. However, time to diagnosis ≥90 days was associated with a higher mean number of relapses [23] (level of evidence 4). Two studies compared the percentages of relapse between patients with MPA and patients with WG [28, 31] and in both studies, relapses were more frequent in patients with WG (odds ratio 2.1, 95% CI 1.58, 2.9) [31] (level of evidence 4). Relapses were also more common in WG in the randomized trial of Jayne et al. [11], although this study was excluded from the review because only patients with less severe renal involvement (serum creatinine > 5.7 mg/dl) were included. The percentage of relapses in patients with MPA was higher than those in patients with PAN [8, 23] (level of evidence 4), whereas relapses in MPA were higher than in patients with Churg–Strauss syndrome (CSS) in one study [8] and lower in another study [26].

Renal survival

Two studies (149 patients) reported renal survival data [3, 21]. Progression to ESRF was documented in 34% of patients [3]. In the study of Guillevin et al. [21], 12% of patients were undergoing long-term dialysis. RSR was 67% at 1 year and 59% at 3 years [3]. Predictors of ESRF are shown in Appendix 10 (available as supplementary data at Rheumatology Online). Serum creatinine concentration at diagnosis was the factor most frequently related to renal survival. One study showed that RSR was lower for WG as compared with MPA or renal-limited vasculitis (RLV) [30].

Outcome of MPA after RT

Six studies (65 patients) [37–42] reported data on the outcome after RT in MPA patients. Results of quality assessment of these studies are shown in Fig. 5. All studies were single centre and retrospective. The follow-up ranged between 43 and 107 months.

The 1- and 5-year survival rates were estimated in two studies [40, 41], with similar results, 86 and 87% for 1-year survival rates and 67 and 69% for 5-year survival rates. Graft survival was 85–94% at 1 year and 51–87% at 5 years [37, 41]. Moreover, in four studies, the outcomes of RT in patients with ANCA-associated vasculitis were compared with matched controls (77 patients with ANCA-associated vasculitis and 27 patients with MPA) [37, 38, 41, 42]. In all studies, the survival of patients and grafts was similar in cases and controls (level of evidence 4). Relapse rate was reported in five studies [37–39, 41, 42]. In two studies, no relapses occurred [41, 42], whereas in the remaining three studies [37–39], 20–33% of patients had a relapse after a mean time of 18–34 months after renal transplant.

Discussion

This systematic review summarizes the prognosis and factors affecting the outcome of patients with MPA according to the best evidence available. Two previous systematic reviews have assessed prognosis in patients with

![Fig. 4 Relapse rates and time to relapse. *Time referred to the entire cohort.](https://academic.oup.com/rheumatology/article-abstract/50/8/1414/1786872/1419)
ANCA-associated vasculitis [5, 6], including all types of vasculitis and mainly focused on data from patients with WG. Data regarding renal survival and renal allograft survival in MPA patients were not reported. The two reviews were limited to MEDLINE database and, in particular, the review of Phillip and Luqmani [6] limited retrieved articles to English-language publications. The present study extends previous information sources and outcomes as well as updating the previous findings.

The present results show that despite treatment, MPA has still a significant mortality rate. The period of time with a higher mortality density is the first year after diagnosis. Older patients, patients with more severe renal involvement or patients with higher BVAS or FFS have a worse prognosis. In comparison with WG, MPA has a higher mortality rate at 1 and 5 years, but it is unknown whether this worse outcome is maintained in the long-term follow-up at 10 or 20 years. The causes of death were not homogeneous among studies, but vasculitis-related death was recorded in nearly one in two patients. In some series, treatment-related death accounted for >50% of the cases.

Relapses are frequent, affecting nearly one in three patients. Time to relapse varies greatly between studies, with >10 years of time to relapse as the upper limit of time in some series [21, 30, 32]. Prolonged treatment schemes [22] (level of evidence 1b-) has been related to a low rate of relapse. MPA relapse rate appears to be lower than in WG.

Renal involvement is frequent in MPA patients. One of three patients progresses to end-stage renal disease requiring renal replacement therapy with chronic dialysis or RT. However, there is little information on the outcome of MPA renal transplant recipients. In our review, only six low-quality studies met the inclusion criteria. In all the series, patients had a good prognosis after transplant. In four case–control studies [37, 38, 41, 42], graft and patient survival rates in patients with ANCA-associated vasculitis were comparable to those of patients with other causes of end-stage renal disease. According to these data, RT should be offered to MPA patients [37]. Data regarding relapse rates in transplanted patients are unclear.

The review reported here has several limitations. A small number of publications with a low quality of evidence met the selection criteria. Only one clinical trial was included. Although the samples of patients from the different studies are quite similar, as in all the studies the CHCC definitions were an inclusion criteria, and the use of CYC in the induction treatment regimen was almost universal, the great variation in study design, length of follow-up and treatment maintenance regimen hampers the possibility of quantitative data synthesis. In contrast to the European League Against Rheumatism (EULAR) review [5], data regarding remission were not assessed in the present study because definition of this outcome varied largely across studies. The selection bias, with the majority of samples comprised of patients attending a tertiary...
Conclusions

Implications for practice

MPA mortality is mainly concentrated in the first month after diagnosis. Treatment side effects are the cause of death in many cases. Early diagnosis and early initiation of a tailored therapy according to risk factors aimed at reducing treatment-related damage are advisable. However, how recognition of risk factors would affect current treatment protocols is still unclear. MPA long-term prognosis is less severe but relapses are frequent, even >10 years after initial diagnosis. Clinicians should be aware of the importance of prolonged follow-up in MPA patients. ESRF is a frequent complication of MPA, but RT could be an effective treatment.

Implications for investigation

Evidence regarding MPA prognosis is weak. Multicentre randomized trials performed with an adequate methodology [43] and a longer follow-up (>10–15 years of previous studies) [1, 44, 45] are needed to achieve a more accurate estimation of the very long-term prognosis of patients with MPA. Risk factors should be assessed in controlled studies. The generation of subgroups of patients according to the different types of ANCA-associated vasculitis and their clinical presentation, and the addition of measures of the perceived quality of life in MPA patients could be of interest.

Supplementary data

Supplementary data are available at Rheumatology Online.

References


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L.C.-G.: development of the study concept and study design; acquisition of data; analysis and interpretation of data; statistical analysis; draughting the manuscript; and generating figures and final approval.

M. B.-C.-B.: development of the study concept and study design; acquisition of data; analysis and interpretation of data; draughting the manuscript; and discussing the figures and final approval.

J.d.P.-M.: development of the study concept and study design; discussing the contents and figures; and revising the draught and final approval.

J.L.L.-M.: development of the study concept and study design; discussing the contents and figures, revising the draught and final approval.

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Rheumatology key messages

- Mortality in patients with MPA is mainly concentrated in the first months after diagnosis.
- Relapses occur in 19–39% of patients even >10 years after diagnosis.
- Prolonged follow-up periods are needed in MPA patients.