Favourable renal survival in paediatric microscopic polyangiitis: efficacy of a novel treatment algorithm

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ABSTRACT

Background. Microscopic polyangiitis (MPA) is one of the most common forms of antineutrophil cytoplasm autoantibodies (ANCA)-associated vasculitis in children. Cyclophosphamide and glucocorticoid-based treatment protocols are still considered gold standard in managing this multi-system disorder. But treatment-related toxicity is a major cause of chronic morbidity and early mortality in MPA. Hence, the search for an effective and safe alternative immunosuppressant is essential.

Methods. A retrospective analysis of baseline clinico-pathological presentation and treatment-outcome was performed among 11 paediatric MPA patients. All of whom were treated with a pre-specified cyclophosphamide free, rituximab- and mycophenolate mofetil (MMF)-based management protocol as per centre practice.

Results. We describe the clinical course of 11 children with MPA over a median follow-up period of 20.9 months. Both patient survival and renal survival at 1 year follow-up were 100%. In spite of the varying degree of renal involvement at presentation, kidney function was recovered in all patients with a median estimated glomerular filtration rate (eGFR) of 79.5 mL/min/1.73m². At last follow-up, 91% (10/11) of patients were in complete remission and one (9%) child continued partial remission state. There was no treatment failure. In total, 73% (8/11) of patients were off steroids at last follow-up and 82% (9/11) of patients never relapsed during follow-up period.

Conclusions. Efficacy and medium-term safety of rituximab- and MMF-based protocol in managing children with MPA was evident in this study.

Keywords: Microscopic polyangiitis, paediatrics, rituximab

INTRODUCTION

Antineutrophil cytoplasm autoantibodies (ANCA)-associated vasculitis is a multi-system disorder characterized by necrotizing vasculitis, few or no immune deposits, predominantly affecting small vessels and presence of circulating ANCA. With the exception of IgA vasculitis and Kawasaki disease, primary systemic vasculitis presenting in childhood is uncommon. Microscopic polyangiitis (MPA), one of the ANCA-associated vasculitis, may be distinguished by the presence of necrotizing glomerulonephritis, occasional presence of pulmonary capillaritis and absence of any granulomatous inflammation [1]. Microscopic polyangiitis rarely occurs in children and incidence of MPA has not been determined among the paediatric population [2]. The use of glucocorticoid, cyclophosphamide and other immunosuppressive agents has favourably changed the prognosis of MPA. However, there is no fixed treatment protocol for the management of paediatric MPA and regardless of the centre-specific treatment, mortality and morbidity of MPA are very high. The multi-system nature of MPA results in considerable heterogeneity in the clinical phenotype and diagnostic delay is common. Many patients develop end stage renal disease, but damage to other organ systems, especially the respiratory tract, and therapy-related damage, is common [3]. In this retrospective study, we reviewed the clinical and pathological features; management and outcome of 11 children with MPA. All children were treated with a pre-specified cyclophosphamide free novel management protocol as per centre practice.
MATERIALS AND METHODS

Study population

We retrospectively reviewed the medical records of all children (<14 years) diagnosed with MPA at NRS Medical College, Kolkata, India between August 2011 and August 2014. The diagnosis of primary MPA was made according to ‘2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides’ [1]. Patients with other small vessel vasculitis, such as granulomatosis with polyangiitis or eosinophilic granulomatosis with polyangiitis, were excluded if they had granulomatosis inflammation or a history of asthma. We excluded patients with suspected secondary form of MPA arising out of malignancy, infections (hepatitis B and C, HIV and tuberculosis) or drugs (propylthiouracil, allopurinol and hydralazine). The study protocol was approved by the Institutional Review Board of NRS Medical College.

Baseline parameters and follow-up data

Patient demographics and clinical courses were obtained from hospital case records. For each patient, the following data were collected: gender, age, age at presentation, clinical manifestations, treatment received, duration of follow-up, any relapse and final outcome. The clinical manifestations included symptoms, signs and organ involvement at presentation. Results of biochemical, immunological and histological investigations were also collected from hospital records.

Treatment protocol

Induction therapy. Induction therapy consisted of intravenous methylprednisolone pulse (15 mg/kg daily for 6 days), alternate day plasma exchange during the first week and dialysis if indicated. This was followed by oral prednisolone (2 mg/kg daily) and two rituximab infusions (375 mg/m² weekly). Circulating B cells were measured 24 h after second rituximab administration. If >5 B cells per mm³ were observed, they were again measured one week later. If the count was still >5 B cells per mm³, third and fourth doses of rituximab were administered. Cotrimoxazole (20 mg/kg; three times a week) was systematically given to all patients during the period of B-cell depletion for pneumocystis prophylaxis.

Maintenance therapy. Maintenance therapy consisted of tapering the dose of daily oral prednisolone and mycophenolate mofetil (MMF) 1200 mg/m² every day in two divided doses. The dose of prednisolone was tapered (1.5 mg/kg/day as a single dose, then reduced by 0.25 mg/kg every two to four weeks) depending on disease activity and continued till one year of relapse-free survival. The patients received maintenance MMF therapy for 2–3 years depending on further relapse and disease activity.

Relapse management. Any relapse was treated with reinstitution of induction therapy, followed by maintenance therapy. No patient was treated with more than two courses of rituximab.

Definitions

Estimated glomerular filtration rate (eGFR) was estimated using the modified Schwartz formula [4]. Hypertension was described as systolic/diastolic blood pressure ≥95th percentile for sex, age and height [5]. Proteinuria was classified as subnephrotic [urine protein–creatinin ratio (Up/UC) between 0.2 and 2] or nephrotic (Up/UC > 2). Other defined terminologies were haematuria (≥5 red blood cells/high-power field in centrifuged specimen); anaemia (haemoglobin < 11 g/dL); thrombocytosis (platelet > 250 × 1000 cells/mm³) and deranged liver function tests (AST or ALT to >50 IU/L). Paediatric Vasculitis Activity Score (PVAS) was used to score disease activity [6].

Treatment response was defined as complete remission if there was attenuation of clinical manifestations of MPA and improvement in kidney function as determined by increasing eGFR after rituximab therapy. Partial remission was defined as partial attenuation of clinical manifestations of MPA with or without improvement of renal function. Treatment failure was characterized with no improvement or deterioration of clinical symptoms and renal function. We diagnosed relapse, if there was reappearance or deterioration of clinical manifestations of MPA with rising titres of immunological parameters after initial post-induction stabilization or improvement.

Primary and secondary outcome

The primary outcome was renal survival. Secondary outcome were patient survival, time to first relapse, number of relapses and drug-related adverse reactions. The end-point for renal survival analysis was starting of long-term renal replacement therapy while that for patient survival was death due to any cause.

Statistical analysis

Considering the limited sample population, we performed non-parametric tests for all statistical analyses. Continuous data were analysed using Mann–Whitney U-test and Wilcoxon signed rank test; and nominal data were examined using Fisher’s exact test. Throughout the text, data are expressed as medians with ranges and percentages as appropriate and P ≤ 0.05 was considered statistically significant. SPSS for Windows version 16 software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

RESULTS

Demographics

In total, 11 children were diagnosed with MPA between August 2011 and August 2014 at NRS Medical College, Kolkata, India. Out of them, 5 were male and 6 were female with a median age at presentation of 7.6 years (range 4.3–11.8 years) and a median disease course (before diagnosis) of 1.2 years (range 0.4–2.2 years). Their baseline characteristics are given in Table 1.

Clinical features

Table 2 summarizes the clinical manifestations at the time of diagnosis. Arthralgia, hypertension and renal involvement with active urinary sediments were the most common manifestations.
of all children suffering from MPA. Nine (81%) children, including three with rapidly progressive glomerulonephritis, were presented with acute kidney injury at the time of presentation necessitating dialysis for variable period. Lung involvement was recognized among five (45%) children and two of them required ventilator support for a brief period. One (9%) child had a history of convulsion and two (18%) children had melena.

### Laboratory findings

In total, 82% (9/11) of patients were suffering from varying degree of normocytic normochromic anaemia at the time of presentation. Seven (64%) patients presented with thrombocytosis. All (100%) patients had renal insufficiency. Five (45%) patients had sub nephrotic proteinuria and nine (82%) patients had haematuria. No patient had nephrotic range proteinuria and gross haematuria was detected in one (9%) patient. Deranged liver enzymes were found among two (18%) patients.

### Immunologic parameters

Table 3 summarizes the detailed results of immunological parameters of all children on presentation. pANCA was positive among 91% (10/11) of patients and all patients were myeloperoxidase (MPO) positive. Four (36%) patients were positive for antinuclear antibody (ANA) and one (9%) child among them was anti-dsDNA positive. In total, 27% (3/11) had decreased complement-3 (C3) levels, whereas only one (9%) child had decreased complement-4 (C4) level. We documented increased erythrocyte sedimentation rates and elevated serum C-reactive protein levels in all patients. No one was positive for cANCA, HBsAg and anti-HCV.

### Renal histology

Detailed renal histologies of all patients were described in Table 4. Six (55%) patients were pauci immune type and five (45%) presented with crescentic glomerulonephritis (presence of crescents in 50% or more glomeruli). Varying degree of fibrinoid necrosis was found in all children and interstitial fibrosis was found among three (27%) patients.

### Outcome after induction therapy

After completion of the induction therapy as per protocol, all of the children showed significant improvement in renal parameters and median eGFR improved from 26.3 (range 12.4–67.7) mL/min/1.73m² at presentation to 81.4 (range 22.6–96.7) mL/min/1.73m² post-induction (P < 0.0001). Out of
11 patients, 9 (82%) needed dialysis after initiation of induction. Eight of these dialysed patients, who responded well to pulse steroid, plasma exchange and rituximab therapy, became dialysis-independent within 1 month. One patient, who needed haemodialysis for 1 month followed by peritoneal dialysis for 4 months, had more chronic glomerular lesions on pathology and poorer presentation of renal function. After a total of 5 months of renal replacement therapy, this patient also became dialysis-independent within 1 month. One patient, who needed haemodialysis followed by peritoneal dialysis for 4 months, developed upper respiratory tract infections but did not require hospitalization. No patient developed neutropenia or infections. Two patients had dizziness and mild dyspnoea soon after infusion of rituximab. No serious adverse events occurred after rituximab therapy. Drug-related side effects might be associated with unfavourable treatment response.

**Prognostic factors**
Both children who relapsed, had disease duration of more than 2 years, age of less than 6 years, PVAS > 20 and presence of interstitial fibrosis on renal histology. So, these factors might be associated with unfavourable treatment response.

**Drug-related side effects**
No serious adverse events occurred after rituximab therapy. Two patients had dizziness and mild dyspnoea soon after infusion but no further complications developed. Two patients developed upper respiratory tract infections but did not require hospitalization. No patient developed neutropenia (<500 per mm3). During MMF therapy, two children had gastrointestinal symptoms, such as abdominal pain, diarrhoea, dyspepsia and flatulence, which settled with symptomatic treatment; however, it is difficult to distinguish drug-related adverse effects from manifestations of MPA itself.

**DISCUSSION**
Microscopic polyangiitis albeit rare is one of the most common ANCA-associated vasculitis in children [7, 8]. Treatment of paediatric MPA is challenging and therapeutic.
options are limited. Moreover, in spite of good initial response, MPA patients always remain prone to further relapse. Glucocorticoid and cyclophosphamide still constitute the crux for effective therapy of MPA. Treatment toxicity is a major cause of chronic morbidity and early mortality in MPA and the focus of clinical research has been the optimization of cyclophosphamide dosing and evaluation of alternative immunosuppressants, both for remission induction and relapse prevention.

In this retrospective study, all paediatric MPA patients were managed with a pre-specified cyclophosphamide free protocol. This single-centre retrospective study is probably the first systematic analysis of paediatric MPA patients treated with rituximab followed by MMF therapy. The point of interest regarding this report is a homogenous novel treatment protocol with adequate B cell depletion followed by daily MMF therapy to maintain the immunosuppressive effect induced by rituximab. Our aim was to save the child with MPA from expected long-term complications of cytotoxic therapy by replacing cyclophosphamide with rituximab during induction; to decrease steroid toxicity by decreasing cumulative steroid load with MMF during maintenance, and to investigate the efficacy of our novel treatment algorithm in achieving complete remission and preventing relapse.

Cyclophosphamide is associated with significant gonadotoxicity and may increase long-term cancer risk. Arulkumaran et al. reported 50% cystitis and 28% infertility in their study cohort [2]. They also pointed out that relative risk of infection as a result of steroid treatment was 2, but rose to 7 with cyclophosphamide and 12 with both steroids and cyclophosphamide [2]. To overcome this therapeutic problem and long-term adverse complications of commonly used cytotoxic therapy, rituximab, a recently introduced immunosuppressant is being increasingly used. There are several reports about the use of rituximab in children with MPA [2, 9]. Eleftheriou et al. treated 25 paediatric patients with primary systemic vasculitis with various biologic agents including rituximab and found significant improvement in score from 8.5 to 4 over a 32-month period and reduction in oral steroid requirement from 1.0 to 0.25 mg/kg/day [9]. Approximately half of a total of 8 children suffering from Wegener’s granulomatosis or MPA were treated with biological agents by Arulkumaran et al. to control disease activity [2]. Reports also suggest successful use of MMF as maintenance therapy in children with MPA [2, 10]. But even now, there is no fixed treatment protocol for these children due to the lack of randomized clinical trials.

Although there have been increasing reports of excellent immunosuppressive effect of rituximab against childhood MPA, most patients are likely to relapse following recovery of B cells [9]. As single cycle of rituximab can deplete B cells for a limited period of time only, the efficacy of additional rituximab administrations just after the re-emergence of B cells has been reported in children with nephrotic syndrome [11]. In this study, all children revealed adequate B-lymphocyte suppression and achieved complete remission at median interval of 42 days after induction therapy. A recent review reported that nearly one-third of the MPA patients usually relapsed within a median period of 15–43 months [3]. In our study, 2 out of 11 children who responded completely, relapsed again at 9 months and 13 months of follow-up. Both children relapsed with regeneration of B-lymphocytes at peripheral blood and following re-induction therapy with rituximab, one of them again achieved complete remission. Out of these two children one relapsed three times and the third relapse occurred in spite of continued adequate B-lymphocyte suppression and the child was not considered for rituximab re-treatment. Interestingly, three children sustained complete remission stage at last follow-up, even after B-cell recovery. So, it may be concluded that B-cell depletion or B-cell recovery is not the only criteria for maintaining remission or relapse. In this study, maintenance therapy with MMF after rituximab induction in children with MPA significantly improved the patient outcome in maintaining remission and preventing further relapse. We chose MMF for maintenance therapy after rituximab induction as serious adverse events are rarely experienced with long-term MMF treatment. We speculate that immunomodulation of MMF has additional impact in maintaining remission even after B-cell recovery.

Some studies have identified prognostic factors associated with ANCA-associated vasculitis [3, 12]. The main factors affecting survival were age, renal involvement and treatment [3]. Higher five factors score and BVAS were also associated with higher mortality rates [12]. We detected that age more than 6 years, duration of disease less than 2 years, PVAS < 20 and absence of interstitial fibrosis on renal histology were associated with favourable response. However, due to the small sample size, values were not statistically significant.

Early diagnosis and prompt management are key factors for improving MPA prognosis. The kidneys are the most frequent organ involved in MPA in children and adults [13]; haematuria and proteinuria are the primary manifestations [14]. In the study of Guillevin et al. [15], 12% of patients were undergoing long-term dialysis. Renal survival rate was 67% and 59% at 1 year and 3 years, respectively [16]. We also detected renal involvement in all patients, and the majority of children presented with both haematuria and proteinuria. In our present study, early diagnosis was not achieved in some patients, as shown by the renal pathological changes; however, all patients responded to induction therapy and achieved 100% renal survival. One patient, who needed 5 months of renal replacement therapy, had more chronic glomerular lesions on pathology and poorer presentation of renal function. But fortunately this patient also became dialysis-independent thereafter. Bakkaloglu et al. reported rapidly progressive glomerulonephritis among 60% of children with MPA at presentation and 40% of children reached end stage renal disease [17]. Similarly, 30% of MPA children reached end stage renal disease in the cohort of Peco-Antic et al. [18]. Cyclophosphamide and steroids were used as induction therapy in both series. So, rituximab induction in combination with methyl prednisolone pulse and plasmapheresis followed by maintenance immunosuppression with MMF and tapering dose of oral steroid were not only effective in achieving and maintaining remission but also favourably reversed the renal function.

Similar to adult MPA, our study revealed high prevalence of hypertension and acute kidney injury in paediatric MPA [3]. Renal histopathology of all children with MPA revealed...
immune complex in kidney biopsy specimens of glomerulonephritis, we detected small amounts of non-specific immune complex and pANCA was more specific for MPA. Specificity of detecting MPA is very high (almost 100%) if the sera found to be positive for both pANCA and MPO [17]. We detected 91% (10/11) children with pANCA positive and 100% with MPO positive in our study. Some of our children with MPA also revealed positive ANA and one of them was anti-dsDNA positive. Sun et al. also reported similar findings in their recent study [10]. Some reports revealed that titres of ANCA decreased to normal levels after treatment in patients with MPA and it may be used for assessing MPA activity [19, 20]. Similar changes were noted in our study. Antineutrophil cytoplasm autoantibodies were negative in all patients during remission after treatment and the titres raised during relapse.

Corral-Gudino et al. concluded in their recent review article that treatment-related side effects are the cause of death in most cases and less than 50% of deaths are related to MPA activity [3]. In this study, we documented minimal drug-related adverse reactions in our patients during the follow-up period. Our report suggests that rituximab and MMF-based protocol might be a better alternative in comparison with cyclophosphamide-based protocol in treating children with MPA.

We recognize several limitations to our study. The patient number was very small and, therefore, statistical analysis may not be conclusive. We did not directly compare the efficacy of rituximab–MMF versus cyclophosphamide among children with MPA. Also, we did not routinely perform therapeutic drug monitoring for MMF, the cost of which exceeds available resources in most developing countries. Although our study is a retrospective study, we conclude that MMF may be an ideal and safe maintenance therapy to consider as an additional immunosuppressant following induction with rituximab in maintaining remission among children with MPA. Further randomized clinical trials are needed among these children to establish the fact.

REFERENCES


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Conflict of Interest Statement

The authors declare no conflict of interest.

Financial Disclosure Declaration

The authors have no financial relationships relevant to this article to disclose.