



Mycophenolate Mofetil for Severe IgA Vasculitis Nephropathy in Children: An Observational Study

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Rationale & Objective: Individuals with IgA vasculitis nephritis (IGAVN) may develop rapidly progressive glomerulonephritis and/or nephrotic-range proteinuria, which are associated with worse prognosis. We report our experience of treatment of children with IGAVN with nephrotic-range proteinuria.

Study Design: Case series.

Setting & Participants: We retrospectively analyzed all children who presented with IGAVN, cutaneous purpura, and nephrotic-range proteinuria from January 1, 2000 until December 31, 2018.

Outcome: We evaluated time required to achieve remission of proteinuria, resolution of hematuria, and glomerular filtration rate (GFR) at 12 months and last follow-up.

Results: Twelve patients, 8 boys and 4 girls, mean age 7.5 years (range 4-15) were included in the study. Mean urinary protein to creatinine ratio (UPC) was 12.5 ± 8.7 mg/mg and GFR 90.7 ± 19.1 mL/min/1.73 m² before initiation of

immunosuppression. All patients were treated with steroids and mycophenolate mofetil. Mean UPC declined progressively from 12.5 mg/mg to 4.6, 2.7, 0.3, and 0.2 mg/mg after 1, 3, 6, and 12 months, respectively. All patients achieved remission of proteinuria (UPC <0.3 mg/mg) and normalization of kidney function (GFR 102.2 ± 8.0 mL/min/1.73 m²) at 12 months. Immunosuppression was successfully withdrawn in all patients, and at last follow-up (mean 33.5 months), all patients except one remained in remission. All patients except one that relapsed maintained normal GFR at the last follow-up.

Limitations: Retrospective study, single-center experience, no standard immunosuppressive protocol, lack of control group.

Conclusions: Remission can be achieved in patients with IGAVN and nephrotic-range proteinuria using mycophenolate mofetil-based immunosuppression. Magnitude of proteinuria is a key laboratory finding that correlates with time to achieve remission. Prolonged follow-up of patients with severe IGAVN is warranted.

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IgA vasculitis (IGAV) is the most common systemic vasculitis in children, with an incidence of approximately 10 in 100,000.^{1,2} Approximately 50% of children with IGAV have some urinary abnormalities within 30 days of initial diagnosis. Whereas most patients with kidney involvement have isolated hematuria and/or sub-nephrotic proteinuria, 20% may present with nephrotic-range proteinuria and 1% with nephritic-nephrotic syndrome.³ Persistent nephrotic-range proteinuria is the most reliable predictor of a poor outcome.⁴⁻⁶ Nephrotic-range proteinuria of 3 months duration is a risk factor for progression of the disease to kidney failure.⁵

A multihit hypothesis for the development of IGAV has been proposed. The first hit is the generation of galactose-deficient IgA1 by B cells and the second hit is the development of autoantibodies to the N-acetylgalactosamine residues on IgA1 exposed by the absence of galactose on the glycan side chain.^{7,8} Persistent activation of B cells can potentiate their differentiation into plasma cells and contribute to the chronicity of the disease.⁹

The optimal treatment for patients with severe IGAV nephropathy (IGAVN) remains unclear.¹⁰ Immunosuppressive medications such as cyclosporine A, cyclophosphamide, azathioprine, mycophenolate mofetil (MMF), high dose intravenous steroid “pulse” therapy, and calcineurin inhibitors have been used to treat severe IGAVN;

however, reports are typically small case series, and these drugs have significant side effects.¹¹⁻¹³

MMF is an immunosuppressive drug that inhibits both T- and B-lymphocyte proliferation and is used extensively in transplantation and treatment of autoimmune disorders such as systemic lupus erythematosus.^{14,15} MMF can result in suppression of B-cell response and prevention of plasma cell formation.¹⁶ MMF has been inconsistently efficacious for treatment of IGAVN in adults.¹⁷⁻²⁰ There are few case reports of the successful treatment of IGAVN using MMF in adults and children.²¹⁻²³ In a single-center study published by Du et al,²⁴ 12 children with severe IGAVN were treated with MMF for 10-15 months after failure of an 8-week course of steroids. All patients responded to MMF within 1-4 months with resolution of proteinuria. No relapses were observed after discontinuation of the MMF.²⁴ The biggest pediatric series is a single-center prospective study by Lu et al,²⁵ who treated 61 children with moderately severe IGAVN and nephrotic-range proteinuria with either steroids alone or low dose steroids and MMF. This study showed a better short-term outcome of the MMF plus steroid group, but after 2-year follow-up, the difference between groups was no longer significant. Another retrospective study which evaluated 18 pediatric patients with severe IGAVN treated with pulse steroids and MMF showed good response in 16 patients with 2 nonresponders.

PLAIN-LANGUAGE SUMMARY

Treatment of IgA nephropathy (IGAVN) can be a challenge in a subset of children who present with rapidly progressive glomerulonephritis and/or nephrotic-range proteinuria. We analyzed our experience of treating patients who presented with IGAVN and nephrotic-range proteinuria with steroids and mycophenolate mofetil. All identified patients (12 children) achieved remission of proteinuria and normalization of kidney function at 12 months. Time to achieve remission correlated to magnitude of proteinuria at onset, suggesting that proteinuria could be the key biomarker to observe in those patients. All patients except one who relapsed maintained normal kidney function and physiologic proteinuria at last follow-up. The analysis of our small cohort of patients suggests that remission can be achieved in majority of children with IGAVN and nephrotic-range proteinuria using mycophenolate mofetil-based immunosuppression.

However, in 2 responding patients, relapse was observed after discontinuation of MMF.²⁶

The aim of our study was to analyze effectiveness of immunosuppressive MMF-based treatment of children with severe IGAVN. Our hypothesis was that MMF-based immunosuppression is effective in achieving remission in children with severe IGAVN.

METHODS

Study population

This retrospective observational study was conducted in accordance with recommendations of New York Medical College Institutional Review Board. This work was deemed exempt by the Institutional Review Board, and the need for informed consent was waived because of the use of deidentified information (NYMC L-11, 953). Using the Henoch-Schönlein purpura (IGAV) diagnosis code we identified 65 patients referred to our clinic for IGAVN from January 1, 2000 until December 31, 2018. Thirteen patients had no evidence of IGAVN and 52 had hematuria and/or proteinuria. Twelve patients (8 boys, 4 girls) with nephrotic-range proteinuria (defined as urinary protein to creatinine ratio [UPC] above 2.5 mg/mg in 2 consecutive samples) were identified and included in the study. Collected data included kidney biopsies graded according to modified Oxford classification, kidney function (estimated glomerular filtration rate was calculated using Chronic Kidney Disease in Children formula), proteinuria (spot UPC), hematuria, and medication side effects.^{27,28} Remission of proteinuria was defined as UPC below 0.3 mg/mg and resolution of hematuria as absence of microscopic hematuria (less than 5 red blood cells per high-power field) in 2 subsequent urine samples.

Treatment

All patients were treated with immunosuppression including steroids and MMF; 2 patients had additional immunosuppression (1 cyclophosphamide and 1 rituximab). Steroid therapy (2 mg/kg) consisted of 8 weeks daily followed by alternate day regimen (1.5 mg/kg) and a taper. The mean duration of corticosteroid therapy was 6.0 months (range 2.8-9.1). All patients received MMF ($1,257 \pm 275$ mg/m²/day) for 10.2 ± 5.7 months. In one patient (patient 11) MMF was changed to cyclophosphamide despite improvement in UPC after 2 months of treatment with MMF. This patient presented with anemia and hyperbilirubinemia during treatment for IGAVN. Because of the possibility that these laboratory findings were related to MMF, it was replaced with cyclophosphamide. This patient was subsequently diagnosed with pyruvate kinase deficiency. Another patient (patient 12) received 2 doses of rituximab for nonkidney IGAV manifestations.

Nine patients who developed hypertension during steroid treatment were treated with either angiotensin-converting enzyme inhibitor (ACE) or angiotensin II receptor blocker (ARB) therapy at standard recommended doses. During treatment with immunosuppressive medications, evaluation was performed at least every 3 months for urinalysis, UPC ratio, serum creatinine, serum albumin, liver function tests, and complete blood count. All patients were followed for at least 12 months after achieving remission (33.5 ± 15.3 months).

Statistical analysis

Continuous data were summarized by mean and standard deviation, and categorical data were summarized as the count of each category. The differences in repeated measurements between every 2 time points were tested with the Wilcoxon signed rank test. Correlation between 2 sets of data points was analyzed using Pearson correlation coefficient. A *P* value < 0.05 was considered statistically significant.

RESULTS

The clinical and laboratory characteristics of patients are presented in Table 1. All patients (8 boys, 4 girls; mean age 7.5 years [range 4-15]) exhibited nephrotic-range proteinuria (12.5 ± 8.7 g/g) and hypoalbuminemia (2.6 ± 0.9 g/dL) at the time of presentation. Three patients exhibited full nephrotic syndrome. All patients demonstrated a decline in proteinuria by 50% in response to combined MMF and steroid treatment within 2 months of therapy except patient number 3, and all entered full remission of proteinuria within 12 months (Fig 1A and B). At 12 months, the mean spot UPC decreased from 12.5 mg/mg to 0.2 mg/mg (*P* = 0.002). Mean albumin increased from 2.6 g/dL at presentation to 4.3 g/dL at 12 months follow up (*P* = 0.005). Time to achieve remission of proteinuria correlated (*r* = 0.6, *P* = 0.05) with severity of proteinuria at presentation (Fig 2).

Table 1. Demographic and laboratory findings of patients at presentation and at last follow-up

N	Age (y)	Sex	BMI (kg/m ²)	BMI (percentile)	Hematuria	Biopsy (Oxford class)	Immunosuppressive treatment	Treatment with ACE or ARB	Laboratory Findings Before Immunosuppression			Laboratory Findings at 12 mo			Time to Normalization of proteinuria (wk)	Time to resolution of hematuria (mo)
									UPC (mg/mg)	Serum Alb (g/dl)	eGFR (ml/min x 1.73M ²)	UPC (mg/mg)	Serum Alb (g/dl)	eGFR (ml/min x 1.73M ²)		
1	4	M	15.4	48	Microscopic	M1E1S0T0	Steroids, MMF	No	10.7	1.8	109	0.12	3.6	120	14	2
2	6	M	14.7	27	Gross	M1E1S0T0	Steroids, MMF	Yes	8.5	2.8	113	0.18	4	107	28	7
3	6	F	17.8	88	Gross	M1E1S0T0	Steroids, MMF	Yes	27	1.8	89	0.26	3.9	106	45	28
4	8	M	18.3	88	Microscopic	M1E1S0T0	Steroids, MMF	Yes	26	1.8	50	0.22	4.6	100	48	19
5	10	M	24.4	97	Gross	M1E1S0T0	Steroids, MMF	Yes	8.7	2.6	98	0.14	4.5	108	50	14
6	5	M	15.5	55	Microscopic	M0E1S0T0	Steroids, MMF	No	4.6	3.8	86	0.11	4.5	91	22	23
7	6	F	24.9	99	Microscopic	M1E1S0T0	Steroids, MMF	No	3.8	3.7	99	0.19	4.4	98	12	5
8	7	F	18.4	88	Microscopic	M1E1S0T0	Steroids, MMF	Yes	19.9	2.2	75	0.13	4.4	90	17	14.5
9	9	M	16.1	41	Microscopic	M1E1S0T0	Steroids, MMF	Yes	13.2	4	90	0.1	4.4	98	13	10
10	9	M	31.3	99	Microscopic	M1E1S0T0	Steroids, MMF	Yes	4.2	3.1	105	0.1	4.1	101	7	4
11	5	M	16.8	83	Microscopic	M1E1S0T0	Steroids, MMF, cyclophosphamide	Yes	19.9	1.5	66	0.3	4.6	104	29	29.5
12	15	F	22	71	Gross	M0E0S1T0	Steroids, MMF, rituximab	Yes	3.1	2.5	108	0.1	4.5	103	18	11
Summary	7.5 ± 3.0	8 boys; 4 girls	19.6 ± 5.0	73.7 ± 24.8	4 gross; 8 microscopic	10 M1E1S0T0; 1 M0E1S0T0; 1 M0E0S1T0		9 Yes; 3 No	12.5 ± 8.7	2.6 ± 0.9	90.7 ± 19.1	0.2 ± 0.1	4.3 ± 0.3	102.2 ± 8.0	25.3 ± 14.9	13.9 ± 9.3
<i>P</i>												0.002	0.002	0.03		

Note: *P* values represent differences between laboratory findings at 12 months and before immunosuppression.

Abbreviations: ACE, angiotensin-converting enzyme inhibitors; Alb, albumin; ARB, angiotensin II receptor blockers; BMI, body mass index; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; UPC, urinary protein to creatinine ratio.

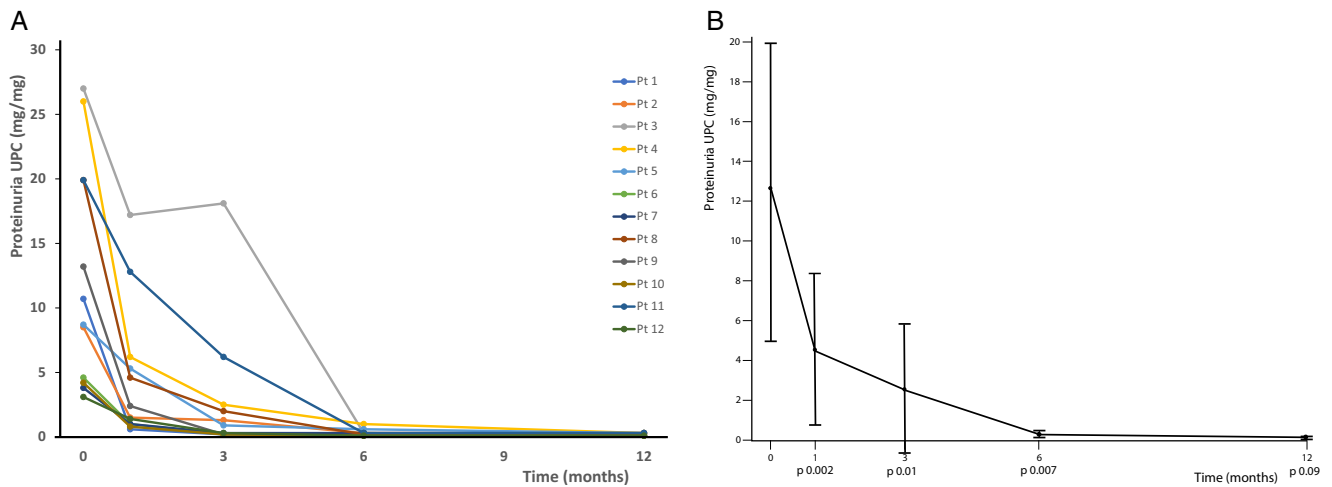


Figure 1. Response of proteinuria to immunosuppressive treatment during 12 months of treatment. (A) Presented in absolute numbers (mg/mg) for each patient. (B) Presented as a mean with standard deviation for each time point. *P* values represent difference to the previous time point. Abbreviation: UPC, urinary protein to creatinine ratio.

Results of initial kidney biopsies are summarized in Table 1; the majority (10 of 12) were M1E1S0T0. No biopsies were performed after the completion of treatment because all patients achieved remission of proteinuria at 12 months of follow-up.

Five patients had GFR below 90 mL/min/1.73 m² at presentation (90.1 ± 19.1 mL/min/1.73 m²). All patients had GFR above 90 mL/min/1.73 m² at 12 months of follow up (102.2 ± 8.0 mL/min/1.73 m²) and all except one patient (patient 7) maintained normal GFR throughout the follow-up period.

Four patients exhibited gross hematuria and 8 showed microscopic hematuria. Hematuria resolved in all patients; mean time to resolution was 14 months (range 2–28 months). Correlation observed between time to normalization of proteinuria and resolution of hematuria ($r = 0.6$, $P = 0.04$).

None of the patients had hypertension at presentation but 7 patients developed elevated blood pressures during

treatment and follow-up and were treated with either ACE or ARB therapy. None of the patients had rebound of hypertension after discontinuation of ACE/ARB therapy.

No complications of drug therapy were observed in any patient during MMF treatment. Specifically, no evidence of anemia, leucopenia, thrombocytopenia, or abnormal liver function tests was documented in any patient except patient 11. This patient had hyperbilirubinemia and anemia and was subsequently diagnosed with pyruvate kinase deficiency. None of our patients reported diarrhea or significant infection. None of the patients required adjustment of MMF dose during the treatment.

One patient (patient 7) experienced relapse 5 years after initial presentation. This patient achieved full remission under MMF and steroids and was lost to follow-up at 24 months from initial presentation. This patient presented at age 11.5 years with relapse of rash and severe IGAVN (gross hematuria and nephrotic-range proteinuria). Repeated biopsy confirmed proliferative IGAVN (M0E1S1T1); therefore, treatment with prednisone and MMF was reinitiated. No response to steroids (prednisone and budesonide) and MMF but partial response to tacrolimus was observed. At last follow-up, the patient had GFR 65 mL/min/1.73 m² and UPC 0.5 mg/mg under treatment with tacrolimus.

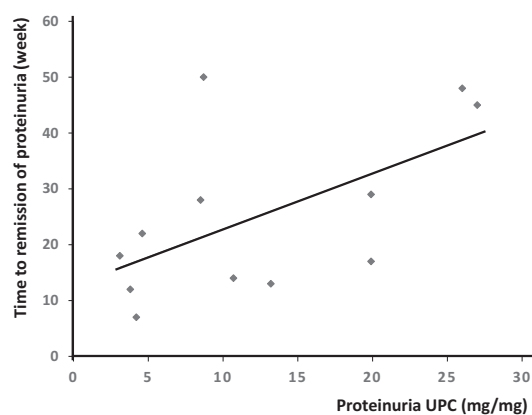


Figure 2. Time to achieve remission of proteinuria correlates with magnitude of proteinuria* * $r = 0.58$, $P = 0.05$ – Trend line. Abbreviation: UPC, urinary protein to creatinine ratio.

DISCUSSION

Currently, there is no consensus on treatment for patients with severe IGAVN. Multiple immunosuppressive protocols have been advocated and used with varying results.^{12,29} Results of our case series support previous studies that demonstrated that a combination of steroids and MMF can be effective for treating children with IGAVN and nephrotic-range proteinuria.^{22–24,26} In our cohort, proteinuria returned to normal and all patients had normal

GFR by 12 months. Remission was maintained after discontinuation of MMF therapy in all except 1 patient.

In our study, time to achieve remission of proteinuria correlated with degree of proteinuria at presentation. To our knowledge, this is the first time when such correlation has been observed. Degree of proteinuria might be a key laboratory finding determining severity of disease and requiring more aggressive approach. Additional studies are needed to address whether treatment should be stratified based on degree of proteinuria and whether earlier initiation of immunosuppressive therapy improves the outcomes. Because of the low number of patients in our study, the correlation power would be lost if we exclude 2 patients who were treated with other than MMF and steroid immunosuppressive agents.

All patients except one maintained remission at last follow-up. That patient (patient 7) experienced relapse of rash and IGAVN 5 years after initial presentation. Relapse didn't respond to various immunosuppressive treatments (prednisone, MMF, budesonide); partial remission was achieved during treatment with tacrolimus. The course of this patient confirms that long-term follow-up is appropriate for patients who recover after severe IGAVN.

Seven patients received ACE or ARB therapy for control of hypertension. Suppression of the renin-angiotensin system is known to decrease proteinuria and protect against deterioration of kidney function in hypertension and diabetic nephropathy.³⁰ Efficacy of ACE inhibition has not been established in IGAVN. We cannot discriminate between the effect of ACE and immunosuppressive therapies; however, adult studies suggest that ACE inhibition cannot reduce proteinuria by more than 40%-50%.³¹

Hematuria eventually resolved in all our patients. In 2 patients, time of resolution was above 100 weeks. In our small cohort, prolonged microscopic hematuria did not predict any worse outcomes and was comparable to other acute glomerular diseases such as poststreptococcal glomerulonephritis.³²

The reported side effects of MMF include gastrointestinal, hematologic, metabolic, and others.¹⁴ We observed no side effects in this patient cohort, and the drug was well tolerated at initial dosage. We did not monitor mycophenolic acid levels in our patients. However, one study suggested the importance of maintaining adequate mycophenolic acid area under the curve.²⁶ The ideal length of treatment with immunosuppressive treatment for IGAVN remains unknown. We discontinued treatment after stable remission for 3 months was achieved.

The major limitations of our study include the small number of patients, lack of a control group, and absence of kidney biopsies after completion of MMF treatment. Also, there was no standard immunosuppressive protocol of steroid and MMF initiation. Some patients started initial treatment with steroids alone, whereas others started MMF and steroids simultaneously. In patients treated from the beginning with MMF and steroids, we cannot discriminate

between the effect of MMF and steroids in achieving remission. Seven patients were treated with ACE or ARB therapy that might contribute to reduced proteinuria. Despite these limitations, our results indicate that MMF is an effective adjunctive agent for treatment of severe IGAVN, and the degree of proteinuria might be a key finding requiring more aggressive treatment.

In conclusion, the results of our retrospective study indicate that MMF-based immunosuppressive therapy is effective for treatment of children with IGAVN and nephrotic-range proteinuria. The magnitude of proteinuria might be a key laboratory finding determining severity of disease and requiring more aggressive approach. Our study provides additional evidence that a larger study is warranted in utilizing MMF as therapy for children with IGAVN.

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