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ORIGINAL ARTICLE

Usefulness of mycophenolate mofetil in Indian patients with C3 glomerulopathy

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ABSTRACT

Background. C3 glomerulopathy (C3G) is a heterogeneous disease caused by alternative complement pathway abnormalities without any standardized treatment. An immunosuppressive agent, mycophenolate mofetil (MMF), has been recently shown to be useful in treating C3G, mainly in studies from the west. We report the clinical outcome of 17 Indian C3G patients treated with MMF with or without steroids.

Methods. The clinical and histology details of the C3G patients treated with MMF for at least 6 months with a follow-up of at least 12 months were retrieved from the medical records of our center.

Results. The median serum creatinine and proteinuria at presentation were 0.8 mg/dL and 3.7 g/day, respectively, with the majority (88.2%) presenting as nephrotic syndrome. The mean dose of MMF was 1.65 (±0.56) g/day, and the median duration of MMF therapy was 18 months. Two-thirds (64%) of the patients responded to the treatment, with complete remission in 4 (23%) and partial remission in 7 (41%) (median time: 9 months). Three patients progressed to end-stage renal disease (ESRD) on follow-up. Of the three patients, one (33%) had an initial response in proteinuria to MMF but did not respond after a relapse and subsequently progressed to ESRD and two (67%) other patients were nonresponsive to MMF from the start of the therapy.

Conclusion. Despite a small sample size and lack of a control arm, this study describes the effectiveness of MMF in treating C3G patients from Asia and forms a basis for future randomized trials.

Keywords: C3 glomerulopathy, mycophenolate mofetil, response

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INTRODUCTION

Isolated C3 glomerular deposits are pathognomonic of C3 glomerulopathy (C3G) [1]. It includes two entities, namely dense deposit disease (DDD) and C3 glomerulonephritis (C3GN), differentiated by electron microscopy [1]. The presence of intense C3 staining without other immunoglobulin deposits in the glomerulus reflects the activation of the alternative complement pathway (AP). The origin of abnormal AP activation is either genetic mutations or autoantibodies involving complement regulating/activating genes, or both [2].

The uniqueness of C3G lies in its diversity of clinical presentation and pathogenesis. The treatment of C3G is yet not structured, probably due to the rarity of the disease and lack of large observational studies/randomized trials with complement blockade therapy. Treatment options include nonspecific, non-immunosuppressive treatment such as renin–angiotensin–aldosterone blockade, nonspecific immunosuppressive therapy such as steroids [3, 4], mycophenolate mofetil (MMF) and specific complement-targeted therapy like eculizumab. Limited experience suggests a role of MMF in C3G [5, 6]. We report our experience of MMF in the management of C3G.

MATERIALS AND METHODS

The present report is a retrospective analysis of C3G patients treated with MMF for at least 6 months and with a follow-up of at least 12 months in the Department of Nephrology and Pediatrics, Post Graduate Institute of Medical Education and Research, Chandigarh, India. We retrieved clinical, histological and serological workup (complement C3 and C4 levels) of these patients from the medical records. Complement C3 and C4 levels were measured using semi-automated nephelometer MININEPHPLUS. Glomerular filtration rate was estimated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation (2009) in adults and the Modified Schwartz formula in children. The Institute Ethics Committee approved the study protocol.

Definitions

C3G was defined as glomerular pathology characterized by dominant C3 staining by immunofluorescence microscopy [5, 6]. DDD was defined as dense osmiophilic glomerular intramembranous deposits [5, 6]. C3GN was defined as C3G that lacked the deposits seen in DDD [7, 8]. Nephrotic syndrome was defined as proteinuria ≥3.5 g/day or ≥1.5 g/day along with serum albumin <2.5 g/dL, edema and hyperlipidemia [9]. Complete remission (CR) was defined as return of serum creatinine to previous baseline, plus reduction in proteinuria to <0.5 g/day or 0.5 g/g creatinine by urinary proteinuria:creatinine ratio (uPCR). Partial remission (PR) was defined as stable (±25%) or improved serum creatinine, but not to normal, plus ≥50% reduction in proteinuria to <3 g/day (or 3 g/g uPCR) [10].

Statistical analysis

Data were entered into an Excel datasheet, and all statistical analyses were done using SPSS Version 23.0. (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as median with interquartile range (IQR) or mean (±SD), and categorical variables are expressed as percentages.

RESULTS

A total of 17 patients with C3G were treated with MMF. The median (IQR) age at presentation was 16 (11–22) years, with 5 children and 12 adults. The most common mode of presentation was nephrotic syndrome (88.20%), with median (IQR) serum creatinine and proteinuria of 0.80 (0.60–1.00) mg/dL and 3.70 (1.90–5.00) g/day at the presentation, respectively. Sixteen (94.11%) patients had microscopic hematuria. Membranoproliferative glomerulonephritis was the most common histological pattern (Table 1). C3 and C4 levels were low in 12 (70.58%) and 1 (5.88%) patient, respectively.

The detailed assessment for genetic variants of the alternative complement pathway proteins was not done in our patients. However, the first 10 out of 17 patients underwent serological evaluation for complement pathway abnormalities with methods as described previously [11]. All the 10 (100%) patients had low AP functional assay (<28%). Five (50%) out of 10 patients were positive for circulating antibodies to complement regulatory proteins. Of the 10 patients, 3 (Patient #1, #4 and #9) were positive for C3Nef, 2 (Patient #2 and #10) were positive for anti-factor H antibody and 1 (Patient #1) was positive for anti-factor B antibody. Low factor B level (<85 mg/mL) and factor H level (<225 mg/mL) were seen in one patient (Patient #1), who also had positive anti-factor B antibody and C3Nef. All the investigations mentioned above were done only at baseline.

The mean dose of MMF was 1.65 (±0.56) g/day, and the median (IQR) duration of MMF therapy was 18 (12–24) months. All the patients received renin–angiotensin–aldosterone system inhibitors right from the diagnosis through the last follow-up. The baseline clinical characteristics of the patients are mentioned in Table 1. Eleven (64.70%) patients received MMF for nonresponse to oral prednisolone therapy (1 mg/kg/day for 8 weeks), and 6 patients received MMF upfront along with prednisolone (1 mg/kg/day). Oral MMF was started at 1 g/day and increased to 2 g/day within 2 weeks in all adults and to 1.2 g/m^2 in children. CR, PR and nonresponse were seen in four (23%), seven (41%) and six (35%) patients, respectively, at the last follow-up visit of median (IQR) 24 (20–48) months. The median (IQR) time to any remission was 9 (6–14) months. Of the 11 patients who received MMF for steroid resistance, 8 (72.72%) patients achieved remission at the last follow-up, with CR in 2 (18.18%) and PR in 6 (54.54%) patients, respectively. The remission rate

Table 1. Baseline clinical characteristics of patients

Variable	Result
Gender (female, male)	7, 10
Age at biopsy, median (IQR), years	16 (11–22)
Clinical presentation	
Nephrotic syndrome (*n*)	13
Acute kidney injury or nephrotic syndrome (*n*)	2
Asymptomatic urinary abnormality (*n*)	2
Histology	
C3GN, DDD	9, 8
Membranoproliferative glomerulonephritis (%)	14 (82.35)
Crescentic glomerulonephritis (%)	2 (11.76)
Mesangial proliferative glomerulonephritis (%)	1 (5.88)
Serum creatinine, median (IQR), mg/dL	0.8 (0.6–1.0)
Estimated GFR, median (IQR), mL/min/1.73 m^2	106.9 (63.6–129.05)
Serum albumin, median (IQR), g/dL	2.6 (2–2.9)
Proteinuria, median (IQR), g/day	3.7 (1.9–5.0)
Hematuria (%)	16 (94)
Low C3 (%)	12 (70)
Low C4 (%)	1 (5)

GFR, glomerular filtration rate; IQR, interquartile range; C3GN, C3 glomerulonephritis; DDD, dense deposit disease.

(CR/PR) was similar between patients with DDD (75%) and C3GN (55.55%). Only two (40%) out of five patients with circulating antibodies achieved a response at last follow-up. The trends in median (IQR) serum creatinine, serum albumin and proteinuria at various time points are shown in Figure 1.

Patient #9, who had not responded to MMF and prednisolone initially, was later (6 months of therapy) found positive for monoclonal proteins and cryoglobulin (2% plasma cells in bone marrow biopsy and negative Hepatitis C virus-polymerase chain reaction viral load) on re-evaluation and was subsequently treated with bortezomib-based chemotherapy. The patient responded with CR to bortezomib-based treatment. The individual trends in serum creatinine, serum albumin and proteinuria at 0, 3, 6, 12 months and at last visit is shown in Table 2 and Supplementary data, Figure S1, respectively.

Patient #3, #8 and #10 developed end-stage renal disease (ESRD) on follow-up. Patient #10, although having advanced renal failure requiring dialysis at presentation (first visit), achieved PR with prednisolone therapy, but later had a gradual increase in serum creatinine and proteinuria despite MMF therapy. There was an initial response (CR) to MMF and prednisolone in one patient (Patient #3), who had a relapse at 14 months of follow-up (within 2 months of stopping MMF), which did not respond to MMF and prednisolone, and progressed to ESRD in 2 years (Table 2).

DISCUSSION

In this article, we report on 17 Indian patients with C3G, treated with MMF. Two-thirds of the patients responded favorably to MMF therapy.

The pathogenesis of C3G is not uniform. It lies in aberrant AP activation [2]. Studies on DDD and C3GN have shown the presence of homozygous genetic mutations involving complement regulatory protein, such as Factor H, Complement Factor H-related protein 5 [12, 13] and complement-activating proteins such as C3 and factor B [14]. AP dysregulation could also result from acquired antibodies that stabilize the C3 and/or C5 convertase by inhibiting the regulatory proteins [15, 16]. The presence of both acquired antibodies and underlying genetic abnormality is also described in patients with C3G [15]. We have not performed a detailed etiological evaluation of genetic or acquired factors in all our patients. Similar to prior reports [17, 18], patients with DDD in the present study had lower C3 (87%) compared with C3GN (62.5%). Forty percent of the patients with circulating antibodies responded to MMF in our study as compared with 8 (80%) out of 11 patients with C3Nef-positive C3GN as reported by Rabasco *et al.* [5]; however, no insightful conclusion could be drawn owing to the small number of patients in our study.

The heterogeneity in the modes of treatment of C3G is owing to the rarity of the disease and limited access to laboratories diagnosing the specific pathogenic pathway. The prognosis remains poor despite treatment with 10-year renal survival being <50% [17]. There are various nonspecific immunosuppressive therapies that have shown a variable response in retrospective cohorts. Steroids, at high dose (1 mg/kg/day), alone or with an other immunosuppressive agent, have been the standard therapy used in treating C3G by various centers across the world [3–5]. Eculizumab, a monoclonal C5 antibody, is a specific complement-targeted therapy used in C3G [19, 20]. In contrast to atypical hemolytic uremic syndrome, where eculizumab is an effective therapy, response rates in C3G patients are heterogeneous, probably due to fundamental differences in pathogenesis. At present, eculizumab is effective, specifically for the C3G subgroup of patients with high soluble membrane attack complex (sMAC) levels [19, 21], with its cost being a significant limitation in its widespread use.

Among all nonspecific immunosuppressive therapies, MMF-based treatment is promising compared with others concerning clinical remission and renal survival [5, 6]. Rabasco *et al.* [5] also noted a trend toward better clinical response and lower rates of ESRD in patients with C3Nef positivity than those without, similar to another report in children with C3Nef-positive C3G who achieved remission with MMF, steroids and plasma therapy [22]. The mechanism behind the success of MMF is not precise. It could be related to its anti-proliferative effects to reduce B-cell production of antibodies.

The usefulness of MMF in treating C3G was shown recently in two studies from the USA [6] and Spain [5]. Avasare *et al.* [6] from the USA compared patients with C3G treated with MMF or other immunosuppressive therapy (cyclophosphamide, calcineurin inhibitors or rituximab and steroids). The most common clinical presentation was asymptomatic urinary abnormalities. Thirty patients received MMF, and 67% of patients had remission within a median time of 291 days. No clinical, histologic or genetic variables were found to be associated with response to therapy statistically, although responders had high sMAC levels. Half of the patients relapsed on coming off MMF within 6 months to 2 years. The other study from Spain [3] compared 22 C3GN patients treated with MMF, 18 with steroids alone or with cyclophosphamide and 20 without any immunosuppression. The most common clinical presentation in these patients was nephrotic syndrome. No patient treated with MMF doubled their

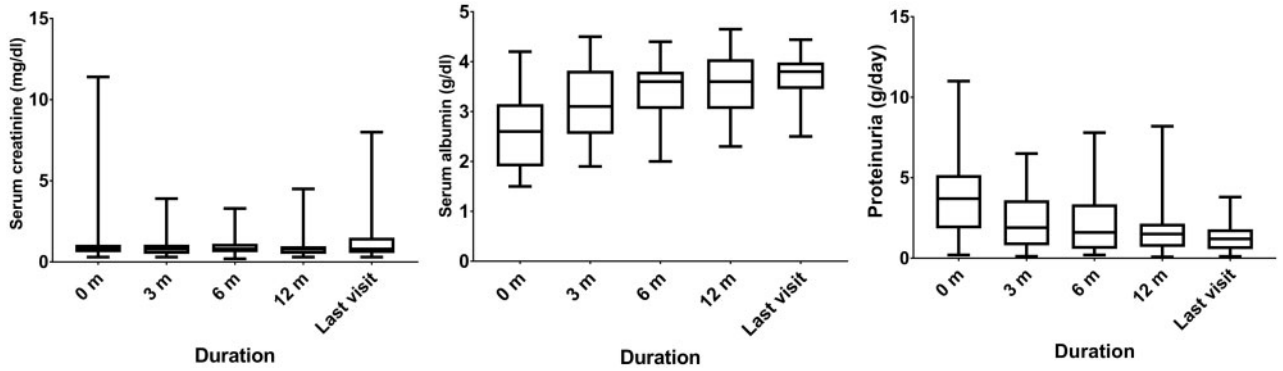

FIGURE 1: Box and whisker plot showing trends in serum creatinine (mg/dL), serum albumin (g/dL) and proteinuria (g/day) (median with IQR) at 0, 3, 6, 12 months and last visit.

Table 2. Trends of serum creatinine (mg/dL), serum albumin (g/dL) and proteinuria (g/day) at 0, 3, 6, 12 months and LV

Patient no	Sr creatinine 0 m	Sr albumin 0 m	Proteinuria 0 m	Sr creatinine 3 m	Sr albumin 3 m	Proteinuria 3 m	Sr creatinine 6 m	Sr albumin 6 m	Proteinuria 6 m	Sr creatinine 12 m	Sr albumin 12 m	Proteinuria 12 m	Sr creatinine LV	Sr albumin LV	Proteinuria LV
1	0.70	2.60	3.70	0.60	3.84	0.80	0.80	3.63	0.52	0.80	3.60	0.50	0.65	2.90	1.50
2	0.30	2.20	1.80	0.50	2.50	3.60	0.30	2.80	3.80	0.50	2.30	2.40	0.30	2.90	1.95
3	1.00	2.20	3.50	0.30	2.50	1.90	0.30	3.80	1.50	0.50	3.90	0.90	6.00	3.40	1.80
4	0.30	1.60	1.90	0.30	3.70	0.80	0.20	3.80	0.20	0.30	3.90	0.12	0.50	3.90	0.11
5	0.90	4.20	0.20	0.86	4.50	0.11	0.70	4.00	0.25	0.90	4.30	0.08	0.96	4.20	0.29
6	1.20	3.60	5.00	1.00	3.30	1.81	0.96	3.60	1.70	1.05	3.60	1.50	1.15	3.50	1.82
7	0.87	2.90	5.33	0.80	4.08	6.20	1.30	3.40	3.70	0.80	3.30	3.00	1.50	4.07	0.95
8	0.90	2.00	8.60	1.50	2.40	5.60	3.30	3.40	4.30	4.50	3.50	1.80	7.20	3.60	1.80
9	1.80	2.70	3.50	1.13	3.10	0.48	1.25	3.20	0.65	1.38	2.90	4.40	0.80	4.44	0.80
10	11.40	3.40	4.80	3.90	3.80	1.30	1.00	4.05	1.80	0.80	4.37	1.70	8.00	3.80	1.80
11	0.80	2.20	4.60	0.80	4.07	2.40	1.00	4.40	0.90	0.90	4.65	1.04	0.90	4.44	0.68
12	0.80	3.60	0.98	0.70	3.60	0.80	0.80	3.80	0.45	0.80	4.20	0.30	0.80	3.80	0.45
13	1.12	1.80	11.00	1.50	1.90	6.50	1.60	2.00	7.80	1.80	2.60	8.20	1.50	2.50	3.80
14	0.60	2.70	5.60	0.80	2.80	3.60	0.60	3.20	3.00	0.80	3.60	1.40	0.80	3.60	1.80
15	0.60	2.90	4.50	0.50	3.10	3.20	0.70	3.60	1.60	0.90	3.80	0.98	0.60	3.90	0.32
16	0.70	1.50	3.00	0.60	2.60	2.60	0.70	2.90	2.60	0.40	3.20	1.90	0.45	3.80	1.20
17	0.40	1.50	1.50	0.50	2.80	1.00	0.60	2.20	1.00	0.40	2.40	1.50	0.50	3.60	0.98

Sr, serum; LV, last visit; m, months.

Table 3. Comparion of studies on effectiveness of MMF in patients with C3G

References	Sample size, N	Inclusion	Age, median (years)	MMF duration, median (months)	Steroid use along with MMF (%)	Serum creatinine, median (mg/dL)	Proteinuria, median (g/day)	Remission rate, n/N (%)	ESRD (%)
Avasare et al. [6]	30	Patients with C3G, treated with MMF for at least 3 months and completed follow-up for at least 1 year	25	24	93	1.07	3.2	20/30 (67)	10
Rabasco et al. [5]	22	Patients with C3GN treated with MMF	35	18	100	1.3	6.5	19/22 (86)	0
Present study	17	Patients with C3G, treated and followed-up with MMF for at least 6 months	16	18	70	0.8	3.7	11/17 (64.7)	17.6

serum creatinine or developed ESRD. Clinical remission was achieved in 86% of the patients treated with MMF. Relapse of proteinuria occurred in 27.27% patients after reduction of MMF dose. Although retrospective in design, these studies support the finding that MMF, an immunomodulatory drug, might be beneficial in treating C3G. Similar to the US group, our patients were younger and included both DDD and C3GN, and similar to the Spanish group, the majority of our patients presented with nephrotic syndrome. A summary of the studies on MMF in C3G is shown in Table 3.

The primary limitation of this study stems from the lack of a control arm and evaluation of alternative pathway of complement dysregulation in all patients. Nevertheless, the strength of the study lies in adequate collection of patient follow-up data at repeated points. Although underpowered by its small sample size and design, our study is the first report of the clinical outcome of patients with C3G treated with MMF from Asia. To conclude, we found remission in two-thirds of the Indian C3G patients treated with MMF. Our results provide a basis for future randomized trials comparing MMF with other immunosuppressive therapy in C3G patients.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

The authors of this article have no conflict of interest to declare, and the results presented in this article have not been published previously in whole or part.

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