Mycophenolate Mofetil after Rituximab for Childhood-Onset Complicated Frequently-Relapsing or Steroid-Dependent Nephrotic Syndrome

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Table 1. Definitions

Term	Definition
Nephrotic syndrome	Heavy proteinuria (nocturnal urine collection ≥40 mg/h/m^2) or first morning urinary protein to creatinine ratio ≥2.0 g/gCr, and hypoalbuminemia (serum albumin ≤2.5 g/dL).
Complicated frequently relapsing/steroid-dependent nephrotic syndrome	Patients who met any one of the criteria I to IV below: I. Diagnosed with frequently relapsing or steroid-dependent disease, then subsequently diagnosed with either of these conditions after discontinuation of treatment with immunosuppressive drugs (e.g., cyclosporin, cyclophosphamide, or mizoribine*). II. Diagnosed with frequently relapsing or steroid-dependent disease, then subsequently diagnosed with either of these conditions during treatment with immunosuppressive drugs (e.g., cyclosporin, cyclophosphamide, or mizoribine*). III. Diagnosed with steroid-resistant disease and achieved remission with immunosuppressive drug treatment (cyclosporin monotherapy or in combination with methylprednisolone), but became frequently relapsing or steroid-dependent after discontinuation of treatment. IV. Diagnosed with steroid-resistant disease and achieved remission with immunosuppressive drug treatment (cyclosporin monotherapy or in combination with methylprednisolone), but became frequently relapsing or steroid-dependent during treatment. *In limited cases where mizoribine was used in combination with any other immunosuppressive drug.
Remission	Tested negative for first morning urinary protein using the dipstick method for 3 consecutive days, or first morning urinary protein to creatinine ratio <0.2 g/gCr for 3 consecutive days.
Remission confirmation date	Date on which remission was confirmed at the medical institution.
Steroid-sensitive	Remission achieved within 4 weeks after the start of daily administration of prednisolone (60 mg/m^2/day).
Relapse	Patients who met any of the following conditions and required prednisolone treatment: I. First morning urinary protein ≥3+ (≥300 mg/dL on quantitative urine protein test) using the dipstick method for 3 consecutive days. II. Urinary protein ≥2+ (≥100 mg/dL on quantitative urine protein test) using the dipstick method and serum albumin ≤3.0 g/dL.
Relapse: Just prior to this study	Relapse that occurred within 35 days before the date of enrollment.
Relapse date	The first of 3 consecutive days on which first morning urinary protein ≥3+ (≥300 mg/dL in urine protein quantitative test) was identified using the dipstick method or the date on which urinary protein ≥2+ (≥100 mg/dL in urine protein quantitative test) and serum albumin ≤3.0 g/dL were identified using the dipstick method (the date of diagnosis of relapse was acceptable for the last 3 relapses before enrollment).
Frequent relapse: Usual diagnosis	Two or more relapses within 6 months after first remission, or four or more relapses within any 12-month period.
Frequent relapse: Last episode before this study	Four or more relapses within 2 years before the last relapse date prior to this study and within any 12-month period.
Frequent relapse date	The date of last relapse that met the definition of frequent relapse.
Steroid dependence: Usual diagnosis	Two consecutive relapses during prednisolone dose reduction or within 2 weeks after its discontinuation.
Steroid dependence: Just prior to this study	Steroid dependency diagnosed within 2 years before the last relapse date prior to this study.
Steroid dependence onset date	Date of second relapse that met the definition of steroid dependency.
Steroid-resistant	Failure to achieve complete remission even with prednisolone (60 mg/m^2/day) administered for 4 consecutive weeks or longer.
Date of transition to steroid resistance	Date of confirmation that the patient was not in complete remission after 4 weeks of daily administration of prednisolone (60 mg/m^2/day) at the medical institution.
Incomplete remission	First morning urinary protein ≥1+ using the dipstick method or first morning urinary protein to creatinine ratio ≥0.2 g/gCr, and serum albumin >2.5 g/dL
Nephrotic state	Urinary protein to creatinine ratio >2.0 g/gCr and serum albumin ≤2.5 g/dL

Cr: Creatinine

Table 2. Baseline features

Variables	MMF group (N=39)	Placebo group (N=39)
Age (years)	9.3 (4.4)	9.7 (4.9)
Disease duration (years)	6.2 (4.3)	6.0 (4.7)
Male/Female	28/11	23/16
Height (cm)	130.0 (22.3)	133.7 (23.5)
Weight (kg)	35.9 (16.6)	36.9 (15.9)
Systolic blood pressure (mmHg)	110.4 (11.5)	107.8 (10.3)
Diastolic blood pressure (mmHg)	65.6 (8.6)	65.3 (10.0)
Serum creatinine (mg/dl)	0.41 (0.16)	0·43 (0.17)
Estimated glomerular filtration rate (ml/min/1.73 m^2)	123.7 (23.4)	122.7 (25.0)
Serum total protein (g/dl)	5.79 (0.91)	5.75 (0.68)
Serum albumin (g/dl)	3.13 (0.88)	3.06 (0.71)
Urinary protein to creatinine ratio (mg/mg)	0.089 (0,083)	0.087 (0.071)
Peripheral B cell count (/μl)	588.7 (573.9)	534.8 (400.1)
Steroid use at relapse immediately before assignment		
Daily dose of steroids	6 (15.4%)	7 (17.9%)
Alternate-day dose of steroids	22 (56.4%)	20 (51.3%)
No steroids	11 (28.2%)	12 (30.8%)
Immunosuppressant use at relapse immediately before assignment		
Cyclosporine + other immunosuppressant	5 (12.8%)	8 (20.5%)
Cyclosporine	16 (41.0%)	14 (35.9%)
Other immunosuppressant	8 (20.5%)	7 (17.9%)
No immunosuppressant	10 (25.6%)	10 (25.6%)
Renal histology		
Minimal change	28 (96.6%)	27 (96.4%)
Diffuse mesangial proliferation	0 (0%)	1 (3.6%)
Unknown	1 (3.5%)	0 (0%)
Days from relapse immediately before assignment to assignment	18.2 (8.1)	16.3 (5.2)
Days from assignment to dosage starting date	4.0 (3.5)	5.0 (3.8)

Data are presented as mean (Standard deviation) or n (%).

Table 3. Time to treatment failure

(a) Throughout the treatment period and follow-up peiod

Group	No. of patients	No. of patients with treatment failure	No. of patients censored	Median (95% CI) (days)	Hazard ratio (95% CI)	Log-rank test
MMF	39	23	16	784.0 (593.0–997.0)	0.593 (0.336–1.049)	P=0.0694
Placebo	39	25	14	472.5 (360.0–793.0)		

(b) During the treatment period

Group	No. of patients	No. of patients with treatment failure	No. of patients censored	Median (95% CI) (days)	Hazard ratio (95% CI)
MMF	39	6	33	not reached	0.202 (0.081-0.503)
Placebo	39	21	18	493.0 (360.0-not reached)	

(c) During the follow-up period

Group	No. of patients	No. of patients with treatment failure	No. of patients censored	Median (95% CI) (days)	Hazard ratio (95% CI)
MMF	33	17	16	386.0 (224.0-794.0)	2.598 (0.872-7.745)
Placebo	17	4	13	not reached (278.0-not reached)	

CI: Confidence Interval

Table 4. Relapse rate during the treatment period

Group	MMF	Placebo
No. of patients	39	39
Mean (SD)	0.43 (0.90)	1.99 (2.37)
Rate ratio (95% CI)	0.257 (0.084–0.480)	

SD: Standard deviation, CI: Confidence Interval

Table 5. Time to relapse

(a) Thoughout the treatment period and follow-up peiod

Group	No. of patients	No. of patients with relapse	No. of patients censored	Median (95% CI) (days)	Hazard ratio (95% CI)	Log-rank test
MMF	39	28	11	654.0 (530.0–769.0)	0.618 (0.367–1.041)	P=0.0679
Placebo	39	30	9	320.0 (266.0–460.0)		

(b) During the treatment period

Group	No. of patients	No. of patients with relapse	No. of patients censored	Median (95% CI) (days)	Hazard ratio (95% CI)
MMF	39	11	28	not reached	0.280 (0.138–0.568)
Placebo	39	27	12	320.0 (266.0–460.0)	

(c) During the follow-up period

Group	No. of patients	No. of patients with treatment failure	No. of patients censored	Median (95% CI) (days)	Hazard ratio (95% CI)
MMF	28	17	11	249.0 (138.0-349.0)	3.513 (1.019-12.106)
Placebo	12	3	9	not reached (56.0-not reached)	

CI: Confidence Interval

Table 6. Time to frequent relapses

(a) Thoughout the treatment period and follow-up peiod

Group	No. of patients	No. of patients with frequent relapses	No. of patients with steroid resitance as competing event	No. of patients censored	Median (95% CI) (days)	Hazard ratio (95% CI)	Gray test
MMF	39	22	1	16	853.0 (593.0–1299.0)	0.561 (0.316–0.999)	P=0.0475
Placebo	39	25	0	14	452.0 (360.0–793.0)		

(b) During the treatment period

Group	No. of patients	No. of patients with frequent relapses	No. of patients with steroid resitance as competing event	No. of patients censored	Median (95% CI) (days)	Hazard ratio (95% CI)
MMF	39	6	0	33	not reached	0.202 (0.084–0.483)
Placebo	39	21	0	18	493.0 (360.0–not reached)	

(b) During the follow-up period

Group	No. of patients	No. of patients with frequent relapses	No. of patients with steroid resitance as competing event	No. of patients censored	Median (95% CI) (days)	Hazard ratio (95% CI)
MMF	33	16	1	16	461.0 (224.0-not reached)	2.373 (0.770-7.319)
Placebo	17	4	0	13	not reached (278.0-not reached)	

CI: Confidence Interval

Table 7. Time to steroid dependence

(a) Thoughout the treatment period and follow-up peiod

Group	No. of patients	No. of patients with frequent relapses	No. of patients with steroid resitance as competing event	No. of patients censored	Median (95% CI) (days)	Hazard ratio (95% CI)	Gray test
MMF	39	22	1	16	853.0 (593.0–1299.0)	0.602 (0.336–1.077)	P=0.0846
Placebo	39	24	0	15	452.0 (360.0–not reached)		

(b) During the treatment period

Group	No. of patients	No. of patients with frequent relapses	No. of patients with steroid resitance as competing event	No. of patients censored	Median (95% CI) (days)	Hazard ratio (95% CI)
MMF	39	6	0	33	not reached	0.220 (0.091–0.528)
Placebo	39	20	0	19	506.0 (360.0–not reached)	

(b) During the follow-up period

Group	No. of patients	No. of patients with frequent relapses	No. of patients with steroid resitance as competing event	No. of patients censored	Median (95% CI) (days)	Hazard ratio (95% CI)
MMF	33	16	1	16	461.0 (224.0-not reached)	2.441 (0.765-7.790)
Placebo	18	4	0	14	not reached (64.0-not reached)	

CI: Confidence Interval

Table 8. Time-to-treatment failure (Per-protocol set)

Group	No. of patients	No. of patients with treatment failure	No. of patients censored	Median (95% CI) (days)	Hazard ratio (95% CI)
MMF	39	21	18	784.0 (593.0–997.0)	0.552 (0.304–1.002)
Placebo	39	23	16	452.0 (350.0–not reached)	

CI: Confidence Interval

Table. 9. Sensitivity analysis with history of rituximab treatment as a stratified factor

History of rituximab treatment	Group	No. of patients	No. of patients with treatment failure	No. of patients censored	Median treatment failure-free period (95% CI) (days)	Hazard ratio (MMF/Placebo) (95% CI)
(−)	MMF	28	18	10	754 (543–997)	0.547 (0.306–0.975)
(−)	Placebo	29	21	8	402 (327–574)	
(+)	MMF	11	5	6	973 (553–1299)	
(+)	Placebo	10	4	6	Not reached (350–not reached)	

CI: Confidence Interval

Table 10. Recovery of peripheral B cell counts during the treatment period

Visit	Day	MMF group			Placebo group			Wilcoxon test (P-value)
		No. of patients	Mean (SD)	Median [min-max]	No. of patients	Mean (SD)	Median [min-max]	
0	Screening period	39	588.7 (573.9)	418 [22-3329]	39	534.8 (400.1)	421 [83-2040]	0.909
1	1	38	674 (454.9)	670.3 [7.2-1722.2]	36	609.9 (551.7)	534.2 [13.6-2384.2]	0.236
2	8	38	5.6 (7.6)	3 [0-35.3]	37	5.9 (10.2)	2.4 [0-50.4]	0.540
4	22	39	4.7 (8)	1.8 [0-34.2]	35	4 (8.5)	1.6 [0-43.7]	0.554
5	29	25	3.3 (5.2)	1.2 [0-22.5]	26	4.6 (9.8)	0.7 [0-44.7]	0.605
6	57	39	3.9 (5.7)	2 [0-28.6]	38	5.1 (11.7)	1.6 [0-67.3]	0.608
8	113	37	4.8 (9.5)	1.7 [0-51.2]	38	11.6 (36.6)	1.5 [0-206.3]	0.961
10	169	37	36.9 (84.1)	7.2 [0-454.4]	38	113.9 (228.8)	9.5 [0-797.2]	0.312
11	225	39	83 (85.3)	65 [0-376.3]	37	187.8 (269.2)	70.5 [0-1176.3]	0.376
12	281	39	182.5 (180.3)	119.6 [0-715]	34	310.7 (564.5)	136.7 [1.3-3015]	0.908
13	337	39	228.2 (162.8)	207.2 [0-670.1]	34	282.8 (322.4)	182.6 [5-1258]	0.804
14	393	36	278.3 (199.9)	267.9 [12.6-881.3]	32	379.5 (554.1)	201.9 [0.6-2826.3]	0.503
15	449	35	282.4 (185.9)	273.5 [7.6-834.6]	30	274 (291.7)	190 [0-1191.3]	0.284
16	505	35	276.6 (165.8)	267.3 [8-575]	29	253.2 (230)	214 [0-856.5]	0.191

SD: Standard deviation, min-max: minimum-maximum

Table 11. Grade 3–4 adverse events other than infusion reactions

Variable		MMF group (N=39)		Placebo group (N=39)	
		No. of patients (%)		No. of patients (%)	
System Organ Class	Preferred Term	Grade 3	Grade 4	Grade 3	Grade 4
Gastrointestinal disorders	Diarrhea	1 (2.6)	0	0	0
	Cyclic vomiting syndrome	0	0	1 (2.6)	0
	Pneumatosis intestinalis	0	0	1 (2.6)	0
	Colitis	1 (2.6)	0	1 (2.6)	0
	Vomiting	0	0	1 (2.6)	0
	Dental caries	0	0	1 (2.6)	0
General disorders and administration site conditions	Fever	0	0	1 (2.6)	0
	Edema	0	0	1 (2.6)	0
Infections and infestations	Influenza	3 (7.7)	0	1 (2.6)	0
	Upper respiratory infection	1 (2.6)	0	2 (5.1)	0
	Nasopharyngitis	1 (2.6)	0	1 (2.6)	0
	Tonsillitis	1 (2.6)	0	0	0
	Herpes nose	1 (2.6)	0	0	0
	Oral Herpes	1 (2.6)	0	0	0
	Chickenpox	0	0	1 (2.6)	0
	Pharyngitis	0	0	1 (2.6)	0
	Periodontitis	0	0	1 (2.6)	0
	Otitis media	0	0	1 (2.6)	0
	Cellulitis	0	0	1 (2.6)	0
Injury, poisoning and procedural complications	Skin abrasion	1 (2.6)	0	0	0
	Forearm fracture	0	0	1 (2.6)	0
Renal and urinary disorders	Acute kidney injury	0	0	1 (2.6)	0
Metabolism and nutrition disorders	Hypoalbuminemia	0	0	2 (5.1)	0
	Hyperuricemia	1 (2.6)	0	0	0
	Obesity	1 (2.6)	0	0	0
Skin and subcutaneous tissue disorders	Dermatitis	0	0	1 (2.6)	0
Blood and lymphatic system disorders	Febrile neutropenia	2 (5.1)	0	0	0
	Lymphadenitis	1 (2.6)	0	0	0
Vascular disorders	Secondary hypertension	0	0	1 (2.6)	0
Investigations	Neutropenia	3 (7.7)	2 (5.1)	2 (5.1)	0
	Clostridium test positive	0	0	1 (2.6)	0