Cost Comparison Between Mycophenolate Mofetil and Cyclophosphamide-Azathioprine in the Treatment of Lupus Nephritis

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ABSTRACT. ***Objective***. To compare the healthcare expenditure associated with mycophenolate mofetil (MMF)-based immunosuppression in contrast to conventional therapy in patients with lupus nephritis.

Methods. Our retrospective single-center study compared the major healthcare costs during the first 24 months of treatment incurred by immunosuppressive medications, hospitalization, and complications in patients with severe lupus nephritis who had been treated with prednisolone and either MMF or sequential cyclophosphamide induction followed by azathioprine maintenance (CTX-AZA).

Results. Forty-four patients were studied (22 in each group). Baseline demographic and clinical measures, and remission rates after treatment, were similar between the 2 groups. Immunosuppressive drug cost was 13.6-fold higher in the MMF group (US$4168.3 ± 1176.5 per patient, compared with $285.0 ± 70.6 in the CTX-AZA group, mean difference $3883.2 ± 251.3; $p < 0.001$). MMF treatment was associated with a lower incidence of infections (12.0 episodes/1000 patient-months, compared with 32.4 in the CTX-AZA group; $p = 0.035$). Combined cost of hospitalization and treatment of infections was 82.5% lower in the MMF group (mean difference –2208.7 ± 1700.6; $p = 0.120$). Overall treatment expenditure on immunosuppressive drugs, hospitalization, and treatment of infections was 1.57-fold higher in the MMF group (mean US $4635.9 compared with $2961.5 in the CTX-AZA group; $p < 0.001$).

Conclusion. While the cost of MMF treatment for severe lupus nephritis is much higher compared with CTX-AZA, the increased drug cost is partially offset by savings from the reduced incidence of complications. (First Release Nov 1 2008; J Rheumatol 2009;36:76–81; doi:10.3899/jrheum.080517)

Key Indexing Terms:
MYCOPHENOLATE MOFETIL CYCLOPHOSPHAMIDE AZATHIOPRINE
INFECTION LUPUS NEPHRITIS

Mycophenolate mofetil (MMF), when given together with prednisolone, is an effective treatment for diffuse proliferative lupus nephritis (DPLN), and the efficacy is comparable to cyclophosphamide (CTX) combined with prednisolone[1-5]. The response to treatment appears more favorable in Chinese and Caucasians than in the African American population[1-4]. The main advantage of MMF over CTX is the reduction in treatment-related adverse effects, in particular infection, leukopenia, amenorrhea, and alopecia[1,2]. This superiority has translated into better quality of life during MMF-based immunosuppressive treatment[6]. With regard to maintenance immunosuppression, unfavorable clinical outcomes have been demonstrated with intravenous CTX pulse treatment given every 3 months[7], but the comparative efficacy between MMF and azathioprine (AZA) remains to be established.

In reality the choice of therapy depends not only on efficacy and tolerability data, but often needs to take into account cost-effectiveness. The accessibility of an apparently preferred therapy is often subject to economic considerations. In this regard, the marked difference in drug cost between MMF and CTX or AZA becomes a pertinent and realistic issue. It is reasonable to speculate that the excess in drug cost with MMF-based treatment can be partly offset by the healthcare savings consequent to the reduced incidence of complications, but such data are lacking. A recently published cost-effectiveness analysis has shown lower overall treatment cost if MMF was given for 6 months in patients with lupus nephritis, compared with intravenous pulse CTX treatment given for the same duration[8]. However, the study was based on simulation modeling using clinical outcome data from previous studies. In addition, the MMF treatment duration of 6 months is probably too short to secure sus-

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tained improvement, and thus may not reflect actual clinical practice.

Information on the magnitude of cost excess associated with MMF treatment is important to inform treatment decisions, and it should be assessed in the context of reduced complications and the improved quality of life during treatment. We have previously conducted a prospective randomized study to compare MMF against CTX followed by AZA, in combination with prednisolone, in the treatment of DPLN[1,5]. Here, we present a retrospective cost analysis based on actual data from patients who have participated in that study, to compare the major treatment costs incurred by medications, hospitalization, and the management of complications associated with the 2 immunosuppressive regimens.

MATERIALS AND METHODS

This was a retrospective single-center study conducted at Queen Mary Hospital, the University of Hong Kong. The records of patients with biopsy-proven DPLN who had participated in a previous randomized prospective study that compared prednisolone and MMF (MMF group) versus sequential immunosuppression with prednisolone and oral CTX as induction followed by AZA as maintenance (CTX-AZA group) were reviewed[1,5]. Patients who received the immunosuppressive regimens for less than 2 months were excluded.

The dosing regimens of immunosuppressive medications have been reported[1,5]. Prednisolone dosing was identical in both groups, starting at 0.8 mg/kg daily orally and tapered to reach 10 mg daily at around 6 months, then to 7.5 mg daily at around 9 months, then maintained at 5–7.5 mg daily after 12 months, depending on body weight. Patients with cellular or fibrocellular crescents that affected more than half of the glomeruli were given intravenous methylprednisolone 500 mg daily for 3 days at the initiation of treatment. In the CTX-AZA group the maximum duration of CTX treatment was 6 months, after which it was replaced by AZA as longterm maintenance immunosuppression. CTX dose was 2.5 mg/kg daily orally. After 6 months, AZA was given at 1.5–2 mg/kg daily, and the maintenance dose in the second year was 1–1.5 mg/kg per day. The dose of MMF was 1 g twice daily in the first 6 months, then 750 mg twice daily for 6 months, and 500 mg twice daily in the second year. In patients who stopped MMF before 24 months, it was replaced by AZA at a dose of 1–1.5 mg/kg per day. The dose of MMF or CTX was reduced in patients who developed adverse effects due to these drugs, as described[1,5]. None of the patients received plasmapheresis or intravenous immunoglobulin.

The hospitalization and outpatient records were studied to retrieve items used in the calculation of treatment costs for each patient during the first 24 months after starting treatment. In patients who had disease relapse occurring within this period, the costs incurred by the flares and the related complications were included. All the costs were expressed in US dollars, and based on figures in December 2007. Conversion to US dollars was based on the exchange rate of 1 US dollar to 7.8 Hong Kong dollars. Discounted cost was calculated at a rate of 3.5% per year[9]. Specifically, the following items were included: (1) Drug costs of immunosuppressive medications were calculated based on actual consumption record in each patient. The unit cost of individual drugs in local government hospitals was as follows: CTX (50 mg) $0.1479, prednisolone (5 mg) $0.0257, MMF (250 mg) $1.6704, AZA (25 mg) $0.1999, AZA (50 mg) $0.3871. (2) Hospitalization cost was calculated based on the average daily cost of $424.359 applicable to general medical wards of local government hospitals. (3) Costs of drugs used in the treatment of complications including infections were calculated based on actual consumption. (4) Costs of expensive diagnostic procedures, such as lumbar puncture, magnetic resonance imaging, etc. would be included.

The 2 groups were also compared with regard to demographic and clinical measures, their response to treatment, the incidence rates of complications and adverse events, the number of days hospitalized, and the number of days used in attending outpatient visits. Responses to induction treatment were classified as complete remission (CR), partial remission (PR), or treatment failure, as defined[1].

Statistical methods. Data were presented as mean ± standard deviation unless specified otherwise. Categorical variables were compared using chi-squared test and Fisher's exact test. The costs of treatment, hospitalization, and medications were expressed as average cost per patient over the 24-month period. Unpaired 2-sided t-test was used in the comparisons of continuous variables. Logarithmic or square-root transformation of cost data was performed before analysis. Differences in treatment costs between groups were expressed as mean difference ± standard error (SE), and 95% confidence intervals (95% CI) of the mean differences were calculated. Rates of infection, expressed as number of episodes per 1000 patient-months, were calculated for each treatment group and compared using the method described by Kirkwood and Sterne[10]. Statistical program SPSS 14.0 for Windows was used in the statistical analysis, and 2-sided $p < 0.05$ was taken as statistically significant.

RESULTS

Forty-four patients, with 22 in each treatment group, satisfied the selection criteria and were included in our study. Baseline characteristics were similar between the 2 treatment groups, and also similar between patients from the clinical trial who had or had not been included in the present cost comparison study (Table 1 and Appendix 1). The 2 groups had similar responses to treatment. Each had 17 of 22 patients (77.3%) achieving complete remission and 5 patients (22.7%) showing partial remission ($p = 1.000$ for both). Disease flares occurred in 2 patients after CR (1 in the MMF group at 9 mo and the other in the CTX-AZA group at 22 mo) and in 1 patient with PR after MMF treatment at 22 months from baseline.

All the patients received prednisolone throughout the followup duration, and the cumulative dose was 9175.8 ± 1566.1 mg per patient in the MMF group and 9769.4 ± 1726.4 mg per patient in the CTX-AZA group ($p = 0.239$). Intravenous pulse methylprednisolone was not used in any

Table 1. Baseline characteristics of patients with diffuse proliferative lupus nephritis treated with prednisolone and oral cyclophosphamide as induction, followed by prednisolone and azathioprine as maintenance therapy (CTX-AZA group) or prednisolone and mycophenolate mofetil (MMF group).

	CTX-AZA, mean (SD), n = 22	MMF, mean (SD), n = 22
Age, yrs	37.0 (9.7)	32.6 (8.0)
Female:male	20:2	18:4
Serum creatinine, μmol/l	112.6 (50.9)	118.7 (75.3)
Creatinine clearance*, ml/min	74.4 (28.6)	64.3 (20.3)
Anti-dsDNA, IU/ml	219.8 (194.5)	179.0 (192.6)
C3, mg/dl	51.7 (17.0)	61.3 (31.7)
Serum albumin, g/l	27.9 (4.2)	27.8 (6.7)

* Cockcroft-Gault formula.

of the patients. In the CTX-AZA group, CTX was given for 5.9 ± 1.5 months with a cumulative dose of 15,695.5 ± 7013.5 mg per patient. The duration of MMF treatment was 16.0 ± 5.5 months and the cumulative dose was 602,686.6 ± 177,506.7 mg per patient. AZA treatment was started in 10 patients after stopping MMF, at 13.1 ± 4.8 months from baseline. Both the duration (5.3 ± 5.8 mo in the MMF group and 16.5 ± 4.1 mo in the CTX-AZA group; $p < 0.001$) and the cumulative dose of AZA (11,002.3 ± 13,046.1 mg and 36,021.1 ± 12,202.0 mg per patient, respectively; $p < 0.001$) was lower in the MMF group. Based on actual consumption data, the cost of immunosuppressive drugs in MMF-treated patients was 14-fold that of the CTX-AZA group (Table 2), primarily due to the high cost of MMF compared with CTX and AZA. Discounting the second-year cost by 3.5% did not alter the results significantly. The 2 groups had similar proportions of patients treated with statins (5 in the MMF group and 3 in the CTX-AZA group; $p = 0.698$) and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (13 in the MMF group and 11 in the CTX-AZA group; $p = 0.545$).

The incidence of infections over the 24-month period was 12.0 episodes/1000 patient-months in the MMF group and 32.4 episodes/1000 patient-months in the CTX-AZA group ($p = 0.035$). Eight patients in the CTX-AZA group and 4 patients in the MMF group had been hospitalized for the treatment of infections (Table 3). For infections that required hospitalization, the MMF group had 8.0 episodes/1000 patient-months and the CTX-AZA group had 19.1 episodes/1000 patient-months ($p = 0.140$). For infections that did not require hospitalization, there were 4.0 episodes/1000 patient-months in the MMF group and 13.4 episodes/1000 patient-months in the CTX-AZA group ($p = 0.062$). There was a trend towards longer hospitalization duration in the CTX-AZA group, although the difference was just below statistical significance (1.05 ± 2.79 days in the MMF group and 6.18 ± 18.17 days in the CTX-AZA group; $p = 0.055$). No patient had to undergo expensive diagnostic or treatment procedures. The combined cost of hospitalization and drugs for the treatment of infections was 82.5% lower in the MMF group, although it did not reach statistical significance ($467.7 ± 1260.3 compared with $2676.4 ± 7876.4 in the CTX-AZA group; mean difference $2208.7 with SE 1700.6; $p = 0.120$; Table 4).

The combined cost of immunosuppressive drugs, hospitalization, and drug treatment for infections was higher in the MMF group compared with the CTX-AZA group from 9-month onwards, and the overall cost within the first 2 years was higher in the MMF group by 56.5% ($4635.9 ± 1632.9 per patient in the MMF group compared with $2961.5 ± 7839.0 per patient in the CTX-AZA group, mean difference $1674.5 with SE 1707.2; $p < 0.001$), or by 58.7% when a discount rate of 3.5% was applied to the second-year costs (Table 5). The number of days off work due to clinic visits was 17.6 ± 4.5 days per patient in the MMF group and 19.6 ± 7.8 days in the CTX-AZA group ($p = 0.316$). The total number of days off work due to hospitalization or clin-

Table 3. Episodes of infection that required hospitalization in patients with diffuse proliferative lupus nephritis treated with prednisolone and oral cyclophosphamide as induction followed by prednisolone and azathioprine as maintenance therapy (CTX-AZA group) or prednisolone and mycophenolate mofetil (MMF group).

	CTX-AZA, n = 22	MMF, n = 22
Pneumonia	5	1
Acute pyelonephritis	1	0
Herpes zoster	1	0
Neutropenic fever	1	0
Otitis media	0	1
Unspecified sepsis	0	2
Total	8	4

Table 2. Cumulative cost of immunosuppressive drugs over the first 24 mo of followup in patients with diffuse proliferative lupus nephritis treated with prednisolone and oral cyclophosphamide as induction, followed by prednisolone and azathioprine as maintenance therapy (CTX-AZA group) or prednisolone and mycophenolate mofetil (MMF group). Drug costs are US dollars per patient.

	CTX-AZA, n = 22		MMF, n = 22		Mean Difference*, MMF – CTX-AZA, $	Cost Difference of MMF Group Compared with CTX-AZA Group, %	p
	Drug Consumption, mg per patient, mean (SD)	Drug Cost	Drug Consumption, mg per patient	Drug Cost			
CTX or MMF	15,695.5 (7013.5)	46.4 (20.7)	602,686.6 (177,506.7)	4027.0 (1186.0)	3980.5 (252.9) [3454.6 to 4506.5]	+8578.9	< 0.001
AZA	36,021.1 (12,202.0)	188.4 (72.8)	11,002.3 (13,046.1)	64.3 (85.2)	–124.0 (23.9) [–172.2 to –75.8]	–65.9	< 0.001
Prednisolone	9769.4 (1726.4)	50.2 (8.9)	9175.8 (1566.1)	46.7 (7.6)	–3.5 (2.5) [–8.5 to 1.5]	–7.0	0.166
Immunosuppressive drug cost		285.0 (70.6)		4168.3 (1176.5)	3883.2 (251.3) [3360.9 to 4405.6]	+1362.6	< 0.001
Immunosuppressive drug cost discounted		273.1 (68.0)		3968.2 (1133.9)	3695.0 (242.2) [3206.3 to 4183.8]	+1353.0	< 0.001

* Mean (SE) [95% CI].

Table 4. Average hospitalization and antibiotics cost (US dollars per patient) for the treatment of infections in patients with diffuse proliferative lupus nephritis treated with prednisolone and oral cyclophosphamide as induction, followed by prednisolone and azathioprine as maintenance therapy (CTX-AZA group) or prednisolone and mycophenolate mofetil (MMF group). Antibiotics listed in Appendix 2.

	CTX-AZA, mean (SD) n = 22	MMF, mean (SD) n = 22	Mean Difference*, MMF – CTX-AZA, $	Difference of MMF Group Compared with CTX-AZA Group, %	p**
Duration of hospitalization, days	6.2 (18.2)	1.1 (2.8)			
Hospitalization cost, $	2623.3 (7709.6)	443.6 (1182.1)	–2179.7 (1662.9) [–5535.5 to 1176.2]	–83.1	0.120
Antibiotics cost, $	53.1 (171.2)	24.0 (81.4)	–29.1 (40.4) [–110.7 to 52.4]	–54.8	0.188
Hospitalization and antibiotics treatment costs for infections, $	2676.4 (7876.4)	467.7 (1260.3)	–2208.7 (1700.6) [–5640.8 to 1223.2]	–82.5	0.120
Hospitalization and antibiotics costs discounted, $	2502.9	436.6	–2066.3 (1587.6) [–5270.3 to 1137.7]	–82.6	0.120

* Mean (SE) [95% CI]; ** Wilcoxon rank-sum test.

Table 5. Comparison of overall treatment cost (US dollars per patient) including immunosuppressive medications, hospitalization, and treatment of infections at different timepoints from baseline.

Overall Treatment Cost	Up to 6 mo	Up to 9 mo	Up to 12 mo	Up to 18 mo	Up to 24 mo	
CTX-AZA group, mean (SD), n = 22	2610.5 (7873.8)	2616.1 (7874.6)	2820.3 (7870.3)	2890.9 (7854.5)	2961.5 (7839.0)	2776.0† (73.17.1)
MMF group, mean (SD), n = 22	2277.5 (1406.0)	2970.9 (1410.0)	3538.8 (1455.8)	4150.6 (1434.1)	4635.9 (1632.9)	4404.8† (1547.7)
Difference*	–333.0 (1705.3)	354.7 (1705.6)	718.5 (1706.4)	1259.7 (1702.3)	1674.5 (1707.2)	1628.8† (1594.5)
p**	0.120	0.024	0.015	0.005	< 0.001	< 0.001

* Mean (SE) of MMF group – CTX-AZA group; ** data were square-root transformed before analysis; † discounted.

ic visits was 18.7 ± 5.1 days per patient in the MMF group and 25.8 ± 24.8 days in the CTX-AZA group (p = 0.196).

DISCUSSION

Access to effective therapy is crucial to ensure optimal outcome in the treatment of severe proliferative lupus nephritis. The high cost of MMF compared with CTX and AZA could be prohibitive in this regard, especially in underprivileged patient groups or in developing countries. Yet in the management of diseases that could result in severe complication or permanent damage to organs, drug cost should not be considered in isolation, but in the context of both tolerability and efficacy, and against comparative treatments. In the short term, a decrease in the incidence of complications such as infection results in reduced expenditure on the treatment of these complications. As a longterm objective in the management of lupus nephritis, the prevention of renal failure has important financial implications in view of the high costs of renal replacement therapies. The data to date show that MMF combined with corticosteroid has high short-term efficacy in terms of inducing remission and is associated with a relatively low rate of renal failure on longterm follow-up[1,2,4,5,11]. In our study, we sought to compare the increased expenditure on drug cost associated with MMF-based immunosuppressive regimen to the healthcare savings consequent to fewer treatment-related complications, when compared with CTX-based induction treatment.

The cost-effectiveness of MMF has been established in kidney transplant recipients[12], but there are few data from patients with lupus. While the costliness of MMF treatment is widely appreciated, there is little information on the actual economic effect of this therapy in the clinical setting. A cost-effectiveness analysis based on simulation modeling using healthcare statistics in the United Kingdom and outcome data from previous studies showed that the overall healthcare cost was lower with MMF compared with intravenous pulse CTX, assuming that both were given for 6 months as induction treatment[8]. Apart from the limitations of simulation modeling based on metaanalysis data, restricting the study duration to 6 months could have missed some infective complications attributed to the delayed effect of CTX. Besides, the experience to date suggests that 6 months of MMF treatment is probably too short to ensure sustained clinical efficacy.

Based on our dosing protocol and with the maximum doses of MMF and CTX set at 1 g bid and 2.5 mg/kg daily, respectively[1], and assuming absolute protocol adherence, for a 70 kg patient the cost of MMF treatment would be

$4209.4 for the first year and $6614.8 for the first 2 years, while that of CTX-AZA treatment would be $165.1 for the first year and $376.5 for the first 2 years. Our results showed that, based on actual consumption data, the immunosuppressive medication cost in the MMF group was 14-fold that in the CTX-AZA group, and amounted to over $3000 in the first year and over $4100 in the first 2 years. At the same time, there was an over 80% reduction in the treatment cost for infections in the MMF group. That this difference in treatment costs for infections between the 2 groups did not reach statistical significance could be attributed to the small sample size and the marked individual variation in the occurrence of infections. Within the first 2 years the overall treatment cost incurred by immunosuppressive drugs, hospitalization, and the treatment of infections was 57% (about $1700) higher in the MMF group than in the CTX-AZA group. Between 6 and 9 months from baseline, the overall treatment costs in the 2 groups were comparable. Thereafter, there was a cost excess in the MMF group, and the difference widened with longer followup, when MMF was compared against AZA and as the incidence of infection came down. It is worth noting that the CTX in our treatment regimen was administered orally. Intravenous CTX pulse therapy would be associated with additional procedural costs, including intravenous hydration with or without anti-emetics, and probably additional days away from work, thereby reducing the magnitude of the difference in treatment cost when compared with MMF.

We have previously reported that compared with CTX-based induction treatment, MMF treatment was associated with improved quality of life, especially with regard to psychological well-being, physical function, and social function[6]. Data from our study suggest that MMF treatment may also be associated with fewer days off work, primarily due to a reduced need for hospitalization.

While there are accumulating data on both the short-term and the longterm efficacy of MMF when given as initial treatment for DPLN, the optimal duration of MMF treatment during the maintenance phase has not been established. Disease flares impose additional burden on health expenditure, consequent to the additional medication costs for the treatment of flares and the management of complications related to disease or treatment. In addition, lupus flares increase damage accrual and nephritic flares result in nephron loss and increase the likelihood of chronic renal failure. Maintenance immunosuppression with intravenous CTX pulses given every 3 months has been associated with a higher incidence of disease flares and inferior survival compared with low-dose prednisone and either MMF or AZA[7], but the data to date do not constitute enough evidence against switching from MMF to AZA in patients who have remained stable during the early maintenance phase.

Although the drug cost of MMF-based immunosuppressive therapy is considerably higher than that incurred by 6 months of oral CTX followed by AZA maintenance, the excessive cost could be partly offset by the significant savings attributed to a reduced incidence of complications, particularly infections.

Appendix 1. Baseline characteristics of patients from the clinical trial who have or have not been included in this cost comparison study[5].

MMF group: 22 patients included and 10 patients not included		Mean (SD)	p
Serum creatinine, μmol/l	Included	118.7 (75.3)	0.454
	Not included	99.5 (37.7)	
Age, yrs	Included	36.8 (8.9)	0.835
	Not included	37.6 (13.1)	
Sex	Included	18 female, 4 male	1.000
	Not included	8 female, 2 male	
Serum albumin, g/l	Included	27.8 (6.7)	0.754
	not included	27.0 (7.1)	
Proteinuria, g/24/h	Included	5.90 (3.30)	0.553
	Not included	6.90 (5.76)	
Creatinine clearance, ml/min	Included	64.3 (20.3)	0.291
	Not included	76.9 (28.7)	
Anti-dsDNA, IU/ml	Included	179 (192)	0.227
	Not included	267 (168)	
C3, mg/dl	Included	61.3 (31.7)	0.211
	Not included	47.3 (19.5)	
CTX-AZA group: 22 patients included and 8 patients not included		**Mean (SD)**	**p**
Serum creatinine, μmol/l	Included	112.6 (50.9)	0.925
	Not included	114.5 (36.6)	
Age, yrs	Included	42.4 (9.8)	0.700
	Not included	43.9 (6.5)	
Sex	Included	20 female, 2 male	0.284
	Not included	6 female, 2 male	
Serum albumin, g/l	Included	27.9 (4.2)	0.380
	not included	26.5 (2.2)	
Proteinuria, g/24/h	Included	4.84 (4.08)	0.322
	Not included	3.33 (1.55)	
Creatinine clearance, ml/min	Included	74.4 (28.6)	0.884
	Not included	76.0 (18.6)	
Anti-dsDNA, IU/ml	Included	220 (194)	0.042
	Not included	482 (490)	
C3, mg/dl	Included	51.7 (17.0)	0.748
	Not included	49.6 (10.8)	

Appendix 2. Anti-infective agents included in the cost calculations.

CTX-AZA group	Cefuroxime*, sulperazone, augmentin†, fortum, tazocin, INAH, acyclovir
MMF group	Meropenem, levofloxacin, augmentin, fortum

* Used in 5 patients; † used in 2 patients.

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