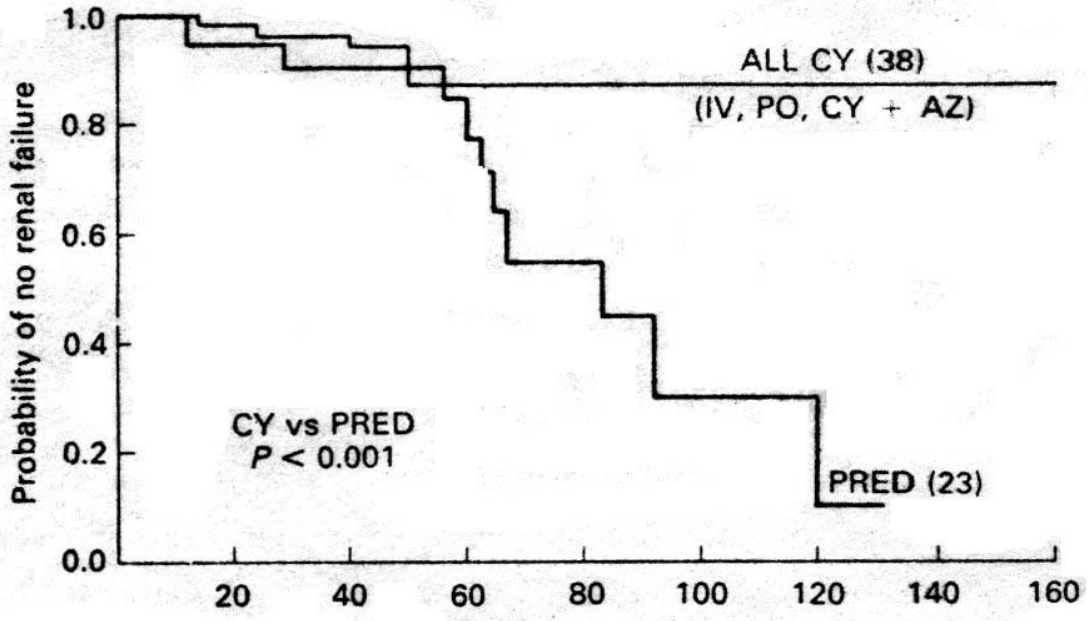
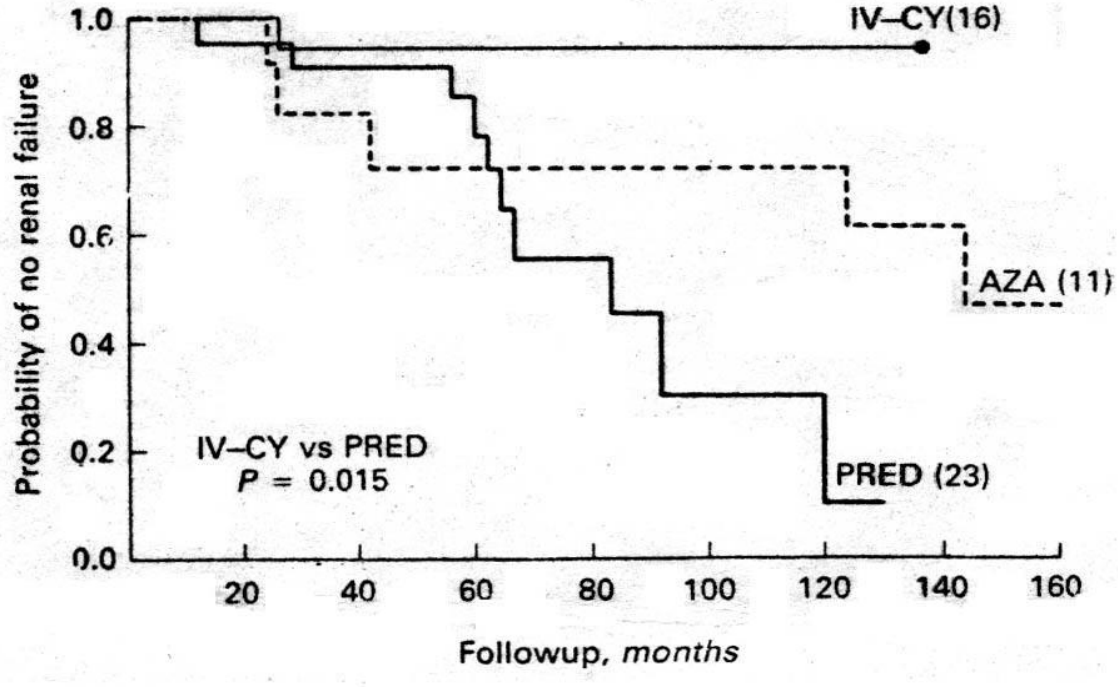
СЕЛЛ-СЕПТ В ЛЕЧЕНИИ ВОЛЧАНОЧНОГО НЕФРИТА

С. Боровой,
2009



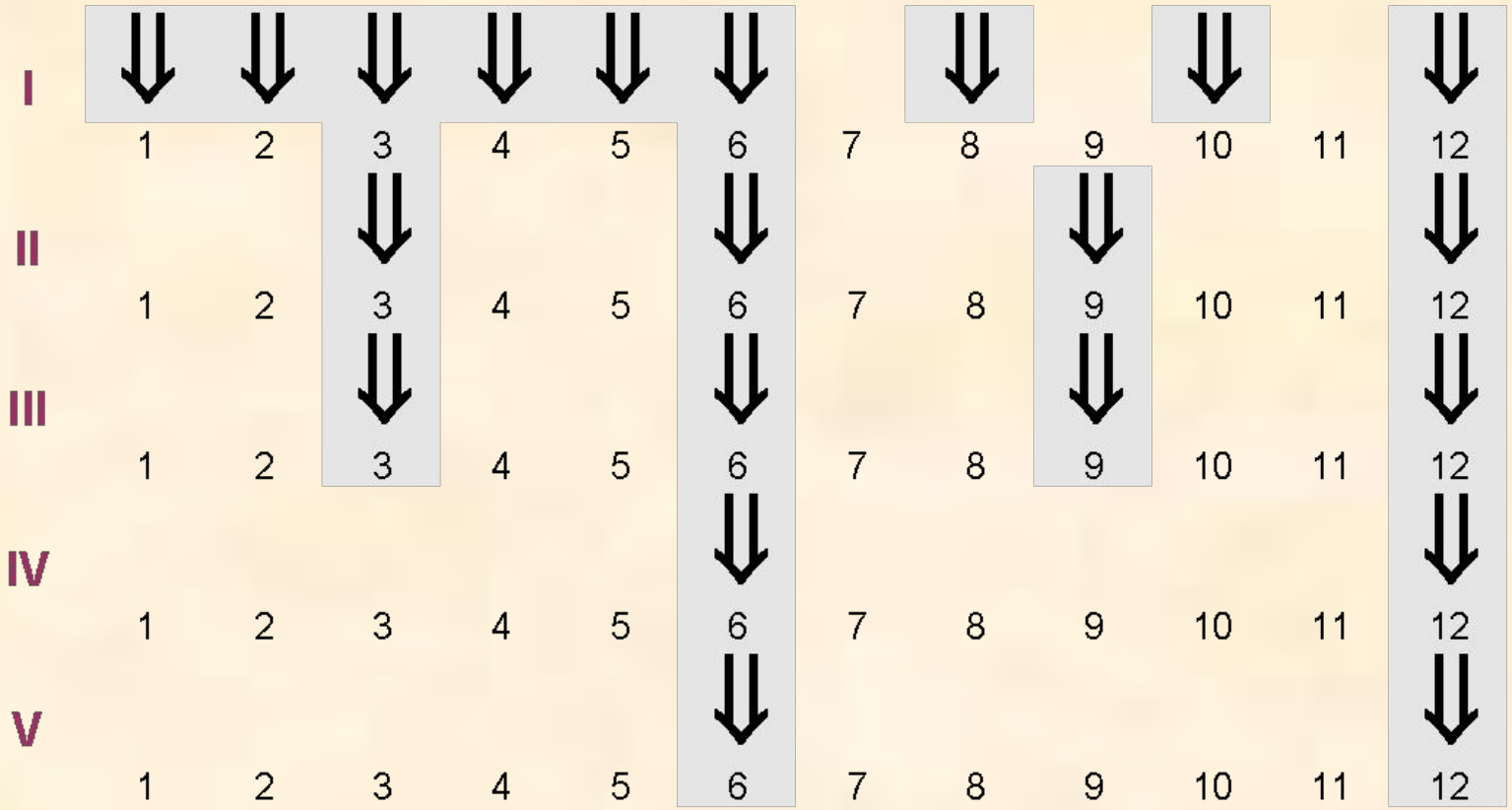


КРИВЫЕ ВЫЖИВАЕМОСТИ БОЛЬНЫХ АКТИВНЫМ ВОЛЧАНОЧНЫМ НЕФРИТОМ ПРИ РАЗЛИЧНЫХ ВАРИАНТАХ ИММУНОСУПРЕССИИ

(данные NIH, США, 70-е годы)

Alfred D. Steinberg
The treatment of lupus nephritis. (Nephrology Forum).
Kidney Intern., 1986, v. 30, 769-87

Схема пульс–терапии волчаночного нефрита циклофосфамидом (1 г на в/в введение)



Суммарная доза при 5-летней терапии – 21 г.

Ритуксимаб неэффективен в лечении волчаночного нефрита

The LUNAR trial tested rituximab in 144 patients in the US, Canada, Mexico, Argentina and Brazil who had class III or IV lupus nephritis - as determined by a renal biopsy within the previous 12 months and proteinuria.

Patients received two infusions of either rituximab or placebo every 6 months, in addition to corticosteroids and mycophenolate.

Analysis revealed that rituximab did not notably improve the likelihood of achieving a renal response (defined as improvement in renal function, urinary sediment and proteinuria) at 52 weeks.

NATURE REVIEWS | NEPHROLOGY Volume 5 | June 2009

СеллСепт

- **Микофенолата Мофетил – иммунодепрессивное средство – на фармацевтическом рынке России с 1997 г.**

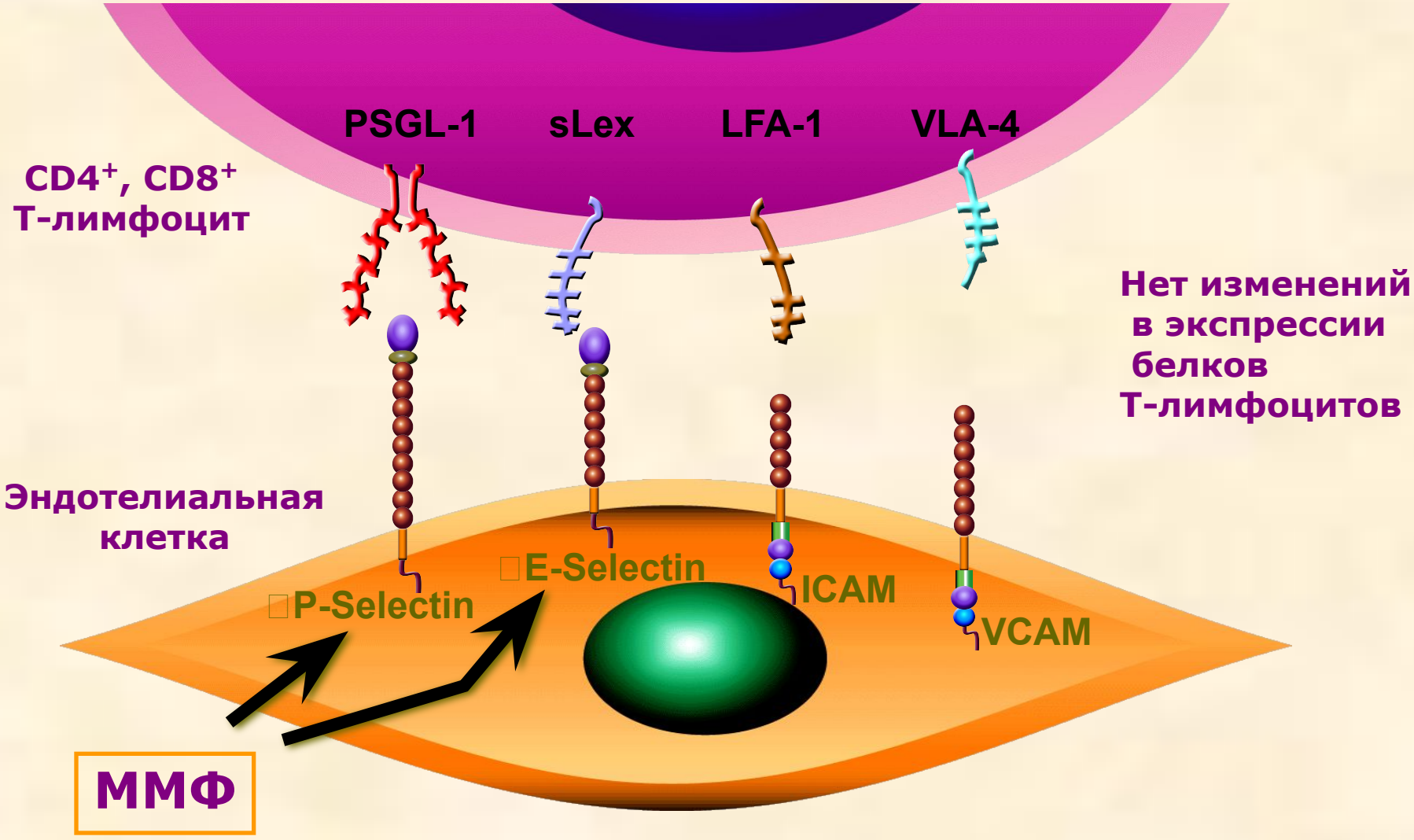
МИКОФЕНОЛЬНАЯ КИСЛОТА (МФК) – мощный, селективный, неконкурентный и обратимый ингибитор инозин монофосфат дегидрогеназы (ИМФДГ)

МФК, связываясь с ИМФДГ, ингибирует синтез пуринов и образование ДНК, что приводит к выраженному цитостатическому действию на ммунокомпетентные клетки и, как следствие, к апоптозу

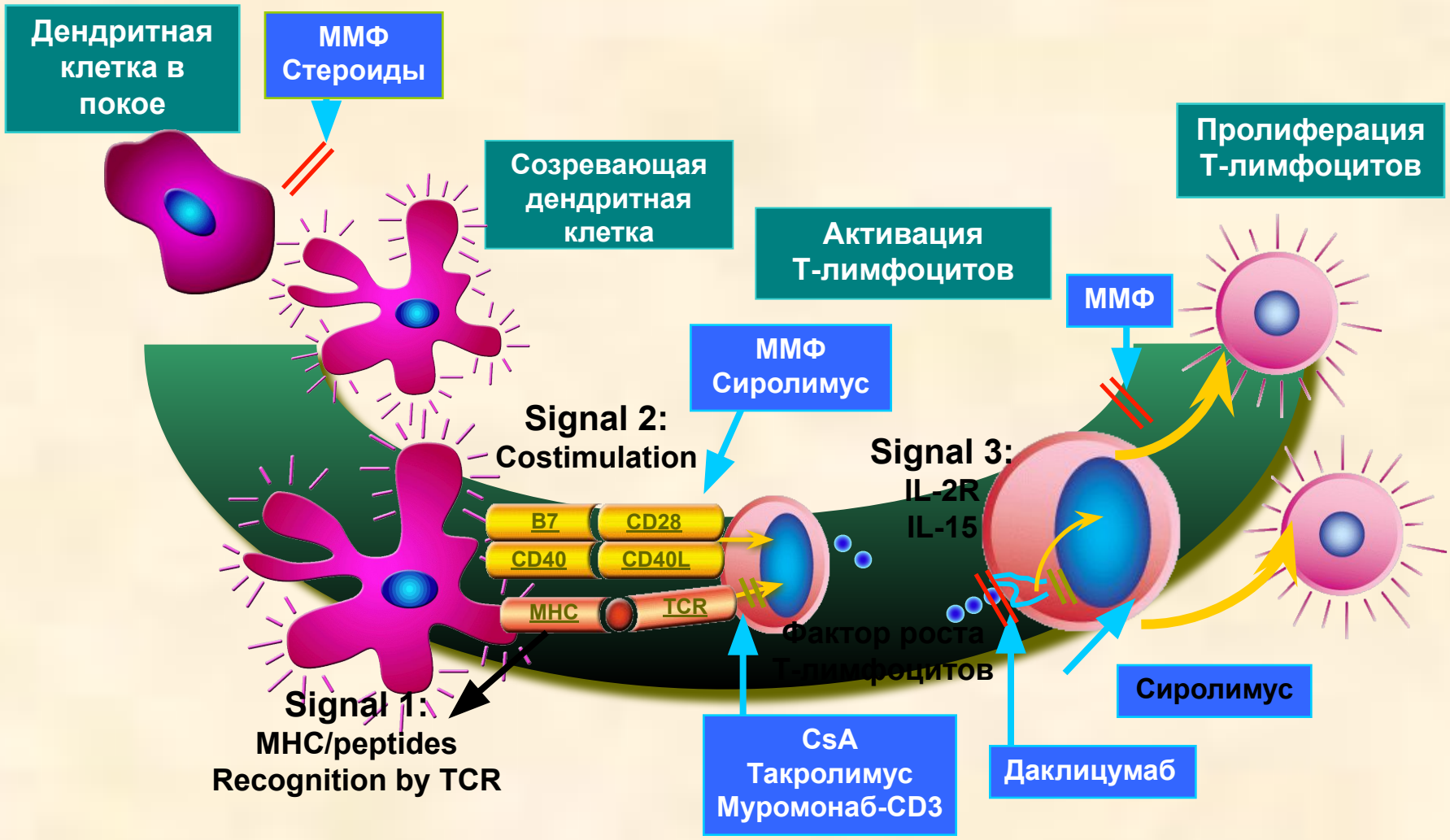
ИМФДГ - ИНОЗИНМОНОФОСФАТДЕГИДРОГЕНАЗА

- **ИМФДГ – ключевой фермент, контролирующий синтез пуринов в Т и В лимфоцитах**
- **Пурины необходимы для построения новых молекул ДНК в активно пролиферирующих клетках**
- **Селективное действие на Т и В лимфоциты обусловлено прямой связью синтеза пуринов *de novo* и пролиферацией, в то время как другие клетки могут переходить на обходные пути метаболизма без участия ИМФДГ**

Эффекты ММФ – влияние на адгезию и пролиферацию Т-лимфоцитов



Механизм действия ММФ



Adapted with permission from Prof. Walter Land and M. Schneeberger, University of Munich, Germany.

СеллСепт: показания к применению

ТРАНСПЛАНТОЛОГИЯ

- **Профилактика острого отторжения и лечение рефрактерного отторжения почечного трансплантата**
- **Профилактика острого отторжения и улучшение выживаемости как трансплантатов печени и сердца, так и больных**

НЕФРОЛОГИЯ

- **лечение стероидо- и циклофосфамид-резистентных гломерулонефропатий**
  - **волчаночный нефрит**
  - **фокальный сегментарный гломерулосклероз**
  - **IgA-нефропатия**
  - **мембранозная нефропатия**
  - **вторичные гломерулонефропатии при васкулитах**
  - **мембрано-пролиферативный гломерулонефрит**

СеллСепт: формы выпуска и дозирование

- **Таблетки 500 мг х 50 в упаковке**
- **Капсулы 250 мг х 100 в упаковке**
  - **2 таблетки по 500 мг эквивалентны 4 капсулам по 250 мг**

Трансплантация почки

- **Профилактика отторжения трансплантата – 1,0 г 2 раза в сутки (суточная доза 2 г)**
- **Лечение рефрактерного отторжения – 1,5 г в сутки (суточная доза 3 г)**

Трансплантация сердца и печени

- **Профилактика отторжения – 1,5 г 2 раза в сутки (суточная доза 3 г)**

СеллСепт: свойства

- **Не обладает нефротоксичностью**
  - **Не ухудшает функций нативной и пересаженной почек**
  - **Безопасен у пациентов со сниженной функцией почек**
  - **Улучшает функции почек – уменьшает гибель клеток клубочка и канальцев**
  - **Предотвращает хроническое отторжение**
  - **Уменьшает проявления хронической нефропатии**

- **Обладает кардиопротективной активностью**
  - **Не вызывает артериальной гипертензии**
  - **Нормализует артериальное давление**
  - **Не вызывает гиперлипидемии – при исключении циклоспорина нормализует уровни липидов и холестерина в крови**

Mycophenolate mofetil for systemic lupus erythematosus refractory to other immunosuppressive agents

M. Y. Karim1,2,, P. Alba1, M.-J. Cuadrado1, I. C. Abbs1,3, D. P. D'Cruz1, M. A. Khamashta1 and G. R. V. Hughes1 **Rheumatology 2002; 41: 876-882**

We studied 21 patients with SLE, most of whom had previously received courses of cyclophosphamide therapy and had also received courses of azathioprine or methotrexate. Indications for treatment included uncontrolled disease activity and worsening renal involvement.

***Results*. MMF treatment resulted in reduced disease activity, as assessed by the SLEDAI (SLE disease activity index) (*P*=0.0001) and decreased proteinuria (*P*=0.027) while allowing a significant reduction in oral corticosteroid dose (*P*=0.0001). Levels of complement factors C3 and C4 and anti-double-stranded DNA antibodies were not significantly affected.**

***Conclusion*. MMF appears to be a safe and effective alternative immunosuppressant for extra-renal and renal disease in SLE not responding to conventional immunosuppressive treatment.**

EFFICACY OF MYCOPHENOLATE MOFETIL IN PATIENTS WITH DIFFUSE PROLIFERATIVE LUPUS NEPHRITIS

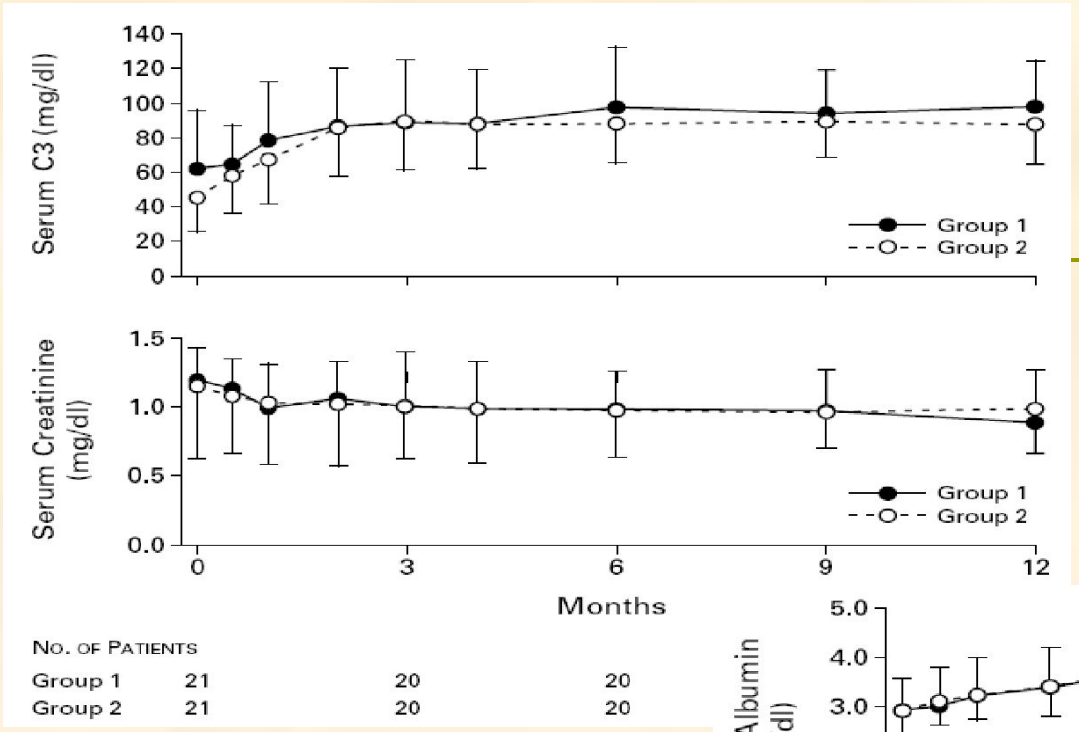
TAK MAO CHAN, M.D., FU KEUNG LI, M.D., COLIN S.O. TANG, B.SC., RAYMOND W.S. WONG, M.D., GUO XIANG FANG, M.D., YU LIAN JI, M.D., CHAK SING LAU, M.D., ANDREW K.M. WONG, M.D., MATTHEW K.L. TONG, M.D., KWOK WAH CHAN, M.D., AND KAR NENG LAI, M.D., FOR THE HONG KONG–GUANGZHOU NEPHROLOGY STUDY GROUP*

TABLE 1. CHARACTERISTICS OF 42 PATIENTS WITH DIFFUSE PROLIFERATIVE LUPUS NEPHRITIS, ACCORDING TO THE ASSIGNED TREATMENT.*

CHARACTERISTIC	GROUP 1 (N=21)	GROUP 2 (N=21)
Sex — M/F	1/20	2/19
Age — yr	36±11	39±9
Duration of lupus — mo	72±69	97±80
Duration of nephritis — mo	54±63	77±76
Organ involvement — no. (%)		
Skin	13 (62)	9 (43)
Joint	15 (71)	12 (57)
Serous membrane	5 (24)	5 (24)
Serum creatinine — mg/dl†	1.2±0.6	1.2±0.3
Creatinine clearance — ml/min/1.73 m² of body-surface area	86±35	77±31
Urinary protein excretion — g/24 hr	5.8±4.6	3.7±1.7
Serum albumin — g/dl‡	2.8±0.6	2.8±0.5
Serum C3 — mg/dl§	62±34	46±20
Serum anti–double-stranded DNA antibody — IU/ml¶	293±204	426±627
Activity score‖	8.6±2.8	8.6±1.8
Chronicity score**	2.8±1.1	3.9±3.0

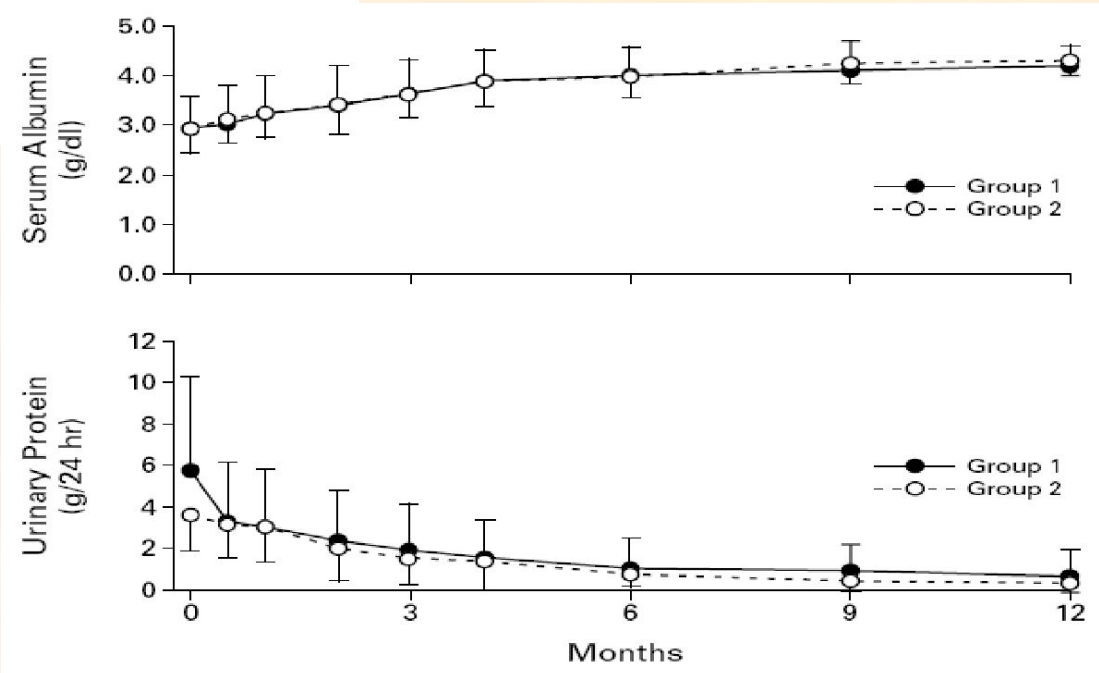
*Patients in group 1 received mycophenolate mofetil with prednisolone for 12 months. Patients in group 2 received cyclophosphamide with prednisolone for six months, followed by azathioprine with prednisolone for six months. Plus–minus values are means ±SD. $P>0.05$ for all comparisons between the two groups.

Conclusions For the treatment of diffuse proliferative lupus nephritis, the combination of mycophenolate mofetil and prednisolone is as effective as a regimen of cyclophosphamide and prednisolone followed by azathioprine and prednisolone. (N Engl J Med 2000;343:1156-62.)



No. of Patients

Group 1	21	20	20	
Group 2	21	20	20	



No. of Patients

Group 1	21	20	20	20	17
Group 2	21	20	20	17	16

TABLE 3. OUTCOME OF TREATMENT.*

VARIABLE	GROUP 1 (N=21)		GROUP 2 (N=21)		DIFFERENCE BETWEEN GROUPS†	P VALUE
	no.	% (95% CI)	no.	% (95% CI)	% (95% CI)	
Complete remission	17	81 (58 to 95)	16	76 (53 to 92)	5 (−20 to 30)	1.00
Partial remission	3	14	3	14	0 (−21 to 21)	1.00
Treatment failure	1	5	2	10	−5 (−20 to 11)	1.00
Relapse‡	3	15	2	11	4 (−16 to 25)	1.00
Discontinuation of treatment	1	5	1	5	0 (−13 to 13)	1.00
Death	0		2	10	−10 (−22 to 3)	0.49
	wk after diagnosis				wk (95% CI)	
Time to complete remission	17±11		22±11		−5 (−13 to 2)	0.15
Time to partial remission	16±14		14±3		2 (−28 to 32)	0.81
Time to relapse§	37, 42, 42		36, 42		1.3 (−8.5 to 11.2)	0.70

TABLE 4. ADVERSE EFFECTS.*

ADVERSE EFFECT	GROUP 1 (N=21)		GROUP 2 (N=21)		P VALUE
	no.	% (95% CI)	no.	% (95% CI)	
Infection	4	19 (5–42)	7	33 (15–57)	0.29
No. of episodes	6		10		0.45
Type					
Respiratory infection†	4	67	5	50	0.63
Tuberculosis	0		1	10	1.00
Urinary tract infection	0		2	20	0.50
Herpes zoster	2	33	2	20	0.60
Other					
Leukopenia	0		2	10	0.49
Hair loss	0		4	19	0.11
Amenorrhea‡	0		3	23	0.09
Transient	0		2	15	0.21
Permanent	0		1	8	0.46
Diarrhea	1	5	0		1.00
Death	0		2	10	0.49

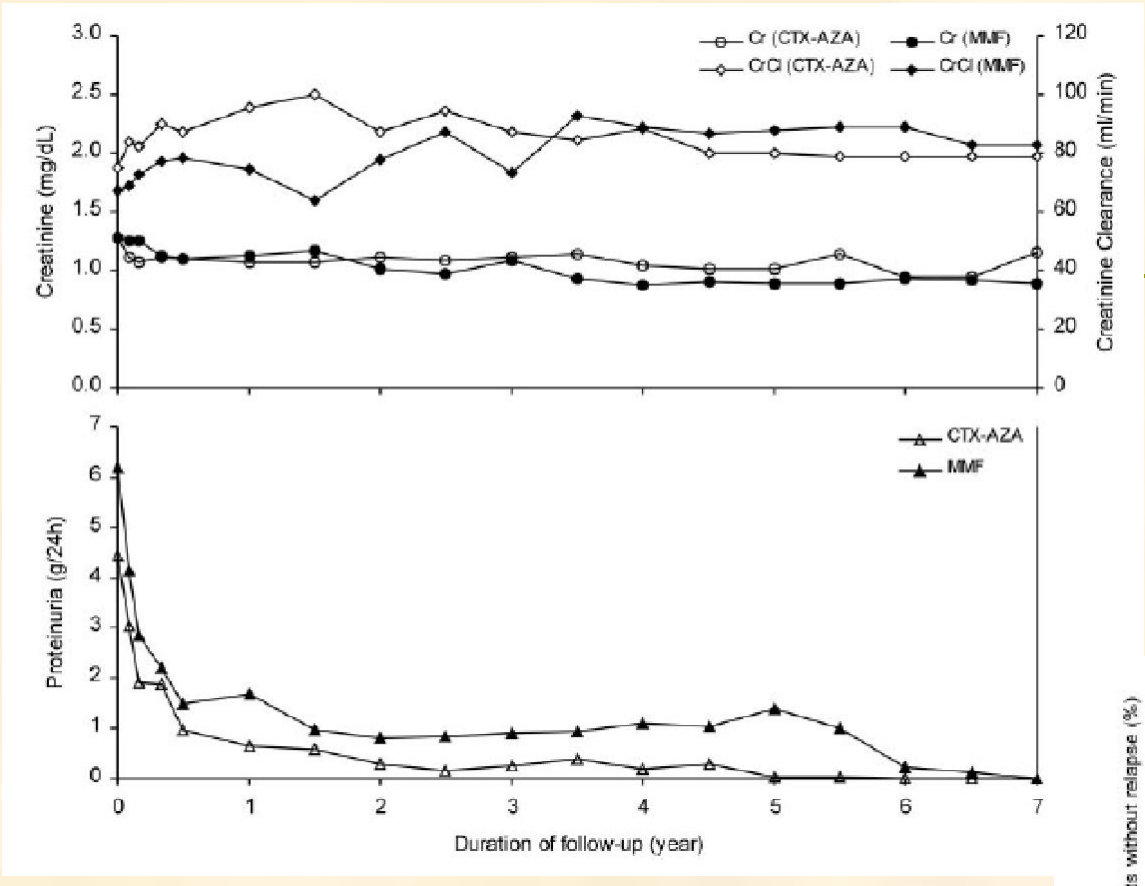
Long-Term Study of Mycophenolate Mofetil as Continuous Induction and Maintenance Treatment for Diffuse Proliferative Lupus Nephritis

Tak-Mao Chan, Kai-Chung Tse, Colin Siu-On Tang, Mo-Yin Mok, and Fu-Keung Li, for the Hong Kong Nephrology Study Group

Department of Medicine, University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong

Mycophenolate mofetil (MMF) and the sequential use of cyclophosphamide followed by azathioprine (CTX-AZA) demonstrate similar short-term efficacy in the treatment of diffuse proliferative lupus nephritis (DPLN), but MMF is associated with less drug toxicity. Results from an extended long-term study, with median follow-up of 63 mo, that investigated the role of MMF as continuous induction-maintenance treatment for DPLN are presented. Thirty-three patients were randomized to receive MMF, and 31 were randomized to the CTX-AZA treatment arm, both in combination with prednisolone. More than 90% in each group responded favorably (complete or partial remission) to induction treatment. Serum creatinine in both groups remained stable and comparable over time. Creatinine clearance increased significantly in the MMF group, but the between-group difference was insignificant. Improvements in serology and proteinuria were comparable between the two groups. A total of 6.3% in the MMF group and 10.0% of CTX-AZA–treated patients showed doubling of baseline creatinine during follow-up ($P = 0.667$). Both the relapse-free survival and the hazard ratio for relapse were similar between MMF- and CTX-AZA–treated patients (11 and nine patients relapsed, respectively) and between those with MMF treatment for 12 or ≥24 mo. MMF treatment was associated with fewer infections and infections that required hospitalization ($P = 0.013$ and 0.014, respectively). Four patients in the CTX-AZA group but none in the MMF group reached the composite end point of end-stage renal failure or death ($P = 0.062$ by survival analysis). It is concluded that MMF and prednisolone constitute an effective continuous induction-maintenance treatment for DPLN in Chinese patients.

J Am Soc Nephrol 16: 1076-1084, 2005. doi: 10.1681/ASN.2004080686



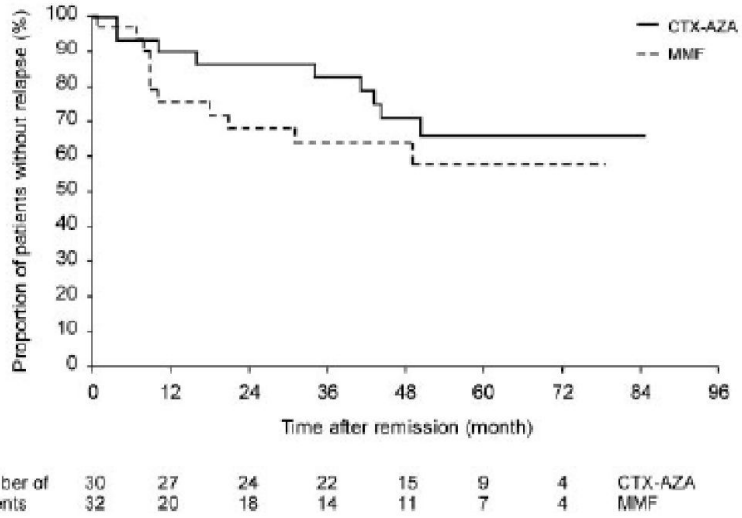


Figure 3. Relapse-free survival after achieving remission in patients with DPLN treated with prednisolone and either MMF (n = 32) or CTX-AZA (n = 30). Relapse-free survival after remission was similar between the two treatment groups (P = 0.338).

N Engl J Med 2005;353:2219-28.

Mycophenolate Mofetil or Intravenous Cyclophosphamide for Lupus Nephritis

Ellen M. Ginzler, M.D., M.P.H., Mary Anne Dooley, M.D., M.P.H., Cynthia Aranow, M.D., Mimi Y. Kim, Sc.D., Jill Buyon, M.D., Joan T. Merrill, M.D., Michelle Petri, M.D., M.P.H., Gary S. Gilkeson, M.D., Daniel J. Wallace, M.D., Michael H. Weisman, M.D., and Gerald B. Appel, M.D.

We conducted a 24-week randomized, open-label, noninferiority trial comparing oral mycophenolate mofetil (initial dose, 1000 mg per day, increased to 3000 mg per day) with monthly intravenous cyclophosphamide (0.5 g per square meter of body-surface area, increased to 1.0 g per square meter) as induction therapy for active lupus nephritis. A change to the alternative regimen was allowed at 12 weeks in patients who did not have an early response. The study protocol specified adjunctive care and the use and tapering of corticosteroids. The primary end point was complete remission at 24 weeks (normalization of abnormal renal measurements and maintenance of baseline normal measurements). A secondary end point was partial remission at 24 weeks.

RESULTS

Of 140 patients recruited, 71 were randomly assigned to receive mycophenolate mofetil and 69 were randomly assigned to receive cyclophosphamide. At 12 weeks, 56 patients receiving mycophenolate mofetil and 42 receiving cyclophosphamide had satisfactory early responses. In the intention-to-treat analysis, 16 of the 71 patients (22.5 percent) receiving mycophenolate mofetil and 4 of the 69 patients receiving cyclophosphamide (5.8 percent) had complete remission, for an absolute difference of 16.7 percentage points (95 percent confidence interval, 5.6 to 27.9 percentage points; P=0.005), meeting the prespecified criteria for noninferiority and demonstrating the superiority of mycophenolate mofetil to cyclophosphamide. Partial remission occurred in 21 of the 71 patients (29.6 percent) and 17 of the 69 patients (24.6 percent), respectively (P=0.51). Three patients assigned to cyclophosphamide died, two during protocol therapy. Fewer severe infections and hospitalizations but more diarrhea occurred among those receiving mycophenolate.

CONCLUSIONS

In this 24-week trial, mycophenolate mofetil was more effective than intravenous cyclophosphamide in inducing remission of lupus nephritis and had a more favorable safety profile.

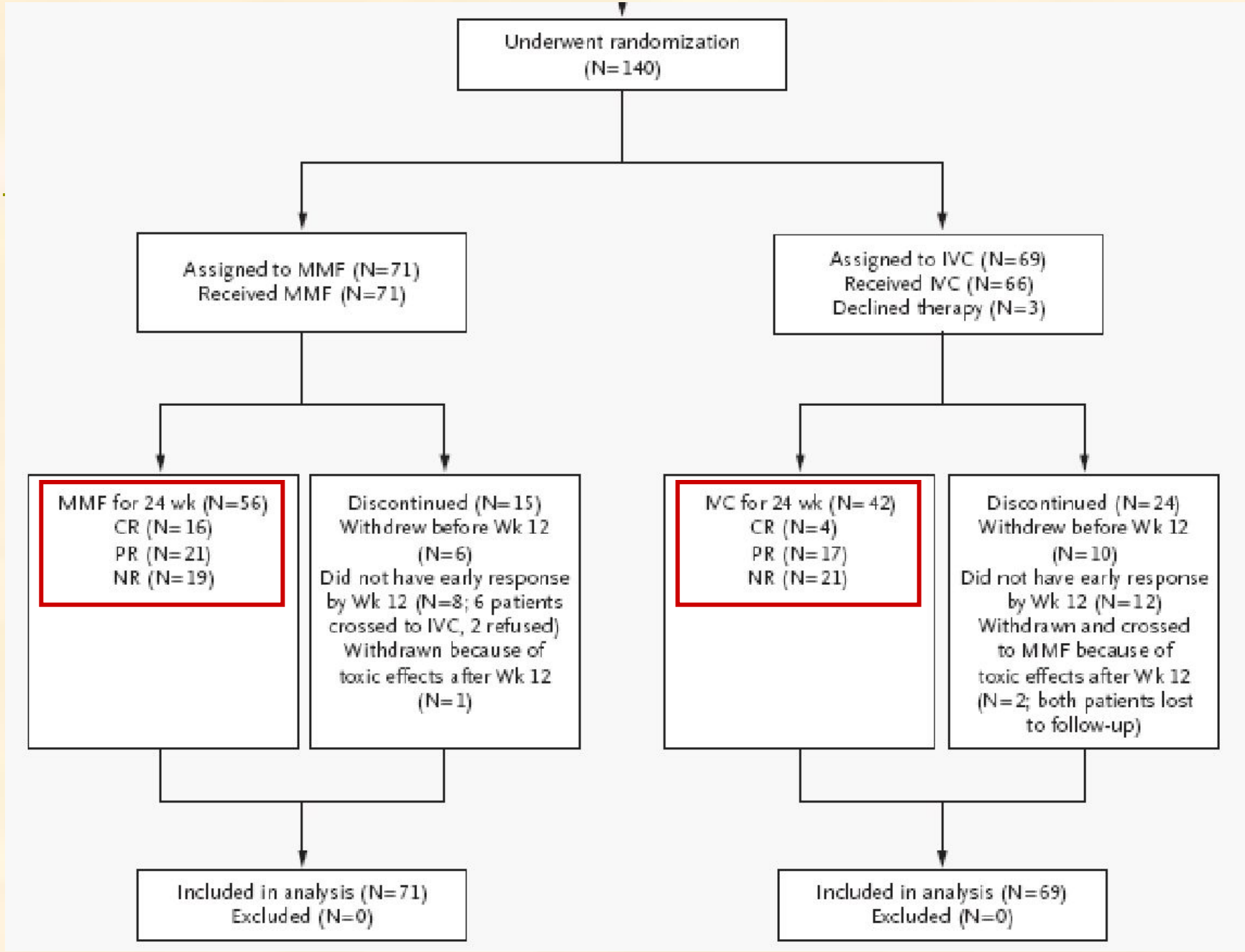

Underwent randomization
(N=140)
Assigned to MMF (N=71)
Received MMF (N=71)
Assigned to IVC (N=69)
Received IVC (N=66)
Declined therapy (N=3)
MMF for 24 wk (N=56)
CR (N=16)
PR (N=21)
NR (N=19)
Discontinued (N=15)
Withdrew before Wk 12
(N=6)
Did not have early response by Wk 12 (N=8; 6 patients crossed to IVC, 2 refused)
Withdrawn because of toxic effects after Wk 12
(N=1)
IVC for 24 wk (N=42)
CR (N=4)
PR (N=17)
NR (N=21)
Discontinued (N=24)
Withdrew before Wk 12
(N=10)
Did not have early response by Wk 12 (N=12)
Withdrawn and crossed to MMF because of toxic effects after Wk 12
(N=2; both patients lost to follow-up)
Included in analysis (N=71)
Excluded (N=0)
Included in analysis (N=69)
Excluded (N=0)

Table 4. Outcomes during Follow-up after Induction Therapy.*

Event	No. of Events		Relative Risk (95% CI)†	P Value
	Mycophenolate Mofetil	Intravenous Cyclophosphamide		
First renal flare	8	8	0.98 (0.37–2.61)	0.96
Renal failure	4	7	0.53 (0.15–1.81)	0.31
Death	4	8	0.48 (0.15–1.60)	0.24

* Relative risks were determined with the use of the Cox proportional-hazards model.

† Values are for mycophenolate mofetil therapy as compared with intravenous cyclophosphamide therapy.

Сравнительный эффект ММФ и циклофосфамида при лечении волчаночного нефрита (24 нед.)

Ремиссия	ММФ (n=71), n (%)	Циклофосф-амид (n=69), n (%)	p
Полная	16 (22,5)	4 (5,8)	0,005
Частичная	21 (29,6)	17 (24,6)	0,51
Без ответа	19	21	

Ginzler EM et al. N Engl J Med 2005; 353:2219-2228.

Table 3. Adverse Events.*

	Mycophenolate Mofetil (N=83)	Intravenous Cyclophosphamide (N=75)
Severe infections†	1	6
Necrotizing fasciitis	0	1
Gram-negative sepsis	0	1
Pneumonia, lung abscess	1	4
Other infections	3	5
Oral or vaginal candida	4	8
Tinea of skin, nails	1	5
Cellulitis, skin abscess	5	7
Herpes zoster	3	4
Mucocutaneous herpes	1	4
Varicella	0	1
URI, bronchitis, pharyngitis	18	18
Urinary tract infection	5	4

Table 3. Adverse Events.*

Upper GI symptoms (nausea, vomiting, bloating, epigastric pain)	23	25
Chronic or recurrent episodes	4	10
Diarrhea	15	2
Persistent	3	0
Rectal bleeding	0	3
Lymphopenia (new onset)‡	18	28
Sustained lymphopenia	5	14
Neutropenia§	1	1
Anemia unrelated to SLE	2	2
Menstrual irregularities	8	11
Change in menstrual cycle	8	13
Amenorrhea	0	2
Alopecia unrelated to SLE	0	8
Severe generalized rash	1	0
Urticaria or angioedema	1	0
Duration of therapy (patient-wk)	1738	1350

REVIEW NATURE CLINICAL PRACTICE NEPHROLOGY MARCH 2009 VOL 5 NO 3

www.nature.com/clinicalpractice/neph

An update on the use of mycophenolate mofetil in lupus nephritis and other primary glomerular diseases

Alice S Appel and Gerald B Appel*

AS Appel is a Research Associate and GB Appel is a Professor of Clinical Medicine at Columbia University Medical Center, New York, NY, USA.

Mycophenolate mofetil (MMF) has been used successfully as an immunosuppressive medication in transplantation for over a decade. Owing to its efficacy and relatively benign adverse effect profile, its use has been investigated in the treatment of several glomerular diseases, as we describe in this Review. Of these, MMF has most extensively been studied in lupus nephritis. Randomized controlled trials have documented the value of MMF in both induction and maintenance therapy for severe lupus nephritis in several different geographic and ethnic populations, and have defined its potential toxicity. In minimal-change disease, focal segmental glomerulosclerosis and membranous nephropathy, promising but limited data on MMF treatment exist from small retrospective and prospective studies. Ongoing, larger, prospective trials, such as the NIH trial in focal segmental glomerulosclerosis, might clarify the value of MMF in the treatment of this disease. The efficacy of MMF in IgA nephropathy remains unclear, despite several small, controlled trials. Conflicting results might reflect differences in the disease process, differences in MMF metabolism, or varying responses to the immunosuppressive agent in different populations. Only through large, collaborative, controlled trials will the true role of MMF be defined for each glomerular disease.

Table 1 Randomized controlled trials of mycophenolate mofetil in lupus nephritis.

Study	Patients	Treatment	Indication	Outcomes	Adverse events
Chan TM *et al.* (2000)[35]	Chinese patients with diffuse proliferative lupus nephritis ($n = 42$)	MMF (2 g daily for 6 months followed by 1 g daily for 6 months) plus steroids, or oral cyclophosphamide (2.5 mg/kg daily) plus steroids for 6 months followed by oral azathioprine (1.5 mg/kg daily) plus steroids for 6 months	Induction and maintenance therapy	No significant differences in the percentage of patients with complete remission, partial remission or relapse at 1 year	Similar incidence of infections at 1 year
Chan TM *et al.* (2005)[37]	As above ($n = 64$)	As above	Induction and maintenance therapy	Similar rates of chronic renal failure, relapse and mortality in the two groups at 5 years	Fewer adverse events with MMF
Hu W *et al.* (2002)[38]	Chinese patients with diffuse proliferative lupus nephritis ($n = 46$)	MMF or induction therapy with intravenous cyclophosphamide for 6 months	Induction therapy	Patients on MMF had less proteinuria and urinary sediment activity and larger decreases in lupus serologic activity	Fewer adverse effects with MMF
Contreras G *et al.* (2004)[39]	US patients; mostly African American and Hispanic people with severe proliferative lupus nephritis ($n = 59$)	(After induction with intravenous cyclophosphamide and steroids) Intravenous cyclophosphamide pulses every third month, or oral azathioprine (1–3 mg/kg daily) or MMF (0.5–3 g daily)	Maintenance therapy	MMF and azathioprine groups had fewer primary end points (deaths or instances of chronic renal failure) and fewer relapses	Adverse events more frequent with cyclophosphamide
Ginzler EM *et al.* (2005)[40]	US patients with severe lupus nephritis ($n = 140$); >50% African American	6 monthly pulses of intravenous cyclophosphamide plus steroids or MMF plus steroids	Induction therapy	MMF group had fewer treatment failures, a greater number of complete remissions and a greater number of complete or partial remissions at 6 months	Adverse effects less serious in the MMF group
Aspreva Lupus Maintenance Study (ALMS)[44,45]	Patients in Asia, US, Canada, Latin America, and Europe with lupus nephritis ($n = 370$)	MMF (titered up to 3 g per day) plus prednisone for 6 months or 6 monthly pulses of 0.5–1.0 g/m^2 intravenous cyclophosphamide with prednisone	Induction therapy	Primary end point (remission of proteinuria and stabilization or improvement of serum creatinine level) occurred in a similar percentage of patients in both arms; MMF had more uniform efficacy than cyclophosphamide among different geographic and ethnic groups	Similar rates of adverse effects and mortality in the groups

- Mycophenolate mofetil (MMF), when used in conjunction with corticosteroids, is effective as induction therapy for severe lupus nephritis; however, its benefits over cyclophosphamide in the treatment of crescentic lupus nephritis and in patients with very low glomerular filtration rates are unclear
- MMF is superior to intravenous cyclophosphamide in maintenance therapy for severe lupus nephritis, but has not yet been shown to be superior to azathioprine for this indication
- MMF has been used successfully to induce remission of the nephrotic syndrome in minimal-change disease and focal segmental glomerulosclerosis, but this finding has not yet been confirmed by any large, controlled trial
- In membranous nephropathy, MMF seems to be as effective as several other immunosuppressive agents in inducing remission of the nephrotic syndrome, but there are concerns about a high rate of relapse on drug discontinuation
- Despite five trials of MMF in IgA nephropathy, whether the addition of MMF is superior to use of supportive therapy alone remains unclear
- Large, multicenter trials, similar to those performed in lupus nephritis, are needed to define the role of MMF in primary glomerular diseases

Mycophenolate mofetil in induction and maintenance therapy of severe lupus nephritis: a meta-analysis of randomized controlled trials

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Study	Number enrolled		Age	Renal pathology type	Renal function	Intervention	Follow-up duration (months)
Ginzler *et al.* [21]	E	71	32.5 ± 10	Class III, IV, V	Ccr > 30 ml/min or Scr < 265 μmol/l	MMF + Pred	36.2 ± 16.9
	C	69	31.0 ± 9.0			IV CYC + Pred	37.2 ± 16.9
Ong *et al.* [22]	E	19	21.8 ± 3.2	Class III, IV, Vb	Scr < 200 μmol/l	MMF + Pred	37.8 ± 7
	C	25	30.5 ± 8.7			IV CYC + Pred	
Chan *et al.* [18]	E	21	36 ± 11	Class IV	Scr < 300 μmol/l	MMF + Pred for 12 mo then AZA	Mean 12
	C	21	39 ± 9			Oral CYC + Pred for 6 mo then AZA	
Chan *et al.* [19]	E	33	38.1 ± 10.2	Class IV	Scr < 400 μmol/l	MMF + Pred for 12 mo then decreased dose of MMF for maintenance	52.2 ± 19.7
	C	31	41.8 ± 8.9			Oral CYC + Pred for 6 mo then AZA for maintenance	63.9 ± 17.6
Contreras *et al.* [20]	E	20	32 ± 11	Class III, IV, Vb	Ccr > 20 ml/min	IV CYC + Pred for less than 7 mo then MMF for maintenance	Median 29
	C	20	33 ± 12			IV CYC + Pred for less than 7 mo then IV CYC for maintenance	Median 25
	C	19	33 ± 10			IV CYC + Pred for less than 7 mo then AZA for maintenance	Median 30

E, experimental group; C, control group; F/M, female to male ratio; Scr, serum creatinine; Ccr, creatinine clearance; Pred, prednisone; MMF, mycophenolate mofetil; CYC, cyclophosphamide; AZA, azathioprine.

In conclusion, MMF with its potency to induce complete remission appears to be superior to pulsed intravenous CYC for induction therapy of severe LN. Induction therapy with MMF is also associated with fewer side effects than induction therapy with CYC. Finally, MMF is an alternative choice for the maintenance therapy of severe LN, with no significant difference in prognosis or the risks of amenorrhoea or herpes zoster from AZA.

Systematic review and meta-analysis of randomised trials and cohort studies of mycophenolate mofetil in lupus nephritis

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Outcomes of randomised trials

Outcome	Number of trials	Number of patients	Percentage with MMF	Percentage with cyclophosphamide	Relative benefit or risk (95% CI)	NNT (95% CI)
Efficacy						
Complete response	4	266	36	23	1.5 (1.1 to 2.1)	7.6 (4.2 to 43)
Complete or partial response	5	306	66	54	1.2 (1.03 to 1.4)	8.0 (4.3 to 60)
Subsequent relapse	2	102	27	34	0.8 (0.4 to 1.4)	
Adverse events						NNTp (95% CI)
Death	5	306	0.7	7.8	0.2 (0.07 to 0.7)	14 (8 to 48)
Hospital admission	2	220	1.7	15	0.1 (0.04 to 0.5)	7.4 (4.8 to 16)
Adverse event discontinuations	3	246	1.6	5.6	0.3 (0.08 to 1.4)	
All infections	4	280	39	73	0.5 (0.4 to 0.7)	3.0 (2.3 to 4.4)
Serious infections	4	304	3.9	15	0.3 (0.1 to 0.6)	8.7 (5.5 to 21)
Leucopaenia	3	122	1.6	25	0.1 (0.03 to 0.5)	4.3 (2.9 to 8.3)
Amenorrhea	5	312	1.9	12	0.2 (0.08 to 0.6)	9.5 (6.2 to 20)
Hair loss	3	240	0.0	16	0.1 (0.01 to 0.4)	6.4 (4.4 to 11)
						NNH (95% CI)
Diarrhoea	4	260	16	4.0	4.0 (1.5 to 10)	8.5 (5.3 to 21)

CI, confidence interval; MMF, mycophenolate mofetil; NNH, number needed to harm; NNT, number needed to treat; NNTp, number needed to treat to prevent one event.

Fetal malformations associated with mycophenolate mofetil for lupus nephritis

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ММФ – тератогенное средство

Here we report a case of a 21-year-old woman who had two flares of class IV lupus nephritis, treated in 2003 and 2005 by 6-month courses of intravenous cyclophosphamide. The lupus was in remission after the last course of cyclophosphamide. She had been on MMF maintenance therapy (1000 mg b.i.d) for 10 months when pregnancy was discovered at 25 weeks gestation. She was also receiving prednisone, hydroxychloroquine and perindopril. The pregnancy was terminated because fetal ultrasonography showed multiple malformations. The feto-pathology examination showed multiple defects affecting the head (bilateral anotia, external auditory duct atresia), lower limb (polydactylia and nail hypoplasia), heart (anterior positioning of the aorta, interventricular communication) and kidneys (asymmetry). Cytogenetic studies revealed a normal karyotype.

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The cost-effectiveness of mycophenolate mofetil as firstline therapy in active lupus nephritis

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Objectives. Systemic lupus erythematosus (SLE) is an autoimmune disorder that can affect any system of the body. Involvement of the kidneys, lupus nephritis (LN), affects up to 50% of SLE patients during the course of their disease, and is characterized by periods of active disease (flares) and remission. For more severe nephritis, an induction course of immunosuppressive therapy is recommended. Options include intravenous cyclophosphamide (IVC) or mycophenolate mofetil (MMF), followed by a maintenance course, typically of azathioprine. The objective of this study is to determine which therapy results in better quality of life (QoL) for patients and which represents best value for money for finite health service resources.

Methods. A patient-level simulation model is developed to estimate the costs and quality-adjusted life-years (QALYs) of a patient treated with IVC or MMF for an induction period of six months. Efficacy, QoL, resource use and cost data are extracted from the literature and standard databases and supplemented with expert opinion where necessary.

Results. On average, the model predicts MMF to result in improved QoL compared with IVC. MMF is also less expensive than IVC, costing £1600 (€2400; US$3100) less over the period, based on 2005 NHS prices. The major determinant and cost driver of this result is the requirement for a day-case procedure to administer IVC. Sensitivity analysis shows an 81% probability that MMF will be cost-effective compared with IVC at a willingness to pay of £30 000 (€44 700; US$58 500) per QALY gained.

Conclusion. MMF is likely to result in better QoL and be less expensive than IVC as induction therapy for LN.

KEY WORDS: Lupus nephritis, Systemic lupus erythematosus, Lupus, Flare, Mycophenolate mofetil, Cyclophosphamide, Economic evaluation, Cost–utility analysis, Resource, Rationing.

TABLE 1. Summary drug therapy and health service activity

Arm	Drugs	Activity
MMF	• 2.7 g MMF daily (range 1–3 g) [3, 7]	• 11 blood tests/24 weeks [8]
IVC	• 1.275 g/28 days IVC (range 0.85–1.7 g) [3, 4] • 20% patients receive goserelin (3.6 mg implant/28 days) • 1.4025 g/28 days mesna • 2 days ondansetron [8]	• 1 × day-case admission for infusion therapy/28 days • 6 blood tests/12 weeks
Common to both arms (therefore, excluded from model)	• 3 × 750 mg intravenous methylprednisolone/28 days • 0.5–1 mg/kg oral prednisolone daily • 20 mg omeprazole daily • Fungal prophylaxis for first six weeks • Bisphosphonates and vitamin D	• 3 × out-patient nephrology visits/12 weeks

MMF strategy. MMF is administered orally, at a mean dose of 2.7 g daily, with doses of between 1 and 3 g reported in trials [3, 7]. It is recommended that patients taking MMF undergo a complete blood count weekly for the first 4 weeks, every 2 weeks for the following 8 weeks and every 4 weeks for the next 52 weeks [8]. This equates to 11 blood tests in the first 6 months.

IVC strategy. There is some variation in dosing regimen for IVC therapy in the UK. For this model, the dosing schedule of IVC was based on Ginzler and Ong [3, 4]: IVC is administered as a monthly bolus of 1.275 g every 28 days (based on an average 0.75 g/m^2 dose; range: 0.5–1 g/m^2, or 0.85–1.7 g per patient per month). Patients usually receive an anti-emetic (typically a 5-HT$_3$ antagonist, such as ondansetron) for 2 days following cyclophosphamide administration. A recommended regimen for 'moderately emetogenic chemotherapy' is 8 mg orally 1–2 h before treatment, then 8 mg every 12 h for up to 5 days [8].

Female patients receiving cyclophosphamide may receive ovarian protection treatment during their therapy. Goserelin is administered as a 3.6 mg implant every 28 days. We assumed that 20% of patients received this.

All patients received mesna to prevent haemorrhagic cystitis. There are a number of infusion regimens. For example, an intravenous bolus approach recommends 20% of cyclophosphamide dosed at 0, 4 and 8 h, or 40% at 0, 1, 4 and 7 h [9]. The total dose is thus between 60% and 160% of the cyclophosphamide dose (0.765–2.04 g).

IVC is administered in an out-patient setting, requiring a day-case appointment for observation and hydration of the patient, in addition to the regular monthly out-patient day-case visit. Patients also received a blood test every two weeks while undergoing therapy with IVC.

TABLE 6. Summary of mean cost inputs

Treatments	Per	Drug(s)	Secondary care activity	Other monitoring	Total
MMF[a]	12 weeks	£792.26	0	£50.99	£843.25
IVC[b]	12 weeks	£174.92	£1524.00	£55.62	£1754.54
Infections	**Per**	**Antibiotics**	**Admission**	**Primary care**	**Total**
Minor infection[c]	Event	£8.08	0	£30.00	£38.08
Major infection[d]	Event	0	£1313.49	0	£1313.49
Other	**Per**	**Drug(s)**	**Out-patient appointment**	**Other monitoring**	**Total**
No immunosuppressive therapy (steroid only)[e]	12 weeks	£90.83	0	0	£90.83
Adverse event leading to discontinuation[f]	Event	0	£123.00	0	£123.00

[a]MMF costs £87.33 for 50 × 500 mg tablets [8]. 12 weeks' treatment @ 2.7 g/day = £792.26. A 10 min consultation with a ward staff nurse costs approximately £6.34 [16] and a blood test £2.93 [17]. Mean 5.5 appointments per 12 weeks = £50.99.

[b]IVC plus sterile reconstitution is approximately £37.50 per 2 g of cyclophosphamide (Baxter Bioscience, Newbury Commercial Communication, 2006). Thus, 12 weeks' treatment @ 1.275 g every 28 days = £71.72. Two days' ondansetron treatment (five doses) @ £71.94 per ten 8 mg doses = £35.97. Goserelin for 20% of patients @ £84.14 per 3.6 mg implant per 28 days [8] over 12 weeks = £50.48 per patient. Mesna @ £3.98 per 10 ml ampoule [8] @ 1.4025 g per 28 days = £16.75 per 12 weeks. The total cost of drugs over 12 weeks is thus £174.92. Day-case appointment for observation and hydration of the patient @ £508 [17] = £1524 per 12 weeks. Fortnightly blood test @ £6.34 for nurse consultation [16] and £2.93 for test [17] = £55.62 per 12 weeks.

[c]The most common infection is herpes zoster. We assumed a patient developing a minor infection visited his or her GP (£30) [16], and was prescribed a course of aciclovir (400 mg × 5 for 5 days = £8.08) [8].

[d]We defined major infection as one severe enough for the patient to be hospitalized as an emergency admission (weighted mean cost = £1313) [17]. See Appendix 1 for details.

[e]For patients unable to tolerate immunosuppressive therapy, intravenous methylprednisolone is administered as a monthly bolus of 1 g/m^2 [11]. Thus, mean dose was 1.75 g (range 1.6–1.9 g) @ £17.30 per 1 g vial [8] = £90.83 per 12 weeks. Intravenous methylprednisolone is administered at the regular monthly out-patient appointments that a patient attends.

[f]We assumed a patient with an adverse event resulting in discontinuation of or change in therapy would visit his or her consultant on an out-patient basis. A follow-up nephrology out-patient appointment costs £123 [17].

Induction therapy with MMF for patients with LN is likely to result in better QoL and be less expensive than IVC. The major factors determining this result are the requirement for a day-case procedure to administer IVC and ensure adequate hydration of the patient as well as the increased incidence of AEs, particularly major infection, in patients receiving IVC.

The evidence base informing us about the longer-term consequences and costs of MMF as a maintenance therapy is currently limited. Further research is under way to evaluate this compared with alternative strategies in maintenance of disease remission for LN patients.

Rheumatology key messages

- IVC and MMF are alternative induction therapies for LN flares.
- Our economic model suggests that induction therapy with MMF results in better QoL and is less costly than IVC.
- Further research is required to establish the outcomes and costs of maintenance therapy.

ВЫВОДЫ

- **ММФ – иммуносупрессор, эффективный как в индукционной, так и поддерживающей терапии волчаночного нефрита**
- **Спектр и частота побочных эффектов у циклофосфамида выше, чем у ММФ**
- **Основное показание для применения ММФ у больных с волчаночным нефритом – неэффективность или непереносимость других иммуносупрессоров**