Critical review on the use of Mycophenolate Mofetil in Induction and Maintenance Therapy for Lupus Nephritis

- Epidemiology of lupus nephritis
- Mycophenolate mofetil for lupus nephritis

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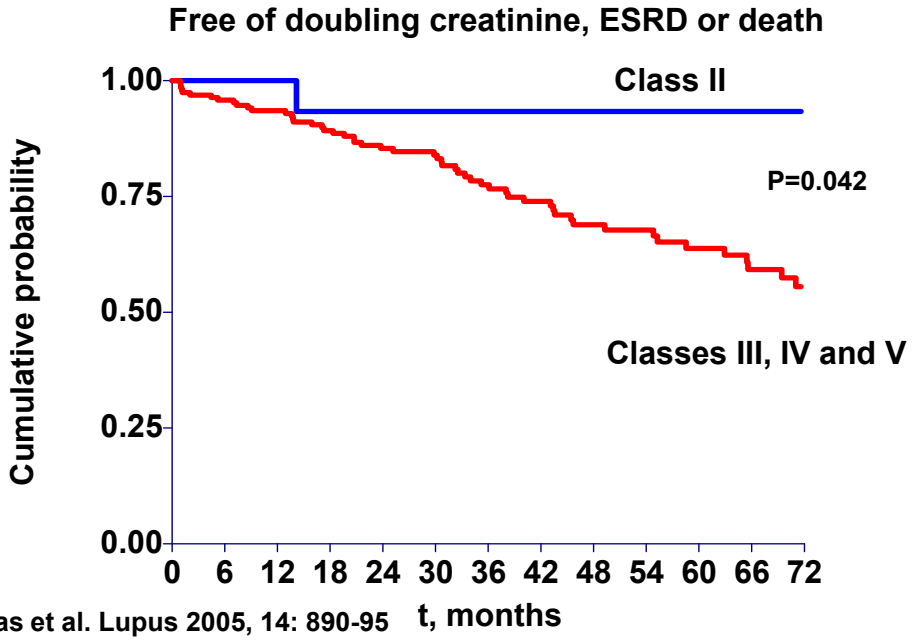
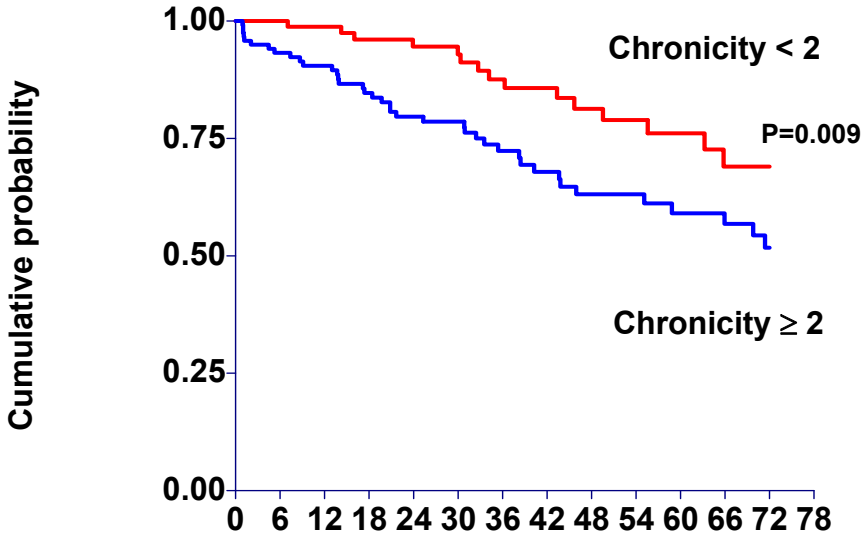
Survival of 213 lupus nephritis patients as a function of WHO classification



Contreras et al. Lupus 2005, 14: 890-95

Survival of 213 Lupus Nephritis Patients as a Function of chronicity index
Free of doubling creatinine, ESRD or deatl

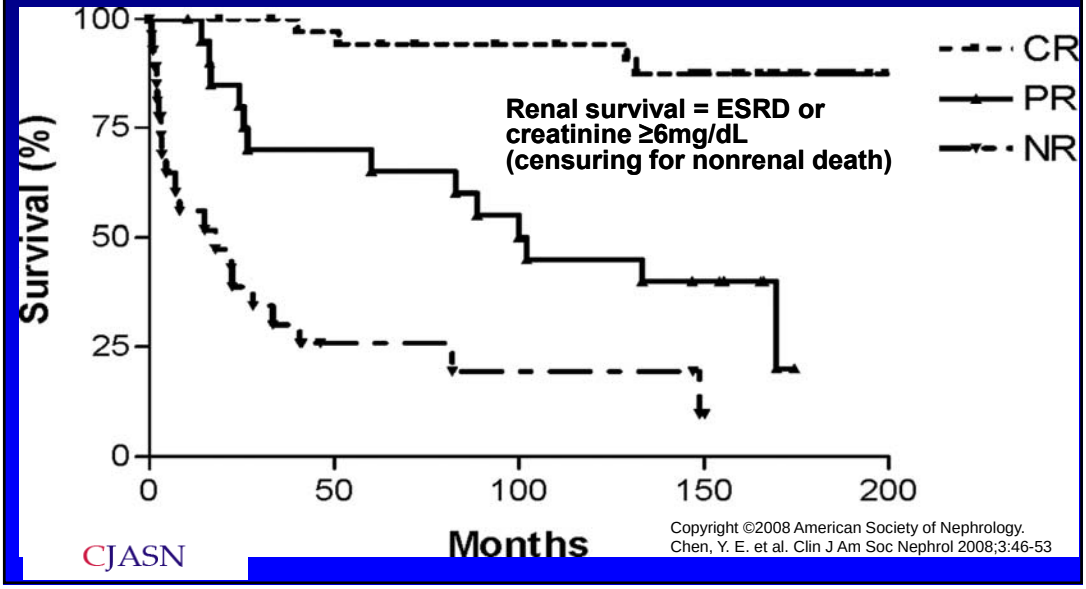


Contreras et al. Lupus 2005, 14: 890-95

Other Factors (than histological parameters) Associated with Increased Risk of Chronic Renal Failure

- African-American
- Hispanic
- Male gender
- Age < 24 years
- Hypertension
- High creatinine
- Nephrotic range proteinuria
- Anemia
- Anticardiolipins
- Lack of remission
- Relapse

Value of a Complete (serum creatinine ≤ 1.4 mg/dL and proteinuria ≤ 0.33 g/day) or Partial (serum creatinine ≤ 25%, 50% ↓ proteinuria and ≤ 1.5 but > 0.33 g/day) Remission in Severe Lupus Nephritis

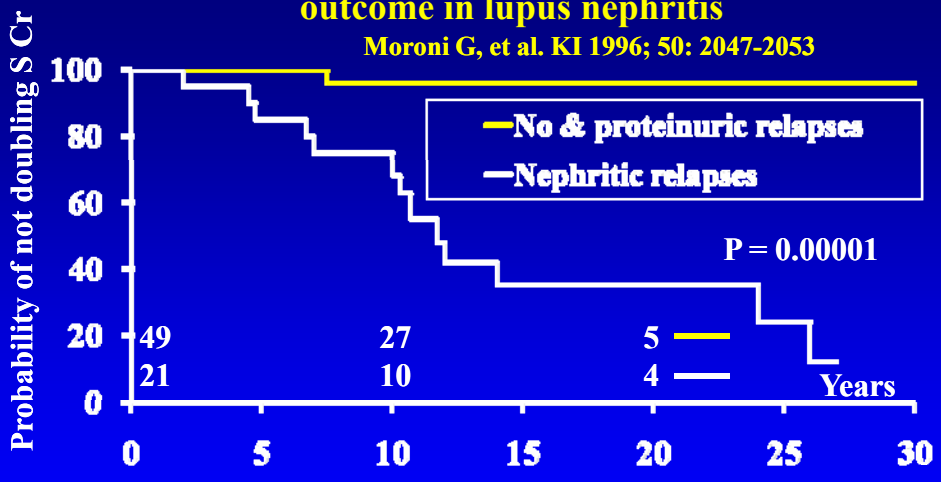


CJASN

Chen, Y. E. et al. Clin J Am Soc Nephrol 2008;3:46-53

"Nephritic relapses" are predictors of bad long-term outcome in lupus nephritis

Moroni G, et al. KI 1996; 50: 2047-2053

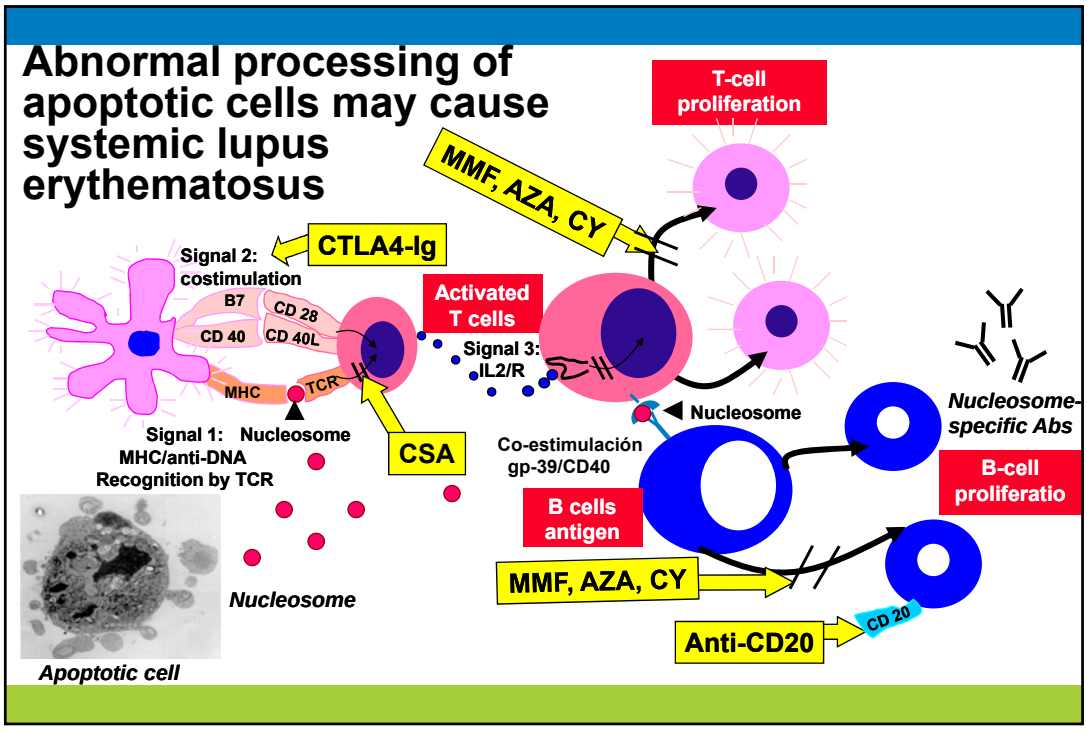


Nephritic relapse: ↑ SCr of ≥ 30 %, active sediment and ↑ proteinuria. By multivariate analysis, male gender (p= 0.015) & HTN (p= 0.004) were independent predictors of nephritic relapses

Rationale to Use Mycophenolate Mofetil (MMF) in SLE

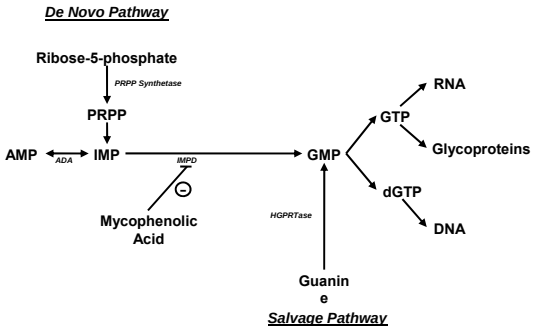
- MMF inhibits inosine 5'-monophosphate dehydrogenase in the de novo pathway of purine synthesis).
- MMF has a selective antiproliferative effect on lymphocytes:
  - Blocks B and T cell proliferation
  - Inhibits autoantibodies formation by B-cells
  - Decreases expression of adhesion molecules and other cytokines
- MMF lowers glomerular complement component C3
- MMF is effective in animal models.
- Potential for reducion of side effects from long-term exposure to cyclophosphamide
- Demonstrated efficacy and safety of Mycophenolate mofetil (MMF) in renal transplantation

Transplantation 1995. European study, Lancet 1995. Tricontinental study, Transplantation 1996. Allison AC, Eugui EM, Mirkovich A, Scand J Immunol 1991. Allison et al. Transplant Proc 1994. Luca et al. Exp Nephrol 2000 Corna et al, KI 1997.

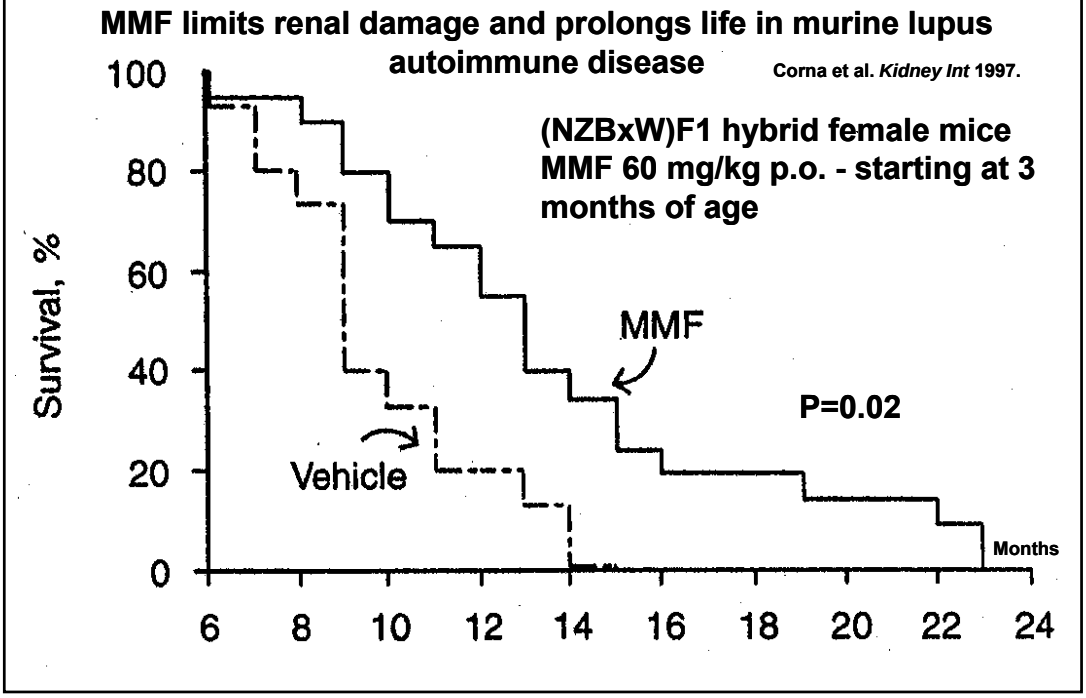


Giblett ER, Anderson JE, Cohen F et al. Adenosine-deaminase deficiency in two patients with severely impaired cellular immunity. Lancet 1972; 2:1067-9

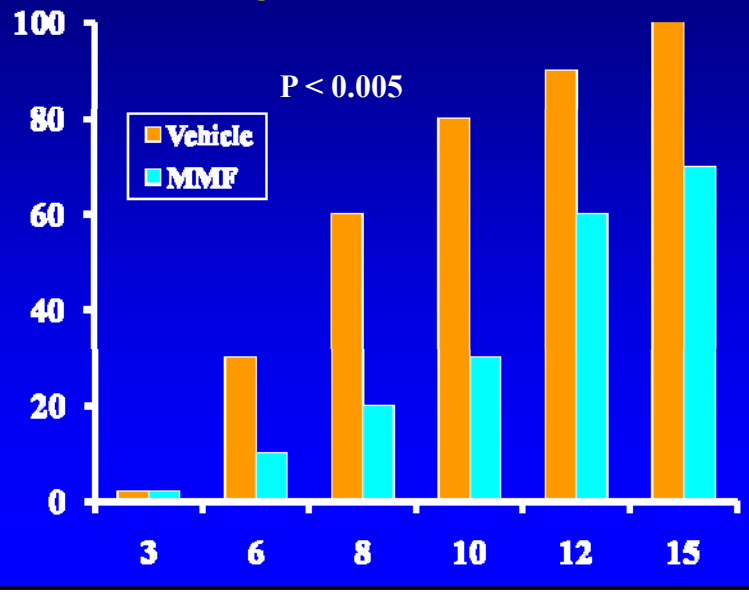
Allison AC, Hovi T, Watts RW et al. Immunological observations on patients with Lesch-Nyhan syndrome, and on the role of de-novo purine synthesis in lymphocyte transformation. Lancet 1975; 2:1179-83



The development of MMF, which is an ester prodrug of mycophenolic acid (MPA) with superior bioavailablility, was based on the observation that patients with adenosine deaminase deficiency have a combined B and T-cell immunodeficiency, while patients with hypoxanthine-guanine-phosphoribosyl transferase deficiency develop neurological abnormalities and gout yet have essentially normal immune functions. Thus, inhibition of the *de novo* purine synthesis appeared to be an attractive option to modulate immune responses while limiting adverse effects of non-selective inhibitors of purine synthesis, such as azathioprine.



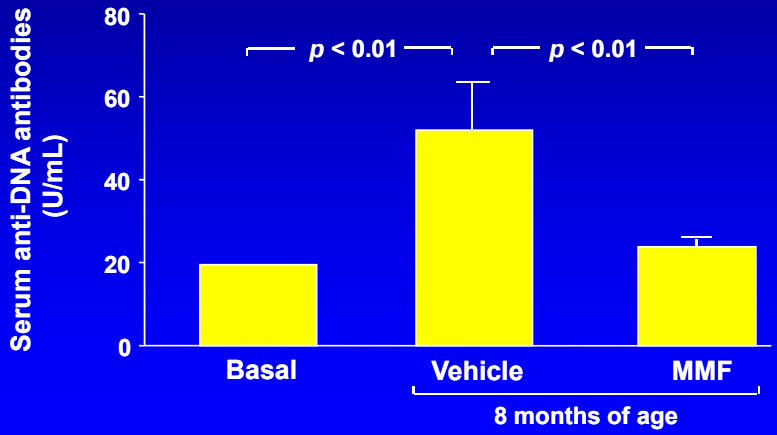
Cumulative Proteinuria > 3 mg/day in NZBxW given vehicle or MMF



Corna et al. Kidney Int 1997.

MMF treatment decreases the production of anti-DNA antibodies in murine lupus autoimmune disease

- (NZBxW)F1 hybrid female mice
- MMF 60 mg/kg p.o. - starting at 3 months of age



Corna et al. *Kidney Int* 1997.

Immunosuppressive Regimens studied in the last decade

Induction	Maintenance
• Mycophenolate Mofetil (MMF)	• Mycophenolate Mofetil (MMF)
• Cyclophosphamide (CY)	• Cyclophosphamide
• Azathioprine (AZA)	• Azathioprine
• Tacrolimus (FK-506)	• Cyclosporine (CsA)
• Anti-CD20	• LJP 394
• Abatacept (CTLA-4-Ig)	

Chan TM, et al, Nephron 1995. Chan TM et al. New Engl J Med 2000; 343:1156-62. Chan TM, et al, JASN 2005; A1010. Houssiau F, et al, Arthritis Rheum 2002;8:2121-31. Contreras G, et al. NEJM. March 2004.

The Role of MMF Induction in Clinical Trials

1. Chan TM et al. New Engl J Med 2000; 343: 1156-62. (Chan TM, et al, JASN April 2005).
2. Weixin Hu, et al. Chin Med J 2002; 115: 705-9.
3. Lin YK, et al: J Clin Derm31: 636 –638, 2002.
4. Flores-Suarez LF, Villa AR. JASN 15: PO257, 2004.
5. Ong LM, et al. Nephrol 10: 504 –510, 2005.
6. Ginzler EM, et al. NEJM 24, Nov 2005.
7. Aspreva lupus management study (ALMS). In press

Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis

Study design: randomized clinical trial

Methods: 42 Asian patients with WHO class IV were randomized to:

1) oral MMF + steroids x 12 months, or

2) sequential oral cytoxan (POCY) + steroid x 6 months then CY was replaced by azathioprine x 6 months

Remission Outcomes:

Complete: Protein<0.3g/d with normal UA, albumin and Cr±15% of baseline

Partial: UP 0.3-2.9 g/d with albumin <3g/dl and stable Cr

Patient characteristics

Histological: Activity Index: 9/24 Chronicity Index: 3.2/12

Mean age 37.5

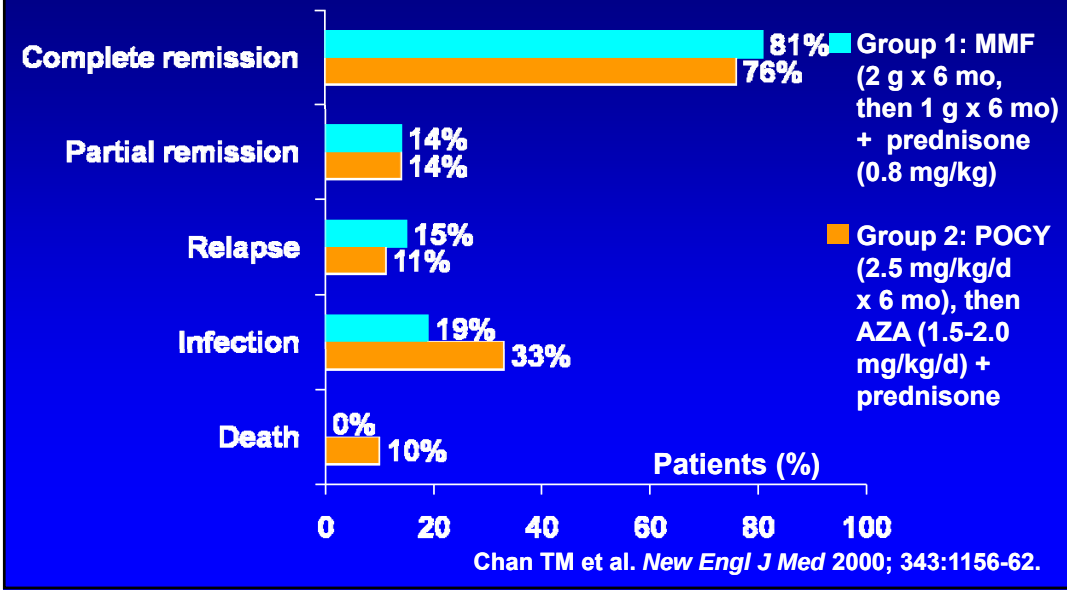
93% female,

24-hs urine protein 5.8 to 3.7 g/day

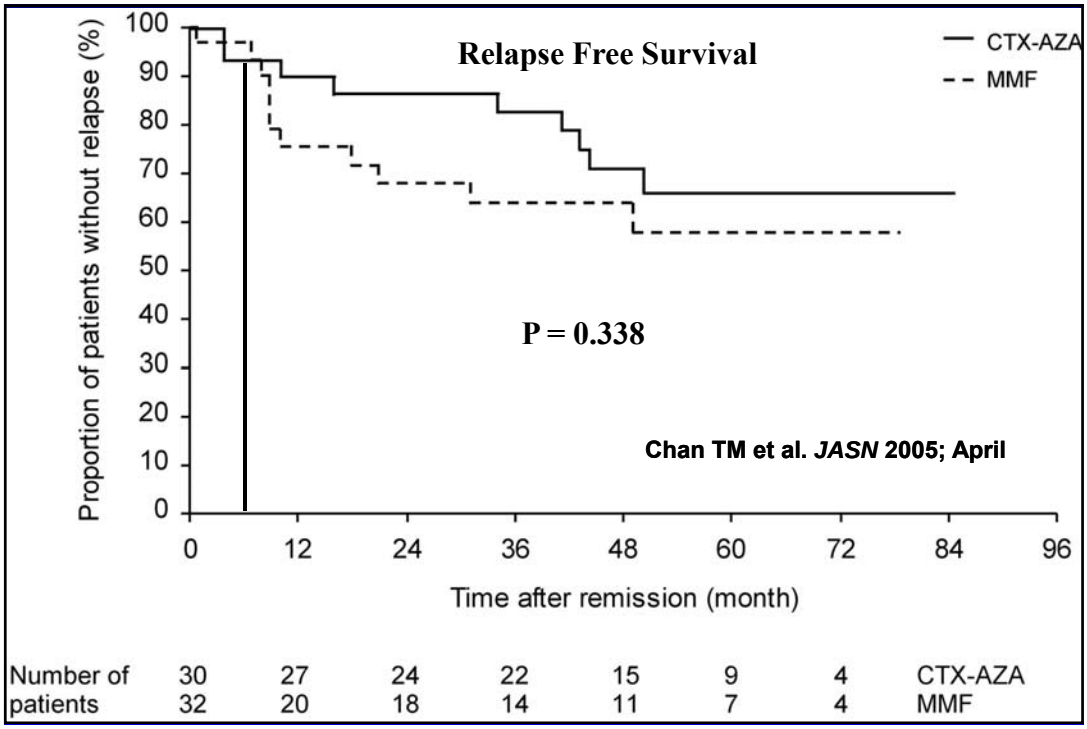
Cr: 1.2 mg/dL

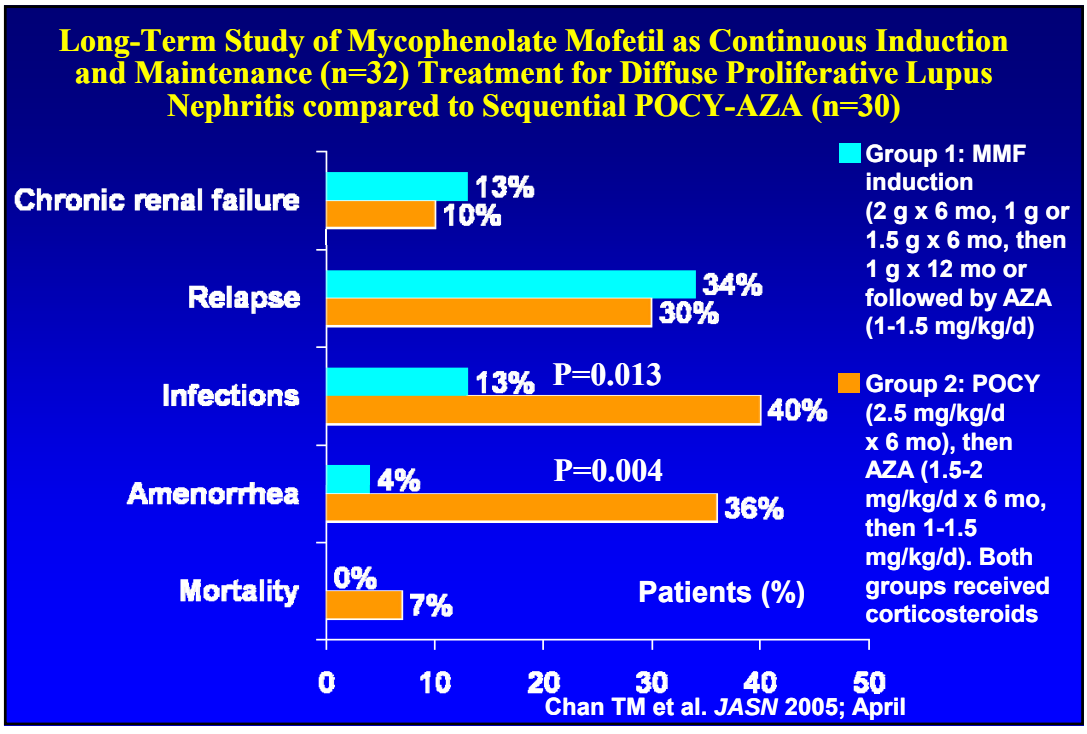
Duration: 12 months **NEJM 2000;343:1156-62**

Efficacy of MMF vs sequential POCY-AZA in 42 patients with diffuse proliferative lupus nephritis

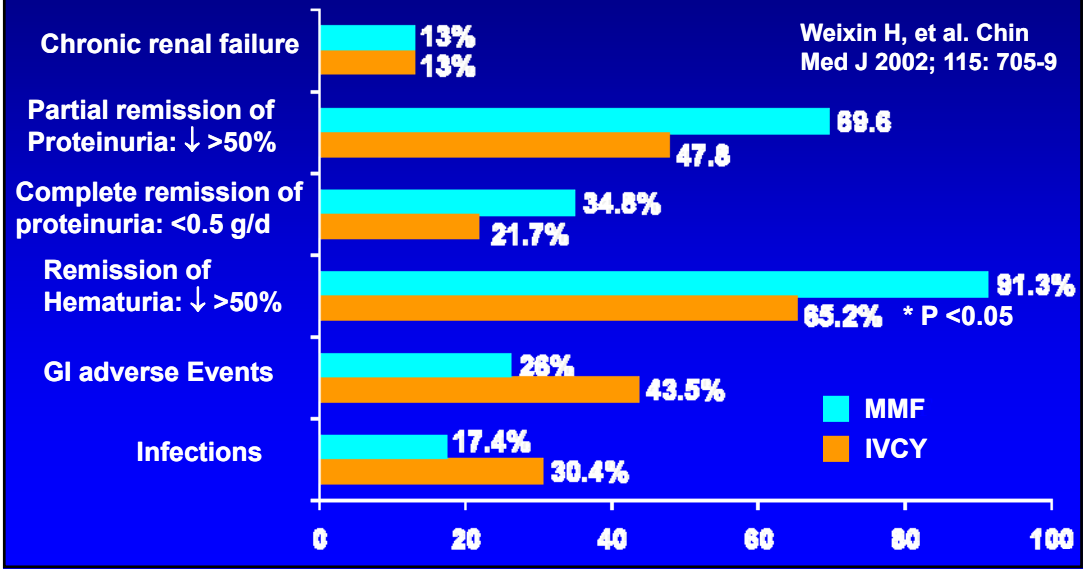


Chan TM et al. *New Engl J Med* 2000; 343:1156-62.

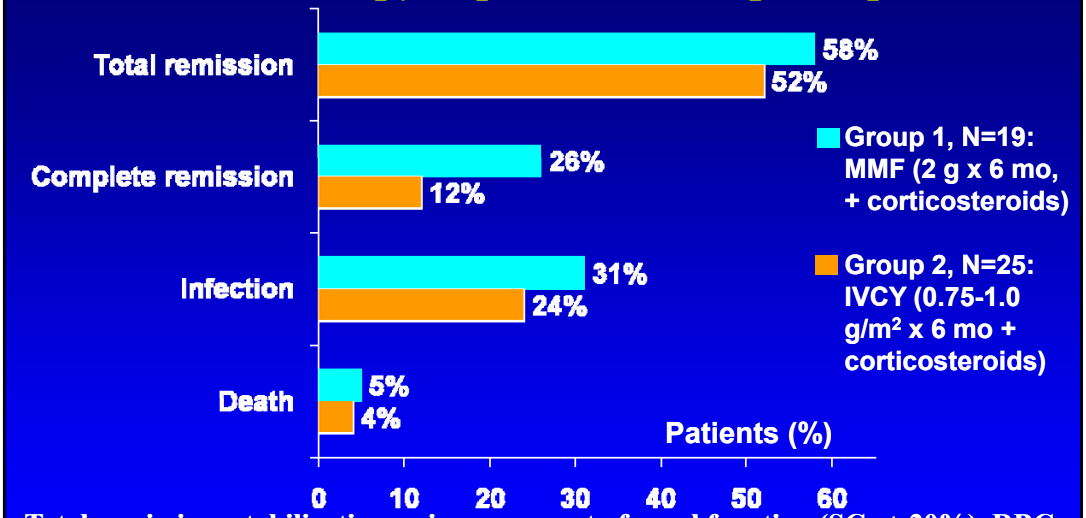

Relapse Free Survival
CTX-AZA
MMF
Proportion of patients without relapse (%)
100
90
80
70
60
50
40
30
20
10
0
P = 0.338
Chan TM et al. JASN 2005; April
0
12
24
36
48
60
72
84
96
Time after remission (month)
Number of patients
30 27 24 22 15 9 4 CTX-AZA
32 20 18 14 11 7 4 MMF


Long-Term Study of Mycophenolate Mofetil as Continuous Induction and Maintenance (n=32) Treatment for Diffuse Proliferative Lupus Nephritis compared to Sequential POCY-AZA (n=30)
Chronic renal failure
13%
10%
Relapse
34%
30%
Infections
13%
P=0.013
40%
Amenorrhea
4%
P=0.004
36%
Mortality
0%
7%
Patients (%)
0
10
20
30
40
50
Group 1: MMF induction (2 g x 6 mo, 1 g or 1.5 g x 6 mo, then 1 g x 12 mo or followed by AZA (1-1.5 mg/kg/d)
Group 2: POCY (2.5 mg/kg/d x 6 mo), then AZA (1.5-2 mg/kg/d x 6 mo, then 1-1.5 mg/kg/d). Both groups received corticosteroids
Chan TM et al. JASN 2005; April

Induction with Mycophenolate mofetil (1.0 to 1.5 g/d) in patients with relapse o resistance to IVCY vs. IVCY induction (0.75 g/m^2) in proliferative lupus nephritis



Randomized controlled trial of pulse IVCY vs. MMF in induction therapy of proliferative lupus nephritis



Total remission: stabilization or improvement of renal function (SCr ± 20%), RBC < 10 x HPF, and reduction of proteinuria < 3 g/day if baseline > 3 and at least 50 % or < 1 if baseline < 3 g/day. Complete remission was defined similarly except for reduction of proteinuria < 0.3 g/day. Ong LM, et al. Nephrology 2005.

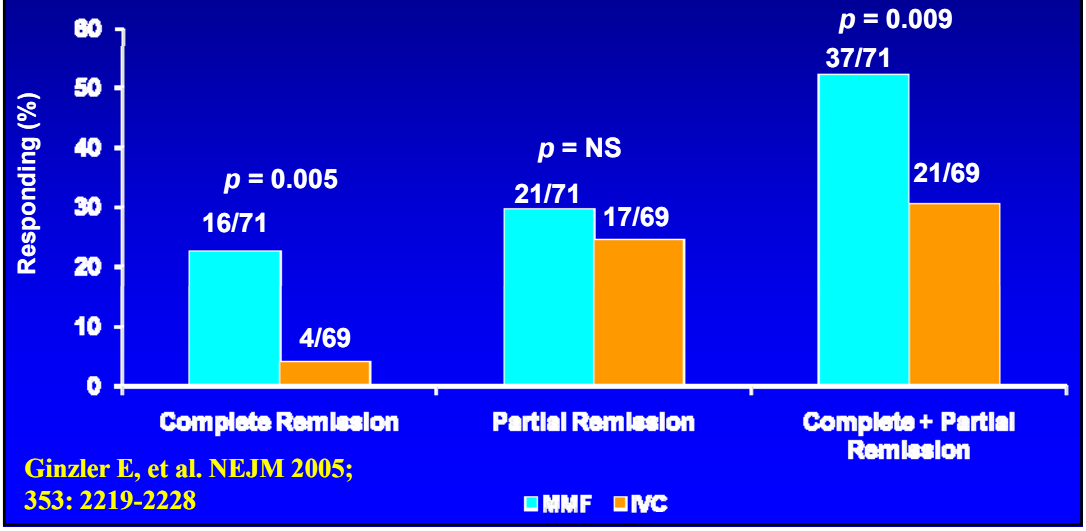
Six months induction: MMF (n=71, 1 g TID) vs. intravenous cyclophosphamide (IVCY) (n=69, 0.75 g/m^2) in severe lupus nephritis, FDA sponsored trial:

- Demographics: Mean age 32,
- 79 (56 %) African Americans
- 90 % female
- Patient WHO histological characteristics
  - Class IV, n = 76
  - Class III, n = 22
  - Class V, n = 27
  - Class V + III or IV, n = 15
- Mean 24-hs urine protein 4.1 – 4.4 g per day
- Mean serum creatinine: 1.1 mg/dL

Ginzler E, et al. NEJM 2005; 353: 2219-2228

Complete remission: at 24 weeks, return of serum creatinine, proteinuria, and urine sediment to normal

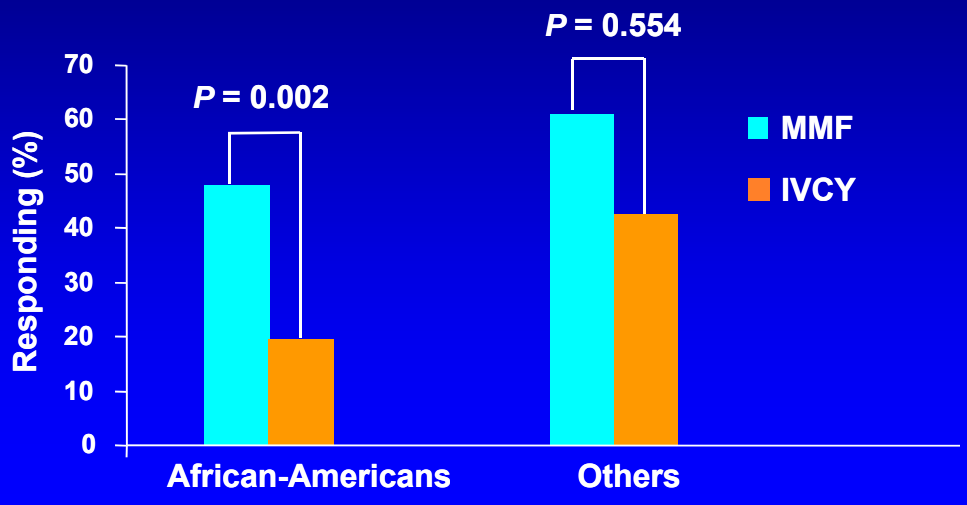
Partial remission: ≥50% improvement in all abnormal renal parameters without worsening of any



Ginzler E, et al. NEJM 2005; 353: 2219-2228

MMF vs IVCY Complete + Partial Remission: African-Americans vs. Others

Intent-to-Treat analysis



Six months induction: MMF vs. intravenous cyclophosphamide (IVCY) in severe lupus nephritis, FDA sponsored trial:

Adverse events	MMF (n = 83)	IVCY (n = 75)
Severe infections	1	6
Necrotizing fascitis	0	1
Gram-negative sepsis	0	1
Pneumonia, lung abscess	1	4
Lymphopenia (< 800/mL^3)	18	28
Neutropenia (< 1000/mL^3)	1	1
UGI (nausea, vomiting, etc)	23	25
Diarrhea	15	2
Amenorrhea	0	2
Severe rash	1	0
Alopecia	0	8
Deaths during treatment	0	3 *

* 1 patient died after declining therapy.

Ginzler E, et al. NEJM 2005; 353: 2219-2228

Aspreva Lupus Management Study (ALMS): Induction-Phase Results

Mycophenolate Mofetil (n = 185) Compared with Intravenous Cyclophosphamide (n =185) as Induction Therapy for Lupus Nephritis

- Patient histological characteristics (N = 370)
  - ISP Class IV = 225
  - Class V = 60
  - Class III = 35
  - Class V + IV =27
  - Class V + III = 23
  - Active = 258
  - Active and Chronic = 122
- Demographics: Mean age 30
- Race: 147 White, 123 Asian, 46 Black and 54 Others
- Ethnicity: 239 Non Hispanics, 131 Hispanics
- Female = 313
- 24-hs urine protein 4.1 g
- Cr: 1.1 mg/dL

JASN 2009; 20: 1103-1112

Treatment Compliance

Oral corticosteroids twice daily

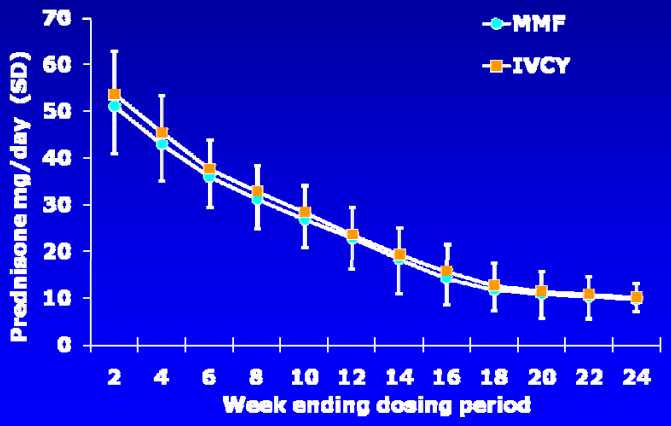
Oral MMF twice daily

Mean (SD):
2.5 (0.58) (g/day)

IVCY in monthly pulses

Mean dose per infusion:
0.78 g/m^2

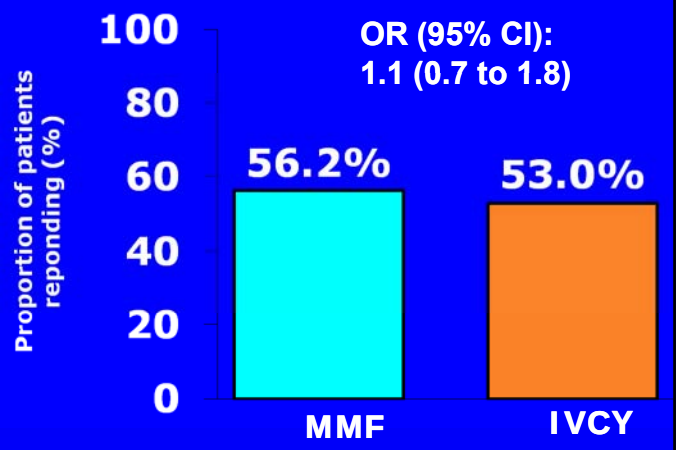
Mean (SD) number infusions: 5.6 (1.1)



JASN 2009; 20: 1103-1112

Primary Endpoint: Responders at 6 Months

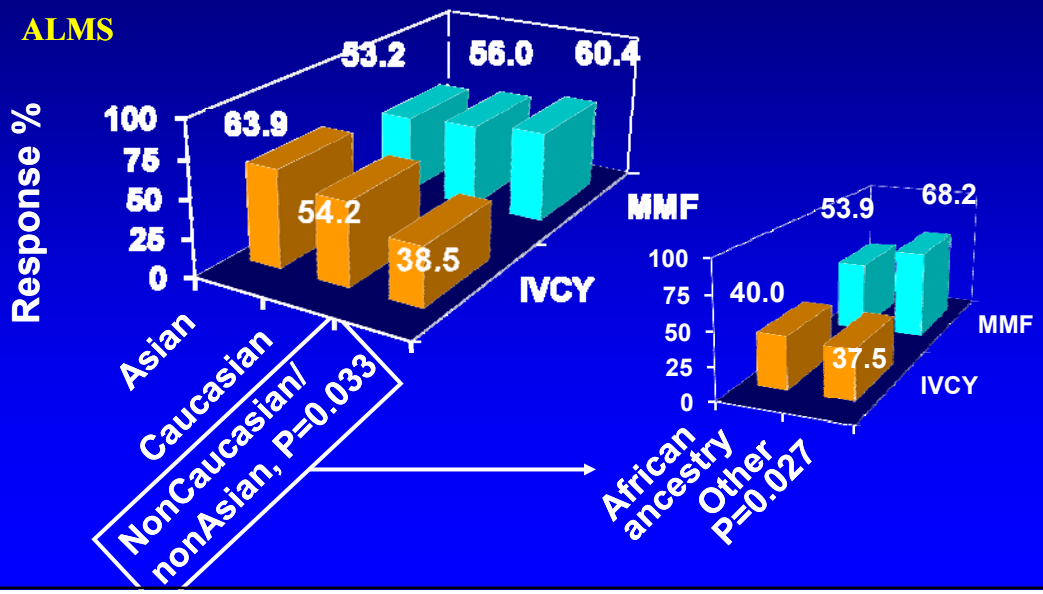
Response was judged by a blinded Clinical Endpoint Committee, by the criteria:
Decrease in Uprot/Ucreat to <3 in patients with baseline nephrotic (≥3) , or by ≥50% in patients subnephrotic (<3) proteinuria and stabilization of serum creatinine level (24-week level ± 25% of baseline) or improvement



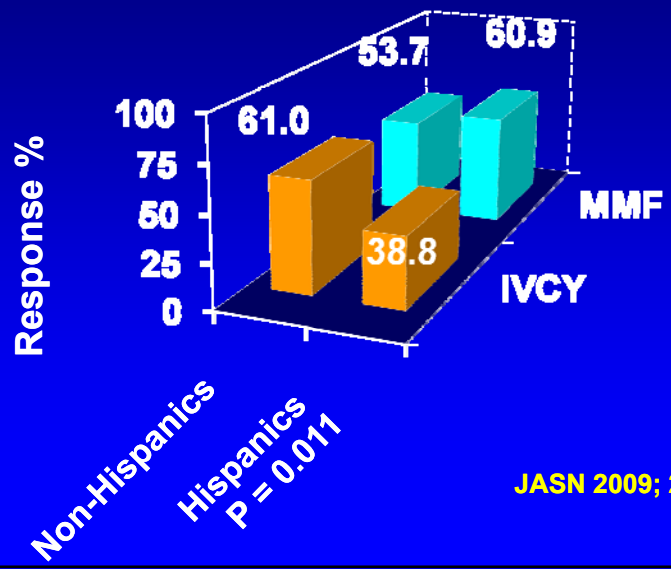
MMF was not superior to IVCP
(p = 0.575)

JASN 2009; 20: 1103-1112

Response to induction of patients with lupus nephritis: Mycophenolate mofetil (MMF) versus cyclophosphamide (IVCY) according to race (P= 0.047 for interaction)

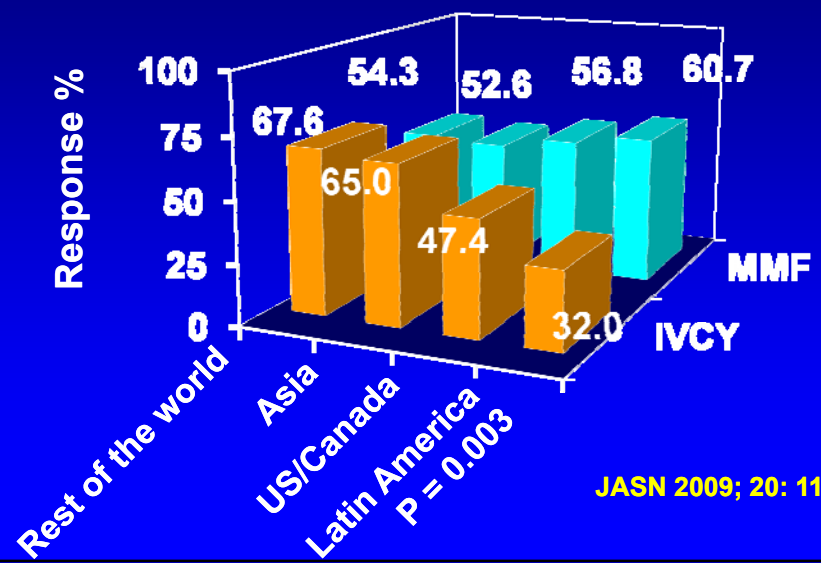


Response to induction of patients with lupus nephritis: Mycophenolate mofetil (MMF) versus cyclophosphamide (IVCY) according to Hispanic Ethnicity



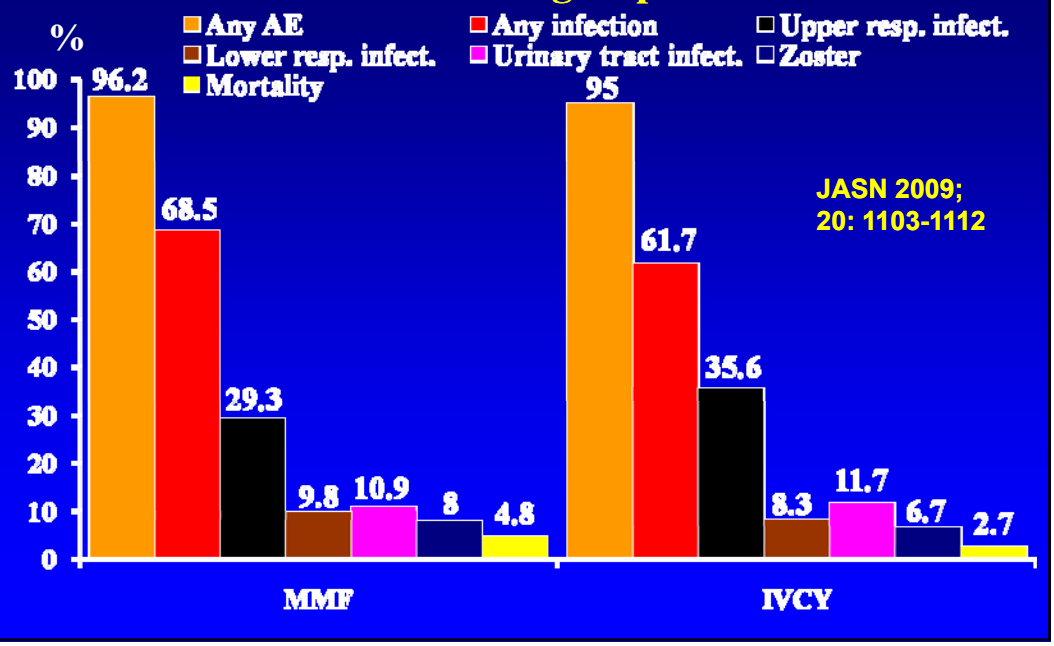
JASN 2009; 20: 1103-1112

Response to induction of patients with lupus nephritis: Mycophenolate mofetil (MMF) versus cyclophosphamide (IVCY) according to Geographic area (P=0.069 for interaction)



JASN 2009; 20: 1103-1112

Percentage of patients reporting adverse events by treatment group



JASN 2009;
20: 1103-1112

The role of MMF Maintenance in Clinical Trials:

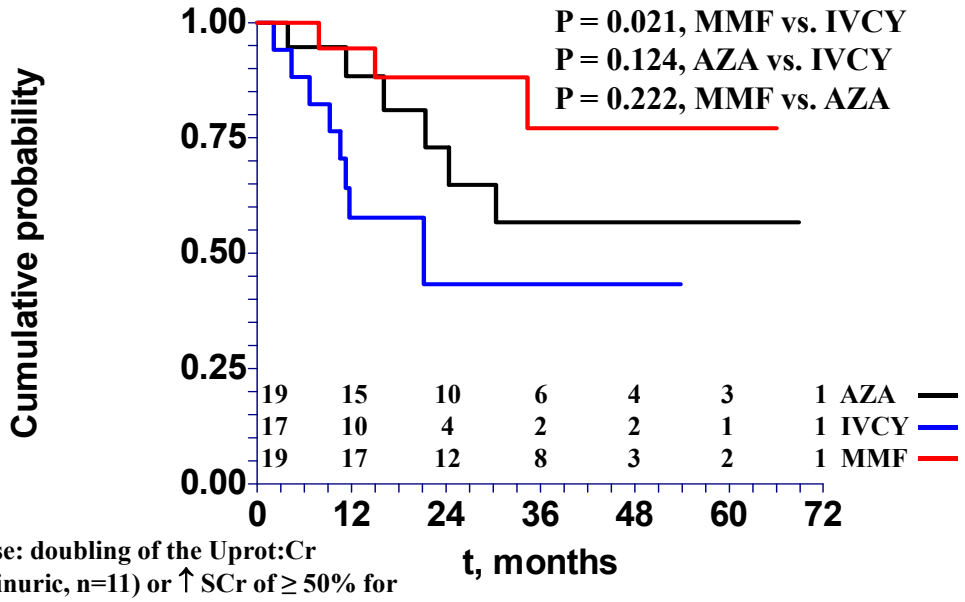
1. Contreras G, et al. NEJM March 2004.
2. MAINTAIN from Euro-Lupus group
3. ALMS (Aspreva Lupus Management Study)

Maintenance Therapy for severe LN: quarterly IVCY vs. AZA vs. MMF after short-term IVCY induction in sequential regimens

- Patient histological characteristics (N = 59)
  - WHO Class III n = 12 — Activity Index: 8/24
  - WHO Class IV n = 46 — Chronicity Index: 1.9-3.6/12
  - WHO Class Vb n = 1
- Demographics: Mean age 33, 46% African-American, 49% Hispanics, 5% Caucasians, 93% female,
- 95% hypertensive
- 64% nephrotic, urine protein/Cr: > 5.0, Alb: 2.7
- Cr: 1.6 mg/dL,

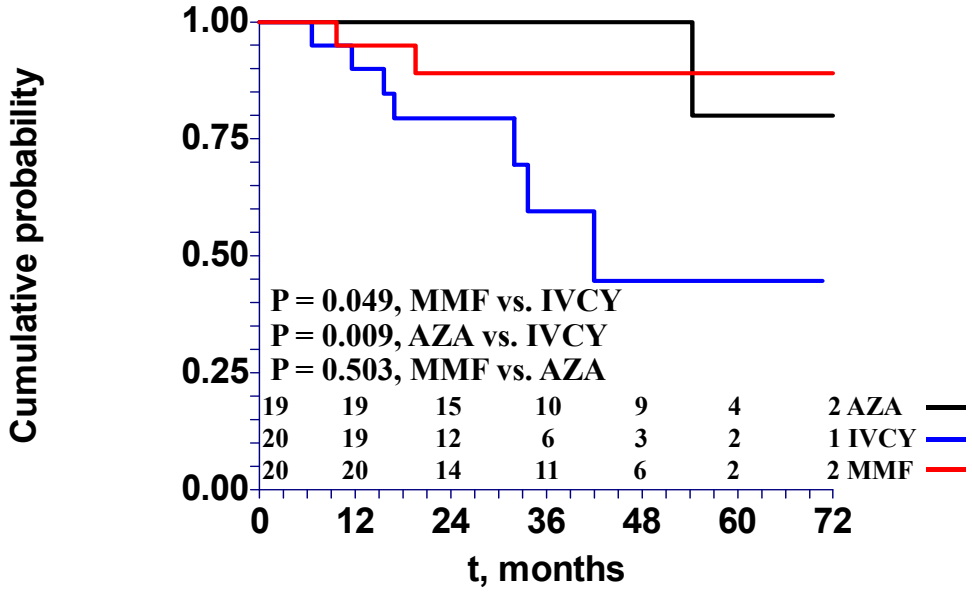
Contreras G, et al. NEJM. March 2004

Results: Free of relapse



Relapse: doubling of the Uprot:Cr (proteinuric, n=11) or ↑ SCr of ≥ 50% for > 1 month (nephritic, n = 6)

Results (IV): Free of clinical event (death or CRF)



Maintenance therapies: IVCY vs AZA vs MMF

Hospitalizations and Side Effects of Therapy

	Hospital days per pt-yr *	Amenorrhea * %	Infections 100 pt-ys Total θ	Major Ω
IVCY	10	32	77	25
AZA	1	8	29	2
MMF	1	6	32	2

AZA or MMF vs. IVCY: * $p \leq 0.03$; θ $p < 0.01$; Ω $p \leq 0.02$.
Major infections: pneumonia, sepsis, meningitis.

Contreras G, et al. NEJM. March 2004

Doses of immunosuppressant received during maintenance therapy

Visit range	AZA mg/kg/d	IVCY mg/m^2	MMF mg/d, median (95%CI)
0-6	1.2 ± 0.4	542 ± 70	1500 (1500-2000)
6-12	1.0 ± 0.5	565 ± 62	1500 (1500-2000)
12-18	1.1 ± 0.6	562 ± 106	1250 (1000-1500)
18-24	0.8 ± 0.6	530 ± 119	1000 (500-1500)
24-30	1.1 ± 0.5	644 ± 4	1000 (500-1250)
30-36	1.1 ± 0.6	541 ± 36	500 (250-500)

MMF dose = median and 95% CI. Data reported as mean ± SD.

Questions:

Induction:

What do we start with: CY or MMF?

Should we switch MMF to maintenance therapy when achieving complete remission, partial remission, at 6 months or longer?

Are there adjuvant therapies that consolidate complete remission?

Questions:

Maintenance:

Is Mycophenolate Mofetil superior to Azathioprine or Calcineurin Inhibitors as maintenance therapy?

Is MMF efficacious as prolong induction-maintenance therapy in Caucasian, Asian, African-American and Hispanic populations?

Should we continue exposing patients to long-term Cyclophosphamide?

Can be stop maintenance therapy after 3 years?