Medical Management of Lupus Nephritis, Current Therapies and Future Directions

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Estimated 5-year patient survival for renal manifestations of SLE (1971)

Survival at 5 years (%)

Total series

All renal disease

Lupus Nephritis Classification ISN RPS 2004

Class I: Minimal mesangial: normal LM, deposits IF o EM

Class II: Mesangial proliferativa with mesangial deposits with/without minimal deposits subepithelial or subendothelial by IF o ME no visible by LM

Class III: Focal (<50 % glomeruli) proliferativa: A, A/C, C

Class IV: Diffuse proliferativa (proliferation intra y/o extracapilar with subendothelial deposits)

Subdivision: Segmental (IV-S) y global (IV-G)

A, A/C, C

Class V: Membranosa: with/without classes III o IV

Class VI: Advanced sclerotic: > 90% glomeruli globally sclerotics
Survival of 213 lupus nephritis patients as a function of WHO classification

Free of doubling creatinine, ESRD or death

Contreras et al. Lupus 2005, 14: 890-95
### Lupus Nephritis Indices of Activity and Chronicity

#### Activity *

- **Glomeruli**
  - Hypercellularity
  - Karyorrhexis or fibrinoid necrosis **
  - Cellular crescents **
  - Hyaline thrombi, wire loops
  - Leukocyte infiltration

- **Tubule/Interstitium**
  - Mononuclear cell infiltration

#### Chronicity *

- **Glomerulosclerosis**
  - Segmental
  - Mesangial
  - Global
  - Fibrous crescent
  - Interstitial fibrosis
  - Tubule atrophy

#### Vascular

- Noninflammatory necrotizing arteritis,
- True vasculitis
- Immune complex deposit
- Thrombotic Microangiopathy

*Score 0-3 for each item. **Multiply by 2 Activity Index

Cumulative survival curves based on 166 lupus-nephritis patients demonstrating the probability of not reaching the renal insufficiency outcome.

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

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{Cumulative probability of survival for Lupus Nephritis patients grouped by chronicity index.}
\end{figure}

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
Outcomes in African Americans and Hispanics with lupus nephritis

Survival: Free of doubling creatinine, ESRD or death

Cumulative probability

Caucasians  P=0.04 vs. African-Americans
Hispanic  P=0.05 vs. African-Americans
African-Americans

Contreras et al. Kidney Inter 69: 1846-1851
Remission Predicts Long-term Outcome in Severe Lupus Nephritis

- 86 patients in trial of high dose prednisone and oral CTX +/- plasmapheresis
- Clinical remission (serum creatinine ≤ 1.4 mg/dL and proteinuria ≤ 0.33 g/day) in 37 patients (43%)

<table>
<thead>
<tr>
<th></th>
<th>At 5 years</th>
<th>At 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>No remission</td>
<td>69%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Renal survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>No remission</td>
<td>45%</td>
<td>31%</td>
</tr>
</tbody>
</table>

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


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

By multivariate analysis, male gender ($p=0.015$) & HTN ($p=0.004$) were independent predictors of nephritic relapses.
Evolving Therapeutic Strategies for Lupus Nephritis

Cyclophosphamide (CY)
Azathioprine (AZA)
Mycophenolate Mofetil (MMF)
Cyclosporine (CyA)
Abnormal processing of apoptotic cells may cause systemic lupus erythematosus
Long term preservation of renal function in 111 patients with Lupus Nephritis

Steinberg AD and Steinberg SC. NIH. Arthritis Rheum 1991;34(8):945-950
## Therapy of lupus Nephritis

<table>
<thead>
<tr>
<th>Complication</th>
<th>Treatment Group</th>
<th>% of the patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pred</td>
<td>AZA</td>
</tr>
<tr>
<td>Major infection</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td>Herpes zoster *</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Hemorrhagic ♠</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cystitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Premature ovarian ♥</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Mortality</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

* p<.05 groups 1 and 2 vs 3, 4 and 5
♠ p<.01 groups 1, 2 and 5 vs 3 and 4
♥ p<0.01 groups 1 and 2 vs 3, 4 and 5

Rate of sustained amenorrhea in patients treated with IVCY according to duration of therapy and age

Age = <25
Age > 25

p = 0.04 short-term vs. long-term IVCY.
Controlled trial: two regimens of pulse IVCY in patients with severe lupus nephritis


Long-term IVCY = monthly x 6 then quarterly x 2 yrs; Short-term IVCY = monthly x 6.

Azathioprine/methylprednisolone, n=37 (MP 1 g IV x 3 days baseline, 2 and 6 weeks with AZA 2 mg/kg/day) versus cyclophosphamide, n=50 (IVCY 0.75 g/m2 q mon x 6 then q3mon) in proliferative lupus nephritis. A randomized controlled trial.

- Patient histological characteristics (N = 87)
  - WHO Class III and Vc = 9% Mean Activity Index: 9/24
  - WHO Class IV and Vd = 91% Mean Chronicity Index: 2-3/12

- Demographics: Mean age 31, 75% Caucasians, 82% female,
- Mean BP 140/80 mmHg
- 53% nephrotic, mean urine 24 hr protein 3.75 g
- Mean Cr: 1.25 mg/dL

Cumulative incidence of first complete or partial remission. Cumulative incidence of first complete or partial remission in the first 2 years of follow-up. PR, partial remission; CR, complete remission; CY, group treated with intravenous cyclophosphamide; and oral prednisone, AZA, group treated with i.v.MP, azathioprine, and oral prednisone.
Kaplan–Meier estimates. Kaplan–Meier curves showing (a) proportion of patients reaching the end point of the study, unsustained doubling of serum creatinine, (b) proportion of patients free of relapse, and (c) proportion of patients free of treatment failure, relapse, or death. RR and 95% CI are given. CY=group treated with intravenous cyclophosphamide and oral prednisone, AZA=group treated with i.v.MP, azathioprine, and oral prednisone. KI
Azathioprine/methylprednisolone, n=37 (MP 1 g IV x 3 days baseline, 2 and 6 weeks with AZA 2 mg/kg/day) versus cyclophosphamide, n=50 (IVCY 0.75 g/m2 q mon x 6 then q3mon) in proliferative lupus nephritis. A randomized controlled trial.

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>AZA</th>
<th>IVCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>All infections per 100 pts-ys*</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Premature ovarian failure, N</td>
<td>2 **</td>
<td>2</td>
</tr>
<tr>
<td>Cancer, N</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Deaths, N</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

* P <0.05, ** received also IVCY
Induction Clinical Trials:


5. Flores-Suarez LF, Villa AR. JASN 15: PO257, 2004


European Lupus Nephritis Trial (ELNT): Sequential regimens of IVCY (low-dose vs. high-dose) induction followed by AZA maintenance with corticosteroids

- Patient histological characteristics (N = 90)
  - WHO Class III n = 21 Activity Index: 10/24
  - WHO Class IV n = 62 Chronicity Index: 1/12
  - WHO Class Vc+b n = 7
- Demographics: Mean age 31, 84% Caucasians, 9% Africans, 7% Asians, 93% female
- 47% hypertensive
- 24-hs urine protein 3.04 g
- Cr: 1.15 mg/dL
Remission: < 10 RBC/HPF, 24-hour proteinuria < 1 g, no DSC

90 pts=WHO III, IV, Vc+d
Methylprednisolone IV
0.75 g x3
LD = Low-dose IVCY: 0.5 g q2 weeks for 6 pulses followed by AZA maintenance + corticosteroids
HD = High-dose IVCY
0.5 g/m2 monthly x 6 followed by 2 pulses q3 months then AZA maintenance + corticosteroids

European Lupus Nephritis Trial: Primary Outcome of Treatment Failure

Patients Free of Failure (%)

Follow-up (months)

- Low dose
- High dose

Treatment failure:
- Steroid resistant flare
- Doubling S creat.,
- Failed to \(<\text{Cr}\ 1.3\)
  (base \text{Cr}\ 1.3-2.6)
- Failed to \(\leq 50\%\ \text{Cr}\)
  (base \text{Cr}\ >\ 2.6)
- Persistent nephrotic
  (UP \(\geq 3\ \text{g/d}\) &
  albumin \(< 3.5\ \text{g/dl}\))

European Lupus Nephritis Trial: Renal Flares

Patients Free of Renal Flares (%)

Follow-up (months)

- **Low dose**
- **High dose**

90 pts = WHO III, IV, Vc+d
Methylprednisolone IV 0.75 g x3

**LD = Low-dose IVCY:**
0.5 g q2 weeks for 6 pulses followed by AZA maintenance + corticosteroids

**HD = High-dose IVCY**
0.5 g/m2 monthly x 6 followed by 2 pulses q3 months then AZA maintenance + corticosteroids

Patients Free of Severe Infection (%)

Follow-up (months)

European Lupus Nephritis Trial: Severe Infections

- Low dose
- High dose

Adverse events in the European Lupus Nephritis Trial:

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Low Dose-IVCY-AZA</th>
<th>High dose IVCY-AZA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia, N (%) *</td>
<td>5 (11)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Bone marrow aplasia, N (%)</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Menopause, N (%)</td>
<td>2 (5)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>AZA induced hepatitis, N (%)</td>
<td>3 (7)</td>
<td>-</td>
</tr>
</tbody>
</table>

* WBC < 4000 per cubic μL occurred in 2 pts in each group during the induction phase.
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 (OCY) + steroid x 6 months
   then CY was replaced by azathioprine x 6 months

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

Group 1: MMF (2 g x 6 mo, then 1 g x 6 mo) + prednisone (0.8 mg/kg)

Group 2: POCY (2.5 mg/kg/d x 6 mo), then AZA (1.5-2.0 mg/kg/d) + prednisone

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)

- **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

- Chronic renal failure:
  - Group 1: 13% (10% Group 2)

- Relapse:
  - Group 1: 34% (30% Group 2)

- Infections:
  - Group 1: 13% (G2: 40%)

- Amenorrhea:
  - Group 1: 4% (36% Group 2)

- Mortality:
  - Group 1: 0% (7% Group 2)

Patients (%)

Chan TM et al. JASN 2005; April

P = 0.013

P = 0.004
Six months induction: MMF (n=71) vs. intravenous cyclophosphamide (IVCY) (n=69) 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

- **MMF**
  - African-Americans: Responding (%)
  - Others: Responding (%)
  - \( P = 0.002 \)

- **IVCY**
  - African-Americans: Responding (%)
  - Others: Responding (%)
  - \( P = 0.554 \)
**Six months induction: MMF vs. intravenous cyclophosphamide (IVCY) in severe lupus nephritis, FDA sponsored trial:**

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>MMF (n = 83)</th>
<th>IVCY (n = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe infections</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Necrotizing fascitis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Gram-negative sepsis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia, lung abscess</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Lymphopenia (&lt; 800/mL³)</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>Neutropenia (&lt; 1000/mL³)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>UGI (nausea, vomiting, etc)</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Severe rash</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Deaths during treatment</td>
<td>0</td>
<td>3 *</td>
</tr>
</tbody>
</table>

* 1 patient died after declining therapy.

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Ginzler E, et al.  
*NEJM 2005; 353: 2219-2228*
Aspreva Lupus Management Study (ALMS): Induction-Phase Results

- Between 27 July 2005 and 6 October 2006, 370 patients with SLE and active nephritis were enrolled at 88 centers in 20 countries in North America, Latin America, Asia, Australia, and Europe.

- Mycophenolate Mofetil (n = 185) Compared with Intravenous Cyclophosphamide (n = 185)

- Demographics: Mean age 30 (range 12 to 75)

- Race: 147 Caucasian, 123 Asian, 100 Non-Caucasian/Non-Asian (from whom 46 were of African Ancestry and 54 of others mixed race)

- Ethnicity: 239 Non Hispanics, 131 Hispanics

- Female = 313

- 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

- 24-hs urine protein 4.1 g and Serum Cr: 1.1 mg/dL

*JASN 2009; 20: 1103-1112*
Treatment Compliance

Oral MMF twice daily
Mean (SD): 2.5 (0.58) (g/day)

IVCY in monthly pulses
Mean dose per infusion: 0.78 g/m²
Mean (SD) number infusions: 5.6 (1.1)

Prednisone mg/day (SD)

Week ending dosing period

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)

OR (95% CI): 1.1 (0.7 to 1.8)

MMF

Proportion of patients responding (%)

56.2%

IVCY

53.0%

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)

<table>
<thead>
<tr>
<th>Race</th>
<th>MMF</th>
<th>IVCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>53.2</td>
<td>56.0</td>
</tr>
<tr>
<td>Caucasian</td>
<td>63.9</td>
<td>60.4</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>54.2</td>
<td>38.5</td>
</tr>
</tbody>
</table>

Asian vs Caucasian, P = 0.033

JASN 2009; 20: 1103-1112
Response to induction of patients with lupus nephritis: Mycophenolate mofetil (MMF) versus cyclophosphamide (IVCY) according to Hispanic Ethnicity

<table>
<thead>
<tr>
<th></th>
<th>Non-Hispanics</th>
<th>Hispanics</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMF</td>
<td>61.0</td>
<td>53.7</td>
</tr>
<tr>
<td>IVCY</td>
<td>38.8</td>
<td>60.9</td>
</tr>
</tbody>
</table>

P = 0.011

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)

<table>
<thead>
<tr>
<th>Geographic Area</th>
<th>MMF</th>
<th>IVCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest of the world</td>
<td>67.6</td>
<td>60.7</td>
</tr>
<tr>
<td>Asia</td>
<td>54.3</td>
<td>56.8</td>
</tr>
<tr>
<td>US/Canada</td>
<td>52.6</td>
<td>60.7</td>
</tr>
<tr>
<td>Latin America</td>
<td>47.4</td>
<td>56.8</td>
</tr>
<tr>
<td>P = 0.003</td>
<td>32.0</td>
<td></td>
</tr>
</tbody>
</table>

JASN 2009; 20: 1103-1112
Key Non-Renal Variables

- Mean plasma concentration (SD)
  - Anti-dsDNA
  - Complement C3
  - Complement C4

- Serum albumin (g/L, SD)

JASN 2009; 20: 1103-1112
Percentage of patients reporting adverse events by treatment group

- **Any AE**: 96.2% (MMF), 95% (IVCY)
  - Upper resp. infection: 29.3% (MMF), 35.6% (IVCY)
  - UTI: 9.8% (MMF), 8.3% (IVCY)
  - Lower resp. infection: 10.9% (MMF), 11.7% (IVCY)
  - Zoster: 8% (MMF), 6.7% (IVCY)

*JASN 2009; 20: 1103-1112*
Number of deaths during induction of lupus nephritis by race and treatment group

JASN 2009; 20: 1103-1112
The role of MMF Maintenance in Clinical Trials:


2. ALMS (Aspreva Lupus Management Study)

3. MAINTAIN from Euro-Lupus group
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 (V): Free of relapse

Cumulative probability

P = 0.021, MMF vs. IVCY
P = 0.124, AZA vs. IVCY
P = 0.222, MMF vs. AZA
Results (IV): Free of clinical event (death or CRF)

<table>
<thead>
<tr>
<th>t, months</th>
<th>Cumulative probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>12</td>
<td>0.75</td>
</tr>
<tr>
<td>24</td>
<td>0.50</td>
</tr>
<tr>
<td>36</td>
<td>0.25</td>
</tr>
<tr>
<td>48</td>
<td>0.00</td>
</tr>
</tbody>
</table>

- P = 0.049, MMF vs. IVCY
- P = 0.009, AZA vs. IVCY
- P = 0.503, MMF vs. AZA

<table>
<thead>
<tr>
<th>t, months</th>
<th>AZA</th>
<th>IVCY</th>
<th>MMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>19</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>20</td>
<td>19</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
<td>14</td>
<td>11</td>
</tr>
</tbody>
</table>

- 2 AZA
- 1 IVCY
- 2 MMF
Maintenance therapies: IVCY vs AZA vs MMF

Hospitalizations and Side Effects of Therapy

<table>
<thead>
<tr>
<th>Hospital days per pt-yr *</th>
<th>Amenorrhea *</th>
<th>Infections 100 pt-ys</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total θ</td>
<td>Major Ω</td>
</tr>
<tr>
<td>IVCY</td>
<td>10</td>
<td>32</td>
</tr>
<tr>
<td>AZA</td>
<td>8</td>
<td>29</td>
</tr>
<tr>
<td>MMF</td>
<td>6</td>
<td>32</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Visit range</th>
<th>AZA mg/kg/d</th>
<th>IVCY mg/m²</th>
<th>MMF mg/d, median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6</td>
<td>1.2 ± 0.4</td>
<td>542 ± 70</td>
<td>1500 (1500-2000)</td>
</tr>
<tr>
<td>6-12</td>
<td>1.0 ± 0.5</td>
<td>565 ± 62</td>
<td>1500 (1500-2000)</td>
</tr>
<tr>
<td>12-18</td>
<td>1.1 ± 0.6</td>
<td>562 ± 106</td>
<td>1250 (1000-1500)</td>
</tr>
<tr>
<td>18-24</td>
<td>0.8 ± 0.6</td>
<td>530 ± 119</td>
<td>1000 (500-1500)</td>
</tr>
<tr>
<td>24-30</td>
<td>1.1 ± 0.5</td>
<td>644 ± 4</td>
<td>1000 (500-1250)</td>
</tr>
<tr>
<td>30-36</td>
<td>1.1 ± 0.6</td>
<td>541 ± 36</td>
<td>500 (250-500)</td>
</tr>
</tbody>
</table>

MMF dose = median and 95% CI. Data reported as mean ± SD.
A randomized pilot trial comparing cyclosporine (CyA) vs. azathioprine (AZA) for maintenance therapy in diffuse lupus nephritis over four years

- **Patient Histological characteristics (N = 69)**
  - WHO class IV: 60
  - WHO class Vc or Vd: 9
  - Activity Index: 7/24
  - Chronicity Index: 2.5-2.8

- **Demographics:** Mean age 32, predominantly Caucasians, 90% female

- **Mean Creatinine 0.9 mg/dL, Urine protein: 2.4 g/24 hr**

Treatment protocol

- **Induction phase**
  - Methylprednisolone 0.5-1.0 g IV daily x 3 followed by prednisone 0.5–1.0 mg/kg/day x 2 months
  - Oral cyclophosphamide 1-2 mg/kg/day x 3 months

- **Central Randomization stratified only by center**

- **Maintenance phase (≈ 2 years)**
  - CyA (neoral®) 4 mg/kg/day titrated to keep trough blood level 75 – 200 ng/mL, creatinine < 30%+ of baseline, and aiming for proteinuria < 1 g/day
  - AZA 1.5 - 2 mg/kg/d titrated to keep WBC > 4000/mm³
  - During maintenance, patients received < 0.5 mg/kg/d prednisone

Primary outcome: overall incidence of SLE relapse over 2 years

<table>
<thead>
<tr>
<th></th>
<th>CyA, N=36</th>
<th>AZA, N=33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephritic relapse, N</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Proteinuric relapse, N</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Extra-renal relapse, N</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Overall, N</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Overall SLE relapses per 100 pts-ys</td>
<td>10.6</td>
<td>13.4</td>
</tr>
<tr>
<td>Overall exposure pts-ys</td>
<td>65.9</td>
<td>59.8</td>
</tr>
</tbody>
</table>

Nephritis relapse: ↑creatinine ≥ 30% of baseline accompanied ↑ proteinuria and/or active urine sediment (≥ 5 RBC x HPF).
Proteinuric relapse: ↑ proteinuria of at least 2g/day (if prior level ≤3.5) or doubling proteinuria.

Moroni G, et al. CJASN. In press
A randomized pilot trial comparing cyclosporine (CyA) vs. azathioprine (AZA) for maintenance therapy in diffuse lupus nephritis over four years.
<table>
<thead>
<tr>
<th>Adverse events</th>
<th>CyA, incidence events per 100 pts-ys</th>
<th>AZA, incidence events per 100 pts-ys</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>6.1</td>
<td>16.7</td>
</tr>
<tr>
<td>Infections</td>
<td>10.6</td>
<td>23.4</td>
</tr>
<tr>
<td>Anemia</td>
<td>7.6</td>
<td>8.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10.6</td>
<td>8.4</td>
</tr>
<tr>
<td>HTN crisis</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>↑ Cholesterol</td>
<td>3</td>
<td>6.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0</td>
<td>1.7</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Gum hyperplasia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Arhtralgias</td>
<td>21.2</td>
<td>5</td>
</tr>
<tr>
<td>GI disorders</td>
<td>16.7</td>
<td>5</td>
</tr>
</tbody>
</table>
Questions:

**Induction:**
What do we start with? CY or MMF?

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

Should we switch to maintenance therapy when achieving complete or partial remission?

Are there adjuvant therapies that consolidate complete remission?
Questions:

Maintenance:
Is Mycophenolate Mofetil superior to Azathioprine or Calcineurin Inhibitors?

Should we continue exposing patients to long-term Cyclophosphamide?

Can be stop maintenance therapy after 3 years?