Treatment of Class III/IV/V Lupus Nephritis

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Overview of immunosuppressive Rx for severe LN

Chinese/Asian data & ongoing studies

Recent developments
Survival Analysis and Causes of Death

n = 230 Chinese lupus nephritis patients in HK
Follow-up 4076 pat-yr (17.7+/−8.9 yr)
24 deaths (10.4%) – 85% after 10 yrs of follow-up

Survival rates – [Renal Survival]

<table>
<thead>
<tr>
<th></th>
<th>5-yr</th>
<th>10-yr</th>
<th>20-yr</th>
</tr>
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<tbody>
<tr>
<td>98.6%</td>
<td>98.2%</td>
<td>90.5%</td>
<td></td>
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<tr>
<td>99.5%</td>
<td>98.0%</td>
<td>89.7%</td>
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</table>

Causes of death - infection (50%), cardiovascular (20.8%), malignancy (12.5%)

SMR - ESRD 26.1, malignancy 12.9, cardiovascular 13.6

Severe Proliferative LN
Class III/IV ± V
Treatments for Lupus Nephritis

*Pre-1970* – corticosteroids alone; adverse effects+ & unsatisfactory efficacy

*1970s* – addition of cyclophosphamide improved renal outcome

*1980s* – iv cyclophosphamide pulses; sequential regimen

*1990s to 2000s* – mycophenolic acid

*Now* – corticosteroids + MPA or CTX then MPA or AZA; CNI; biologics & others?
Induction Rx for Severe Prolif LN – why is Remission important?

Response to induction Rx → Long-term renal survival

Remission → renal & patient survival

<table>
<thead>
<tr>
<th>Remission</th>
<th>Renal survival</th>
<th>Patient survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>94% 94%</td>
<td>95% 95%</td>
</tr>
<tr>
<td>No</td>
<td>46% 31%</td>
<td>69% 60%</td>
</tr>
</tbody>
</table>


Results with iv CTX

- Renal outcome better with ivCTX + Pred (vs Pred)
- Complete response 73/145; partial response 19/145; 41 (45%) renal relapse & 11 ESRF over 117 months
- Importance of maintenance immunosuppression
- ‘Prolonged FU’ necessary to examine the impact of treatment on renal survival
- ↓adverse effects with iv CTX vs prolonged p.o., but still considerable
- Sub-optimal renal / patient survival *long-term*
Euro-Lupus Study – 10-yr Data

n = 84       FU 115+/-30 months
7 deaths
6 ESRD
Euro-Lupus Treatment Regimen

CTX iv + pred
low dose (500 mg q2wk x6) vs high dose (6 q1m + 2 q3m)
followed by azathioprine

FU 41.3 months n = 90
Remission 71% vs 54%, p = n.s.
Infection seemed more frequent in high dose group
Similar efficacy

## MMF vs CTX as Induction Rx for IV+-V LN

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Endpoint</th>
<th>Dosage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan-HK</td>
<td>64</td>
<td>12 mon</td>
<td>[MMF 2 g/d]</td>
</tr>
<tr>
<td>Hu-China</td>
<td>46</td>
<td>6 mon</td>
<td>[MMF 1-1.5 g/d]</td>
</tr>
<tr>
<td>Ong-Malaysia</td>
<td>44</td>
<td>6 mon</td>
<td>[MMF 2 g/d]</td>
</tr>
<tr>
<td>Ginzler-USA</td>
<td>140</td>
<td>6 mon</td>
<td>[MMF 3 g/d; 63%; M 2.68 g/d]</td>
</tr>
<tr>
<td>ALMS</td>
<td>370</td>
<td>6 mon</td>
<td>[MMF 3 g/d; M 2.6 g/d]</td>
</tr>
</tbody>
</table>

Chan TM. Am J Med 2012; 125: 642-8
MMF in Class IV Lupus Nephritis

MMF (2 g/d) + Pred as induction therapy
→ high efficacy (CR >80%), similar to Pred+CTX
→ fewer adverse effects vs CTX (alopecia, amenorrhea, leukopenia, infection)
→ better QoL (rehabilitation)

**ALMS - Induction Phase Results**

Response (endpoint): ↓ proteinuria & stable/improved creatinine

MMF dose achieved → mean 2.6 g/d     median CTX 0.75 g/m$^2$

1. response rate (*week 24*)
   - MMF 104/185 (56.2%)      CTX 98/185 (53.0%)      p=0.58

2. remission, proteinuria, creatinine – no significant difference

3. tolerability
   - **CTX 40.6% more adverse events (episodes)**
   - serious AE - MMF 27.7% & CTX 22.8%
   - infection - MMF 12.0% & CTX 10.0%
   - withdrawal due to AE - MMF 13.0% & CTX 7.2% (p=0.07)
   - deaths - MMF 9 & CTX 5 (infections, 7 MMF deaths Asians)

### ALMS - Induction Phase Data

<table>
<thead>
<tr>
<th>Response</th>
<th>MMF</th>
<th>CTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>53.2%</td>
<td>63.9%</td>
</tr>
<tr>
<td>White</td>
<td>56.0%</td>
<td>54.2%</td>
</tr>
<tr>
<td>Other</td>
<td>60.4%</td>
<td>38.5%</td>
</tr>
<tr>
<td>Black</td>
<td>53.9%</td>
<td>40.0%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>60.9%</td>
<td>38.8%</td>
</tr>
<tr>
<td>Latin American</td>
<td>60.7%</td>
<td>32.0%</td>
</tr>
</tbody>
</table>

Patients with very severe disease

Pooling data of patients with Class III/IV and –
✧ >15% crescents
✧ abnormal serum creatinine at presentation

[ALMS, Chan, Ginzler, Mok, Hooi, …]

Findings -
Pred + CTX / MMF – similar early response
CTX ⇒ ? fewer disease flares and less renal failure
Maintenance Immunosuppression
MMF vs AZA as Maintenance Rx of Lupus Nephritis - MAINTAIN Trial

N=105 III/IV +/-V

Euro-Lupus induction immunosuppression
Maintenance from Wk12 with steroid +
AZA (2 mg/kg/d, n=52) or MMF (2 g/d, n=53)

Median FU 53 months (24 drop-outs):
1. renal flare in 13 AZA patient and 9 MMF patient
2. AZA vs MMF similar $\rightarrow$ time to flare (renal or systemic);
renal remission; infection
3. cytopenia more with AZA
4. doubling of baseline creatinine - 4 AZA and 3 MMF

Aspreva Lupus Management Study (ALMS)

III, IV, V or mixture

Induction (n=370) → MMF (3 g/d) vs iv CTX (1 g/m²) q4wk
+ steroid (up to 60 mg/d)

Responders re-randomized at Week 24 (n=227)
→ MMF 1 g bid (n=116) or AZA 2 mg/kg/d (n=111) + steroid

Maintenance phase lasted 36 months
Outcome: Time to ‘treatment failure’ [death, ESRD, doubling of baseline creatinine, renal flare, rescue therapy]

**Result**  [55.9% completed the study]

*MMF regimen better than AZA*

- ‘time to treatment failure’ – HR 0.44, CI 0.25-0.77, P=0.003
- ‘time to renal flare’ – HR 0.50, CI 0.26-0.93, P=0.03
- ‘time to rescue therapy’ – HR 0.39, CI 0.18-0.87, P=0.02

- ‘treatment failure’ - 16.4% [MMF] vs 32.4% [AZA]
- renal flare - 12.9% [MMF] vs 23.4% [AZA]
- rescue treatment - 7.8% [MMF] vs 17.1% [AZA]
- withdrawal due to adverse events more with AZA (39.6% vs 25.2%, P=0.02)

Long-term Results with Pred+MMF in LN

65 patients with Class III/IV+/-V LN  FU 92+/-48 months
■ Treated with Pred+MMF continuously from the early (induction) phase to the maintenance phase
■ MMF → AZA and/or CNI in 34 patients

10-yr patient survival    renal survival

         91%              86%

Relapse-free survival at 5-yr

MMF-MMF      76%
MMF-AZA       56%

Survival % (no. at risk)

<table>
<thead>
<tr>
<th>Dur of MMF</th>
<th>Survival %</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 24 mo</td>
<td>88% (15)</td>
<td>81% (1)</td>
</tr>
<tr>
<td>&lt; 24 mo</td>
<td>48% (12)</td>
<td>28% (3)</td>
</tr>
</tbody>
</table>

Reducing MMF dose within 18 months after treatment response \(\rightarrow\) 6-fold increase in risk of relapse \((p=0.001)\)

N=184   FU 195+/-94 months

Rx of Class III/IV±V LN

Induction – Pred (?MP) + MMF/CTX/?CNI

Maintenance – pred + MMF/AZA/?CNI [+hydroxychloroquine]

Non-immunological → renal & vascular outcomes, …
Membranous LN

Class V
Treatment of Membranous Lupus Nephritis

randomized controlled trial

Response Rate at 1 yr –

steroid alone  27%
cyclophosphamide  60%
cyclosporine  84%

Effect of Immunosuppressive Treatment in Membranous Lupus Nephritis

meta-analysis of 21 studies

*Response rate* –
  - steroid alone  <60%
  - other immunosuppressive agents  83%
    [AZA 89%, CTX 77%, MMF 84%, CYA 84%]

*Non-response rate* –
  - steroid alone  39%
  - other immunosuppressive agents  17%

**MMF vs CTX as Induction Treatment in Membranous Lupus Nephritis**

Pooled data from two studies: 33 MMF vs 32 IVC

Similar efficacy at 24 wk

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>N</th>
<th>Urine protein (g/24 h)</th>
<th>Serum creatinine (μmol/l)</th>
<th>Serum albumin (g/l)</th>
<th>Serum C3 (g/l)</th>
<th>Serum C4 (g/l)</th>
<th>Anti-dsDNA</th>
<th>Nephrotic (%)</th>
<th>Use of RAASI (%)</th>
<th>% Change in urine protein</th>
<th>% Change in serum creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>MMF</td>
<td>8</td>
<td>1.5 ± 1.1, P=0.007</td>
<td>79 ± 9, P=0.026</td>
<td>34 ± 6</td>
<td>129 ± 37</td>
<td>36 ± 11</td>
<td>0.1 ± 0.3</td>
<td>0</td>
<td>62.5</td>
<td>−61 ± 29</td>
<td>16 ± 18</td>
</tr>
<tr>
<td></td>
<td>IVC</td>
<td>7</td>
<td>1.6 ± 1, P=0.046</td>
<td>66 ± 25, P=0.283</td>
<td>34 ± 4</td>
<td>130 ± 35</td>
<td>27 ± 15</td>
<td>0.6 ± 1</td>
<td>0</td>
<td>71</td>
<td>−71 ± 21</td>
<td>9 ± 18</td>
</tr>
<tr>
<td>ALMS</td>
<td>MMF</td>
<td>25</td>
<td>1.8 ± 2, P &lt; 0.001</td>
<td>63 ± 21, P=0.073</td>
<td>36 ± 8</td>
<td>111 ± 37</td>
<td>30 ± 17</td>
<td>0.4 ± 0.7</td>
<td>12</td>
<td>80</td>
<td>−63 ± 29</td>
<td>−6 ± 22</td>
</tr>
<tr>
<td></td>
<td>IVC</td>
<td>25</td>
<td>2.7 ± 2.4, P=0.001</td>
<td>71 ± 32, P=0.539</td>
<td>34 ± 3</td>
<td>71 ± 33</td>
<td>22 ± 12</td>
<td>1 ± 1.1</td>
<td>32</td>
<td>76</td>
<td>−48 ± 51</td>
<td>3 ± 23</td>
</tr>
</tbody>
</table>

17 MMF & 23 IVC nephrotic → responder 11/17 vs 14/23

Pred+Tac vs Pred+MMF in LN V with Nephrotic Syndrome

prospective randomized pilot study with 16 patients
[MMF 7, Tac 9]       FU 24 months
proteinuria 4.7 & 4 g/d at baseline
MMF 0.75-1 g bid     Tac trough level 6-8 ng/mL

Yap DYH, et al. Nephrology 2012; 17: 352-357
Response rate  55.6% vs 71.4%  P=0.515

Yap DYH, et al. Nephrology 2012; 17: 352-357
ACR & EULAR Guidelines for Class V LN

⇒ Nephrotic → pred + MMF (2-3 g/D)

Rx of Class V LN

*Significant* proteinuria → immunosuppression

Pred + MMF / CTX / (AZA) / CNI
Recent Developments
Emerging Therapies
Calcineurin Inhibitors (CNI)

- cyclosporine, tacrolimus, ...
- effective immunosuppression (T lymphocyte)
- standard immunosuppressive therapy in kidney transplantation \( \Rightarrow \) corticosteroids + CNI + MPA
- reduce proteinuria (effect on podocyte) \( \Rightarrow \) efficacy in MN, FSGS, relapsing MCD
CyA vs ivCTX Induction Rx in III/IV LN (CYCLOFA-LUNE)

Pred+CyA (19) vs Pred+ivCTX (21) III/IV FU 9+9 months activity 9.3/9.9 chronicity 3.5/4.0 UP 3.8/2.5 g/D
CTX – 10 mg/kg q3wk x2, q4wk x4, q6wk x2
CyA – 4-5 mg/kg/D for 9 m then reduce
Drop-outs: ind phase – 1 CTX & 1 CyA; maint phase – 3 CTX
Response (9 mon): 11/21 CTX vs 8/19 CyA, p=0.75
Response (18 mon): 8 vs 11, p=0.21

38 patients median FU 7.7 yr
CTX vs CyA similar → creat, UP, renal failure, SLICC damage score, adverse events

Tacrolimus vs ivCTX as Induction Rx in III/IV LN

Pred+Tac (42) vs Pred+ivCTX (39)
III/IV+/−V   V (11%)
Tac trough blood level 5-10 ng/mL

6-month outcome –
CR   52.4% vs 38.5%   P=0.2
Response  90.5% vs 82.1%   P=0.7
Tac → lower proteinuria level after 1 mon
Adverse effects less frequent in Tac group
Tac ≈ esp useful for class V

open-label randomized prospective controlled trial
induction Rx 6 mon III / IV / V (pure V 19%)
responders maintained with pred+AZA
Tac (n=74) dose not guided by TDM (started with 0.1 mg/kg/D)
MMF (n=76) dose could go up to 3 g/D
achieved Tac trough 7.8+/-3.9 µg/L

CrCl did not change in Tac group but improved in MMF group
Tac resulted in numerically higher response rate than MMF in Class V
One death (infection), more zoster (18% vs 3%) and diarrhea in MMF group
**Some patients in Tac group had reversible SCr increase by 30%

Pred+Tac vs Pred+MMF in Nephrotic Class V LN

prospective randomized pilot study with 16 patients
[MMF 7, Tac 9]       FU 24 months
proteinuria 4.7 & 4 g/d at baseline
MMF 0.75-1 g bid, Tac trough level 6-8 ng/mL
Response rate   71.4% vs 55.6%   P=0.515

Pred+MMF+Tac as Induction Rx for IV+V LN

MP-Pred+MMF+Tac (20) vs MP-Pred+ivCTX (20)
Tac trough blood level 5-7 ng/mL
MMF 0.5 g bid, MPA AUC0-12h 20-45 mg.h/L
Treatment duration 6-9 months

Outcome –

<table>
<thead>
<tr>
<th>CR/PR</th>
<th>MT</th>
<th>Pred+ivCTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-mon</td>
<td>50%/40%</td>
<td>5%/40%</td>
</tr>
<tr>
<td>9-mon</td>
<td>65%/30%</td>
<td>15%/40%</td>
</tr>
</tbody>
</table>

Triple regimen better tolerated than Pred+ivCTX

Pred+ MMF+Tac vs ivCTX as Induction Rx for III/IV/V LN

Tac 4 mg/D, MMF 0.5 g bid vs ivCTX 0.75 g/m² q4wk for 6 mon
ivMP 0.5 g/D for 3 days creat <265.2 micromol/L

1° Endpoint: CR after 24 wks of treatment – MT superior (45.9% vs 25.6%, p<0.001) [response 83.5% vs 63.0%, p<0.001]


368 randomized
24 lost to FU
28 discont assigned Rx

Serious AE
MT 7.2% vs CTX 2.8%

AE related drop-out
MT 5.5% vs CTX 1.7%
Tacrolimus vs AZA as Maintenance Rx in III/IV LN

70 patients with III/IV+/-/V after response to induction Rx
Pred+Tac (34) vs Pred+AZA (36)
Tac trough blood level 4-6 ng/mL     AZA 2 mg/kg/D

6-month outcome
renal flare - 2 in AZA group, none in Tac
AZA asso with leukopenia and liver abnormality

Long-term Data on Tac in LN

retrospective Tac treatment >6 mon target trough 4-6 μg/L
N=29 [41.2 ± 9.2 yr; 24F 5M]
17 III/IV ± V → Tac added to pred+MMF
10 V → Pred+Tac 2 relapsing podocytopathy
Tac duration 46.9 ± 37.9 mon [18(62.1%) >36 mon]

Tac 6 mon 12 mon
Dose 3.39 ± 1.91 3.41 ± 1.72 mg/D
Trough 4.72 ± 2.9 4.17 ± 1.91 μg/L

Long-term Data on Tac in LN

Renal Response –

Complete  UP ≤0.5 g/D, creat ±15% of baseline
Partial  UP↓ by 50%, non-nephrotic, stable creat

<table>
<thead>
<tr>
<th>Response rate</th>
<th>Complete</th>
<th>Partial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class III/IV ± V</td>
<td>40%</td>
<td>26.7% [12-mon]</td>
</tr>
<tr>
<td></td>
<td>46.7%</td>
<td>33.3% [24-mon]</td>
</tr>
<tr>
<td>Class V</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>40%</td>
</tr>
</tbody>
</table>

37.9% had UP↓ by 50% after 6 months of Tac

Biologics

- anti-CD20
- atacicept
- abatacept
- belimumab
- Others – e.g. PKC inhibitors
- Importance of Proteinuria response to treatment
- What level of Proteinuria should one target
CSG Data

Remission achieved?

YES  ⇒  renal & patient survival >90%
NO   ⇒  renal survival 46% / 31% at 5 / 10 years
        patient survival 69% / 60% at 5 / 10 years


Proteinuria reduced by 50% or more after Rx for 6 months?

YES  ⇒  5- / 10-yr ESRF rate 15% / 26%
NO   ⇒  5- / 10-yr ESRF rate 41% / 50%

**ALMS Data**

baseline eGFR <30mls/min ⇒ worse renal prognosis

C3 normalize / ↓proteinuria of >25% by 8 weeks ⇒ favorable outcome


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**Treatment response and Long-term outcome**

- **Remission**
  - Not on Dialysis at 10 years: 92%
  - On Dialysis at 10 years: 8%

- **Responder**
  - Not on Dialysis at 10 years: 43%
  - On Dialysis at 10 years: 57%

- **Non-Responder**
  - Not on Dialysis at 10 years: 13%
  - On Dialysis at 10 years: 87%

Diagram courtesy of N Solomon, Aurinia Pharm
ELNT & MAINTAIN Data

Follow-up (MAINTAIN): 110 months (median) [range 18-156 mon]
↓ Proteinuria more rapid ⇒ better long-term renal prognosis
↓ Proteinuria alone (vs creat vs creat+uRBC) drives PPV of 12-mon treatment response on 10-yr renal prognosis – 92% (vs 94% vs 93%)

Proteinuria at 12-mon –
<0.8 g/D (ELNT) → good long-term renal outcome
(defined as 7-yr creat ≤1 mg/dL)
[sens 81%; spec 78%]

<0.7 g/D (MAINTAIN) → good long-term renal outcome
[sens 71%; spec 75%; PPV 94%; NPV 29%]

IgG and Infection in LN Patients
Pre-mature termination of APRIL LN Study 28113 after three of four atacicept-treated patients showed IgG <3 g/L, with pneumonia/bacteraemia affecting two patients

Pred+MMF Does Not Lead to ↓↓IgG in LN Patients

N=46  26.1% had low IgG level at baseline (none below 3 g/L)

Low IgG level asso with heavier proteinuria (6.8 vs 4.4 g/D)

After Rx  ⇒  ↓IgG level after 2 wks, trough at 8 wks, then increase

One patient had IgG <3 g/L after Rx

5/12 infections asso ↓IgG (RR 1.863, CI 0.466-6.818, p=0.28)

Yap DYH, et al.
Lupus 2014; 23: 678-83
MPA Therapeutic Drug Monitoring
MPA Therapeutic Drug Monitoring in LN Treatment

- MPA pharmacokinetics vary between patients
- MMF (not EC-MPS) → relatively good correlation between trough (other single time-point) MPA level and AUC
- Drug exposure ~more related to efficacy than adverse events
- [SLE/Vasculitis] AUC 35-45 mg.h/L or Trough MPA 3.5-4.5 mg/L ≅ favorable clinical outcome  [MMF dose approx 1.8 g/D]; Trough MPA 3 mg/L → 92% NPV for flare

de Winter BC, et al. Ther Drug Monit 2009; 31: 585-91
Concentration-controlled MPA Treatment Regimen

N=19, III/IV      MMF dose commenced at 1.5 g/D
Target MPA-C1 >13 mg/L

Response rate –
24 Wk      17/19 (89%) [4 CR]
48 Wk      8 CR

78% achieved MPA-AUC_{0-12h} target 45 mg.h/L
Required MMF dose ⇒ >2 g/D in 83.3%

Treatment of Lupus Nephritis

*Then*: corticosteroids $\rightarrow$ corticosteroids + CTX; suboptimal efficacy; morbidities; unsatisfactory long-term outcomes

*Now*: corticosteroids + MPA or CTX then MPA or AZA; additional choices e.g. CNI & biologics etc; ↓ dependency on corticosteroids; individualization
Thank you