



# LUPUS NEFRİTİ

TANI ve İNDÜKSİYON TEDAVİSİ

**Dr. Mansur Kayataş**

Cumhuriyet Üniversitesi Tıp Fakültesi  
Nefroloji Bilim Dalı

# SLE

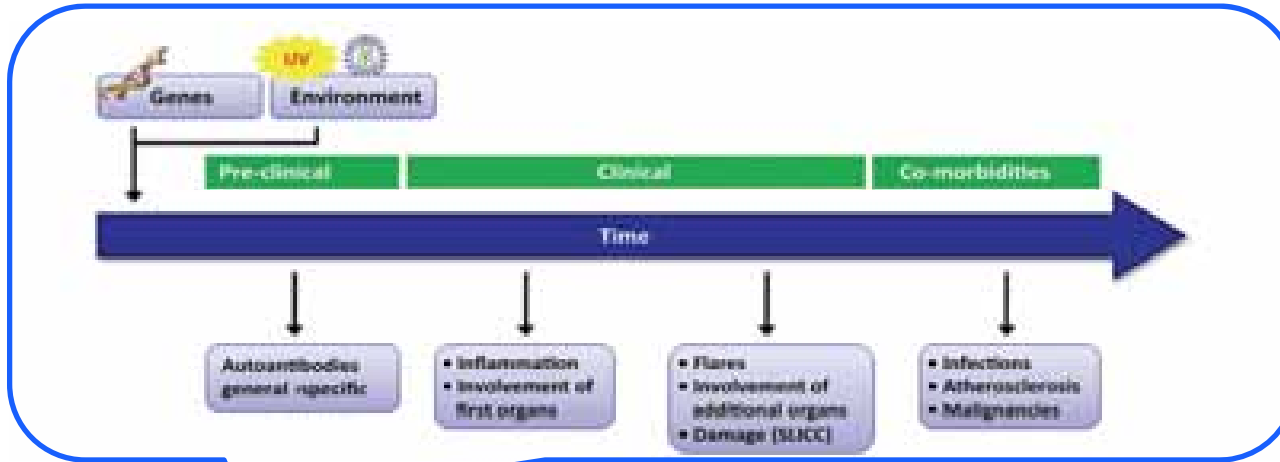
- Hemen hemen **tüm organları tutabilen, etyolojisi bilinmeyen, immünolojik anormalliklerin eşlik ettiği kronik inflamatuvar** bir hastalıktır.

**PREVALANS**                      **40 - 200 / 100.000**

**İNSİDANS**                        **1.8 - 7.6 / 100.000**

 **7-12/1**

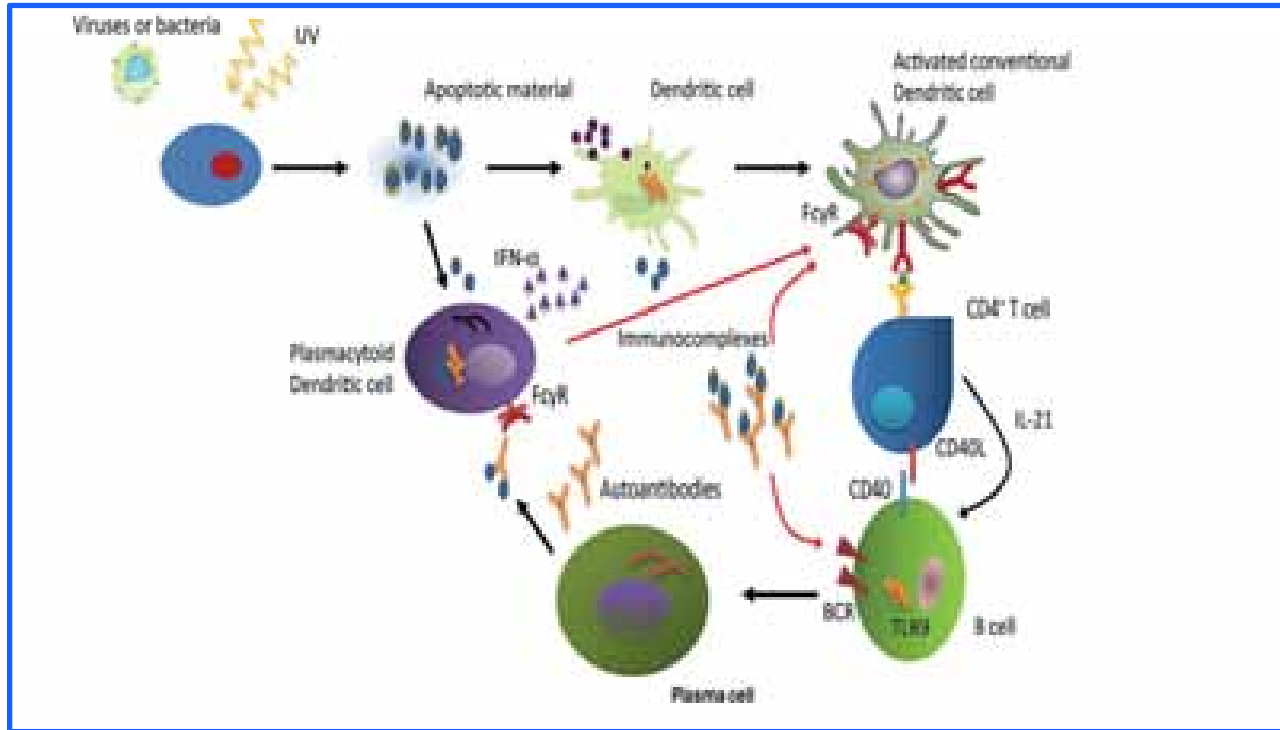
# Patogenez ve Patofizyoloji



Renal patogenez

**Proliferatif LN**  
Ig G<sub>1</sub> ve Ig G<sub>3</sub> İK ↗

**Membranöz LN**  
Ig G<sub>2</sub> ve Ig G<sub>4</sub> İK ↗



Tübulointerstisyel hasarlanma

**Monositlere bağlı tübüler ve mezangiel hücrelerde**  
↗APOPTOZİS

# BAZI SEMPTOM, DOKU VE ORGAN TUTULUM ORANLARI

	BAŞLANGIÇ (%)	SONRAKİ SÜREÇTE (%)
<b>AKCİĞER TUTULUMU</b>	<b>2-12</b>	<b>24-98</b>
-Plörezi	17	30-45
-Effüzyon		24
-Pnömoni		29
<b>KARDİAK TUTULUM</b>	<b>15</b>	<b>20-46</b>
-Perikardit	8	8-48
-Üfürüm		23
-EKG değişikliği		34-70
<b>LENFADENOPATİ</b>	<b>7-16</b>	<b>21-50</b>
<b>SPLENOMEGALİ</b>	<b>5</b>	<b>9-20</b>
<b>HEPATOMEGALİ</b>	<b>2</b>	<b>7-25</b>
<b>SANTRAL SINIR SİSTEMİ</b>	<b>12-21</b>	<b>25-75</b>
-Fonksiyonel		Çoğunda
-Psikoz	1	5-52
-Konvülziyon	0.5	2-20

Von Feldt JM, Postgrad Med 1995; 97:79.

# BAZI SEMPTOM, DOKU VE ORGAN TUTULUM ORANLARI

	BAŞLANGIÇ (%)	SONRAKİ SÜREÇTE (%)
YORGUNLUK	50	74-100
ATEŞ	36	40-80+
KİLO KAYBI	21	44-60+
ARTRİT VE ARTRALJİ	62-67	83-95
CİLT	73	80-91
KELEBEK DÖKÜNTÜ	28-38	48-54
FOTOSENSİTİVİTE	29	41-60
MUKOZ MEMBRAN LEZYONLARI	10-21	27-52
ALOPESİ	32	18-71
RAYNAUD FENOMENİ	17-33	22-71
PURPURA	10	15-34
ÜRTİKER	1	4-8
<b>BÖBREK TUTULUMU</b>	<b>16-38</b>	<b>34-73</b>
-NEFROTİK SENDROM	5	11-18
GASTROENTESTİNAL TUTULUM	18	38-44

Von Feldt JM, Postgrad Med 1995; 97:79.

# Lupus Nefriti Prevalans/Cohort

## AVRUPA

- **1000** ardışık hasta, **12** merkez
- **Tanı:** >0.5 gr/proteinüri (veya +++/çubuk), hücrel silendirüri, s. kreatininde  $\geq 0.8$  mg/dl (başka bir nedene bağlı olmayan)

Tanı anında: **% 16**

10 yıllık takip süresince: **% 28**

## ABD

- **1378** hasta
- **Tanı:** >0.5 gr/p.ü,  $\geq 5$  eritrosit/BBA, s. kreatininde  $\geq 1,5$  mg/dl veya diyaliz veya Transplantasyon

Tanıdan sonraki 1 yıl içinde: **% 32**

Tanıdan sonraki 9 yıl içinde:

> 0.5 gr/proteinüri	<b>% 47</b>
↓ GFH	<b>% 6</b>
SDBY	<b>% 4</b>

*Medicine (Baltimore)*. 1993;72(2):113.  
*Medicine (Baltimore)*. 2003;82(5):299.

*Medicine (Baltimore)*. 2006;85(3):147.  
*Arthritis Rheum*. 2005;52(12):4003.

## BAŞLANGIÇ KLİNİK BULGULAR

- Beklenmeyen özgün olmayan semptomlar; ateş, yorgunluk veya kilo kaybı
- Fotosensitif döküntü
- Artralji veya artrit
- Raynaud fenomeni
- Serözit (plörit, perikardit, peritonit)
- Nefrit veya nefrotik sendrom
- Nörolojik semptomlar (epilepsi, psikoz, kognitif disfonksiyon, inme veya baş ağrısı)
- Alopesi
- Flebit, arteriyel ve/veya venöz tromboembolik olay
- Tekrarlayan düşük
- Anemi

## GENÇ BİR KADINDA AŞAĞIDAKİ BULGULAR VARSA ŞÜPHELENMELİDİR

- Purpura,
- Kolay morarma
- Yaygın adenopati
- Hepatosplenomegali
- Periferik nöropati
- Endokardit,
- Miyokardit
- İnterstisyel pnömoni
- (+) Coombs testi
- Kompleman düşüklüğü
- Cilt biyopsisinde epidermal-dermal bileşkede immün depolanmalar

# TANISAL TESTLER

*En öncelikli istenmesi gereken otoantikörler*

- **Antinükleer antikor (ANA)**
- Antifosfolipid antikorlar
- Anti-dsDNA
- Anti-Smith (Sm) antikorlar

- Direkt Coombs testi
- Kompleman düzeyleri

# ANA

**ANA = 1:160** hemen hemen tüm SLE' lilerde (+)

**ANA = 1:40** pozitiflikte % 30 yalancı pozitiflik  
**“Yüksek duyarlılık, düşük özgünlük”**

**ANA = 1:320** SLE'nin sadece % 3'ünde pozitif  
**“Düşük duyarlılık, yüksek özgünlük”**

# ÖZGÜN ANTİKORLAR



## Pozitiflikleri

### ELISA

DUYARLILIK	% 66 -95
ÖZGÜNLÜK	% 75-100
PREDIKTIF DEĞER	% 89-100

ANA POZİTİF SLE ORANI → % 95 - 99

ANA NEGATİF SLE ORANI → % 1-5 <sup>①</sup>

Teknik yetersizlik veya dolaşan immünkomplekslerde ANA'nın hapsedilmesi ??

Çok ↗ oranda ANTI-RO antikor pozitifliği (2/3),  
Çok ↗ oranda KUTANÖZ tutulum,

Çok ↘ oranda SSS tutulumu  
Çok ↘ oranda RENAL tutulum

2,3

- 1- Arch Pathol Lab Med 2000, 22:447-474
- 2- Medicine. 1981;60:87-94
- 3- J Am Acad Dermatol. 1981;4:84-89.

# SLE'nin ARD (American Collage of Rheumathology) kriterleri

**Malar döküntü**

**Diskoid döküntü**

**Fotosensitivite**

**Oral ülserler**

**Artrit**

**Serozit**

**RENAL HASTALIK**

**Nörolojik hastalık**

**Hematolojik hastalık**

**ANA**

**İmmünolojik bozukluklar**

**> 0.5 gr/gün proteinüri**

**veya**

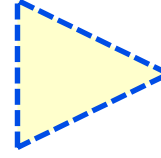
**> +++ proteinüri**

**veya**

**Silendirüri**

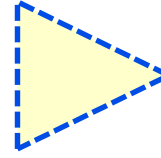
**(eritrosit, hemoglobin, granüler ,tübüler veya mikst)**

ARD kriterlerinin çoğu varsa



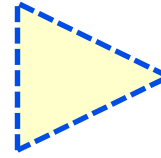
Klasik SLE

ARD kriterlerinden 4 veya daha fazlası varsa



Kesin SLE

4'den az ARD kriteri varsa



Muhtemel SLE

Farklılaşmamış bağ dokusu hastalığı  
(OVERLAP)

# Farklılaşmamış bağ dokusu hastalığı (OVERLAP)

“SLE veya bir diğer otoimmün hastalığın tanı kriterlerini tamamlamayan, ancak FM’de **inflamasyon bulguları olan** ve **pozitif seroloji** saptanan hastalar”

10 yıllık takiplerinde

**% 40-60**

Başlangıç bulguları ile seyreder

**% 5-30**

**RA,  
SLE,**

**SKLERODERMA**

veya

**İNFLAMATUVAR MIYOPATI**

gelişir

Lupus. 2004;13(2):85.  
J Rheumatol. 1980;7(6):831

Nat Clin Pract Rheumatol. 2008;4(6):328.  
Clin Exp Rheumatol. 2003;21(3):313  
Arch Intern Med. 1989;149(11):2473.

## ARA/ARD

### AMERIKAN ROMATOLOJİ DERNEĞİ

Malar döküntü

Fotosensitivite

Diskoide döküntü

Oral ulserler

Anti-Sm

**Böbreğe sınırlı  
lupus  
tanımlanmamış**

Hematolojik hastalık

ANA

İmmünolojik bozukluklar

**4/11 kriter**

ARTHRITIS RHEUM 1997; 40:1725.

## SLICC/SLUKİ

### SİSTEMİK LUPUS ULUSLARARASI KLİNİKLER İŞBİRLİĞİ

- Akut kutanöz lupus
- Kronik kutanöz lupus
- Alopesi (skar bırakmayan)
- Ağız veya burun ülserleri
- Eklem hastalığı
- Serözit
- Renal
- Nörolojik
- Hemolitik anemi
- Lökopeni veya lenfopeni
- Trombositopeni

**KLİNİK (11 ADET)**

- ANA
- Anti-dsDNA
- Anti-Sm
- Antifosfolipit
- Düşük kompleman
- Direkt Coombs testi

**İMMÜNOLOJİK (6 ADET)**

- 1- **4/17** SLICC kriteri; en az 1 klinik, 1 immünolojik
- 2- **ANA veya anti-dsDNA (+)** ve biyopsi kanıtlı lupus nefriti

ARTHRITIS RHEUM 2012; 64:2677.

4/17 SLCC/SLUKİ kriteri	(SLICC/SLUKİ) Sistemik Lupus Uluslararası Klinikler İşbirliği
↘ Akut kutanöz lupus	<b>↘ Klinik kriterler (11 adet)</b>
Kronik kutanöz lupus	
Alopesi (skar bırakmayan)	
Ağız veya burun ülserleri	
Eklem hastalığı	
Serözit	
<b>RENAL</b>	<b>İDRAR PROTEİN/KREATİNİN (VEYA 24 SAATLIK İDRAR) &gt; 500 MG/GÜN PROTEİNÜRİ VEYA ERİTROSİT SİLENDİRÜRİ</b>
Nörolojik	
Hemolitik anemi	
Lökopeni veya lenfopeni	<4000/mm <sup>3</sup> veya <b>&lt; 1000/mm<sup>3</sup></b>
Trombositopeni	<100,000/mm <sup>3</sup>
↘ ANA	<b>↘ İmmünolojik kriterler (6 adet)</b>
Anti-dsDNA	
Anti-Sm	
Antifosfolipit	Lupus antikagülan, anti-kardiyolipin, anti-β2-glicoprotein I (IgA, IgG, veya IgM)
Düşük kompleman	↓ C3; ↓ C4; veya ↓ CH50
Direkt Coombs testi	(hemolitik anemi yoksa)

# 2003 ISN / RPS Klasifikasyonu

## **Klas I: Minimal Mezangial Lupus Nefriti**

- IM: Glomerüller normal,  
IFM: Mezangial immün depozitler

## **Klas II: Mezangial Proliferatif Lupus Nefriti**

Mezangial hiperselülarite  $\pm$  mezangial matriks artışı + mezangial immün depozitler

## **Klas III: Fokal Lupus Nefriti**

- Klas III (A) Aktif lezyonlar: Fokal Proliferatif LN  
Klas III (A/C) Aktif ve kronik lezyonlar: Fokal Proliferatif ve Sklerozan LN  
Klas III (C) Skarlı kronik inaktif lezyonlar: Fokal Sklerozan LN

## **Klas IV: Diffüz Lupus Nefriti**

- Etkilenen glomerüllerin  $\geq$ %50'sinde segmental lezyon: IV-S  
Etkilenen glomerüllerin  $\geq$ %50'sinde global lezyon: IV-G  
Klas IV-S (A) Aktif lezyonlar: Diffüz Segmental Proliferatif LN  
Klas IV-G (A) Aktif lezyonlar: Diffüz Global Proliferatif LN  
Klas IV-S (A/C) Aktif ve kronik lezyonlar: Diffüz Segmental Proliferatif ve Sklerozan LN  
Klas IV-S (C) Skarlı kronik inaktif lezyonlar: Diffüz Segmental Sklerozan LN  
Klas IV-G (C) Skarlı kronik inaktif lezyonlar: Diffüz Global Sklerozan LN

## **Klas V: Membranöz Lupus Nefriti**

Global veya segmental subepitelyal immün depozitler  $\pm$  mezangial değişiklikler

## **Klas VI: İleri Sklerozan Lupus Nefriti**

$\geq$ %90 glomerülde global skleroz (rezidüel aktivite yok)

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## Klass III Fokal Proliferatif ve Klass IV Diffüz Proliferatif tedavileri aynıdır

- Klass III'ün tüm indüksiyon tedavilerindeki oranı % 10-20
- **Klass III ile IV'ün kesin ayrımı için IM'da gerekli glomerül sayısı 100 olmalıdır**
- Rutin biyopsi materyalinde nekrotik ve kresentik lezyonları göstermek mümkün olmayabilir

Fokal proliferatif LN ile diffüz proliferatif LN'in (hatta ciddi biyopsi ve klinik bulguları olanları ile) uzun dönem progresyonları benzer bulunmuştur.

## SLE'de diđer b6brenk patolojileri

- Overlap (Lupus ve ANCA glomer6lonefrit)
- B6brenge sınırlı lupus-like nefrit
- T6b6lointerstisyel nefrit
- Vask6ler hastalık
- Trombotik mikroanjiyopati
- Sessiz lupus nefriti
- İlaça bađlı lupus
- Glomer6ler podositopati
- Collapsing glomer6loskleroz

# BÖBREK BIYOPSISI İLE TANI

*Böbrek tutulumuna ait bulgular varsa  
böbrek biyopsisi mutlaka yapılmalıdır.*

## Gerekçeler

Tedavinin **2003 ISN / RPS Klasifikasyonu** histolojik alt grubuna yönelik düzenlenmesi

Klinik görünüm histolojik bulguların ciddiyetini her zaman yansıtamayabilir.  
“Minimal proteinüri ve normal serum kreatinin düzeylerinde bile proliferatif lupus  
nefriti olabilir”

**Takipleri sırasında;** < 500 mg/gün proteinüri ve normal idrar sediment varlığında,  
böbrek fonksiyonlarında bozulma olmadığı müddetçe renal biyopsiye gerek yoktur

## **Böbrek biyopsisinde LN'nin karakteristik bulguları**

- “Full house” biçiminde immün flöresan boyanma
- “Ekstraglomerüler immün tip depolanmalar”
- Glomerüler depolanmaların aynı anda mezenşiyum, subendotelyal ve subepitelyal alanlarda gösterilmesi
- “Tübüloretiküler inklüzyonlar”

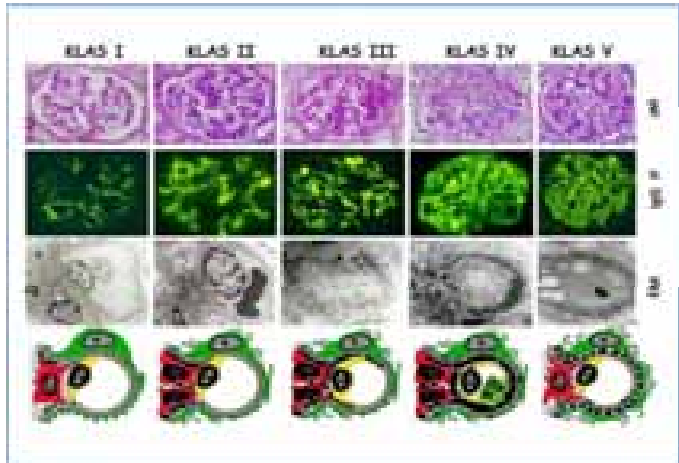
## Böbrek biyopsisinde LN'nin karakteristik bulguları

“**Full house**” biçiminde **immün flöresan boyanma**

**IgG** (daha belirgin), **IgA**, **IgM**, **C<sub>3</sub>** ve **C1q** (+)

**Ayırıcı tanı/**

Endokardit, HIV, HCV, Porto-sistemik şant, Post-streptokoksik GNF



*J Nephrol.* 2007;20(6):745.  
*Arthritis Rheum.* 2000;43(12):2801.



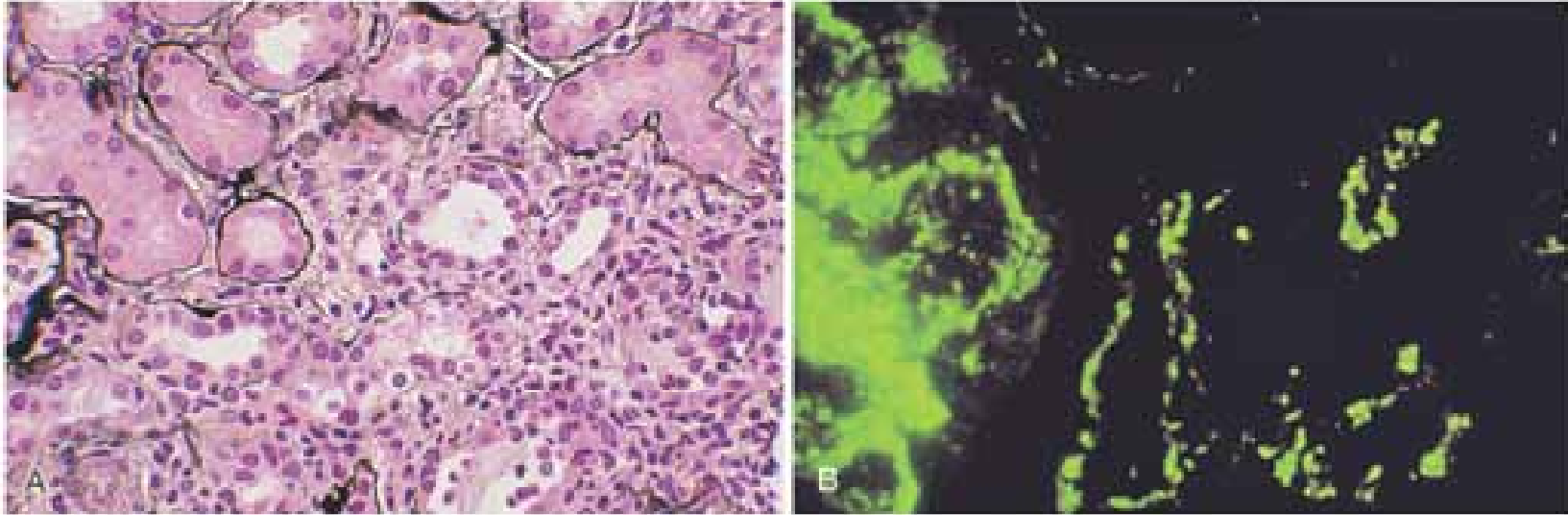
Figure 25.4 ISN/RPS class I minimal mesangial lupus nephritis. Light microscopy is normal, but immunofluorescence shows C1q localization associated with IgG and C3 throughout the mesangial area.

*Kidney Int.* 2005;67(4):1381.  
*Nephrol Dial Transplant.* 2001;16(11):2258.

## Böbrek biyopsisinde LN'nin karakteristik bulguları

Tübüler bazal membran, intersitisyum ve damarlarda

“Ekstraglomerüler immün tip depolanmalar”



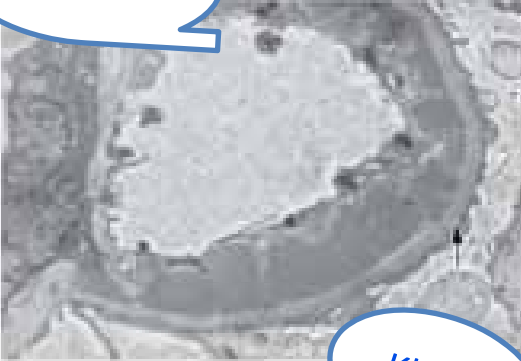
Tüm lupus nefritlerinde ortalama % 60-65 (+)  
Klas II'de % 20

Klas IV'de % 75

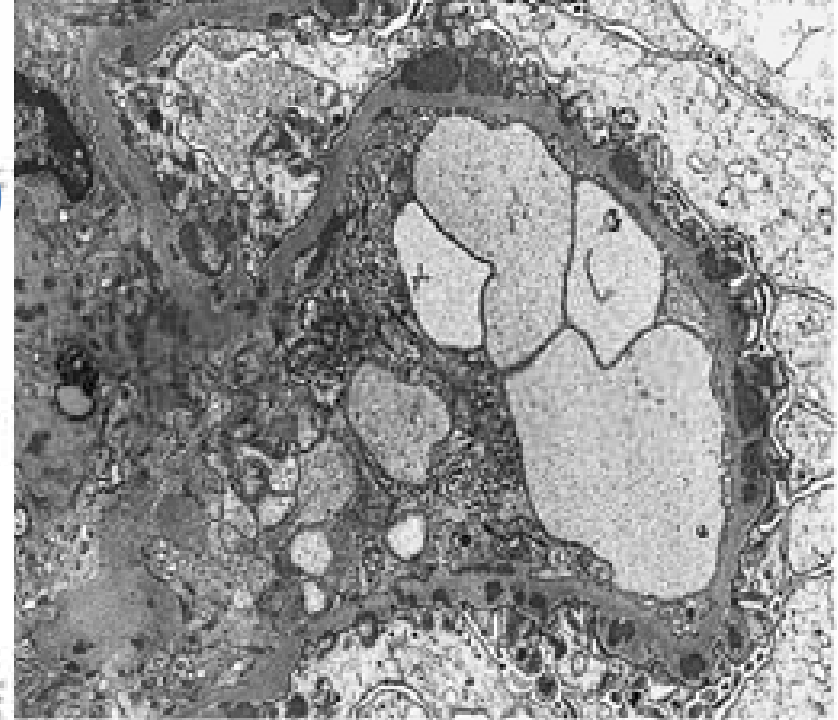
## Böbrek biyopsisinde LN'nin karakteristik bulguları

- Glomerüller depolanmaların aynı anda mezenşiyum, subendotelyal ve subepitelyal alanlarda görülmesi

Klas IV



Klas V LN, spike görüntü (gümüşleme)



Klas V



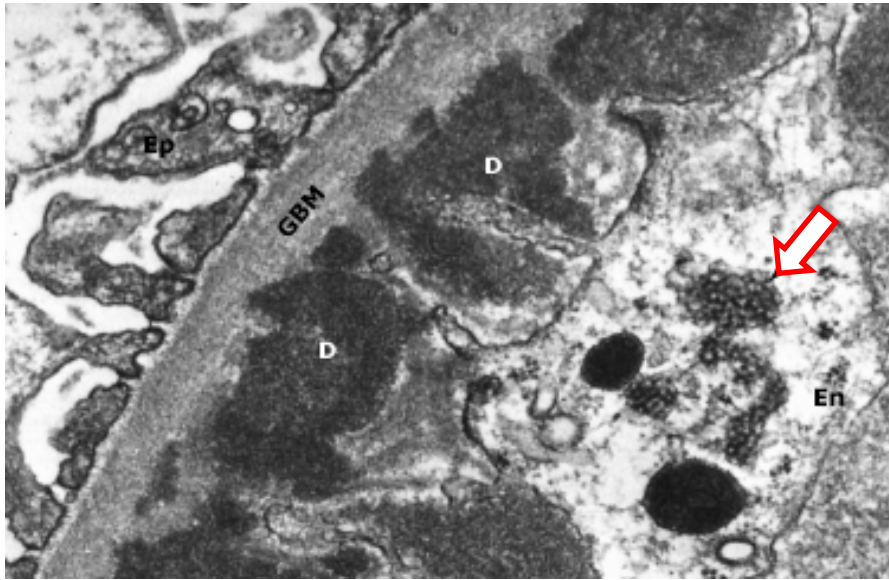
# Böbrek biyopsisinde LN'nin karakteristik bulguları

Glomerüler endotelial hücrelerinde

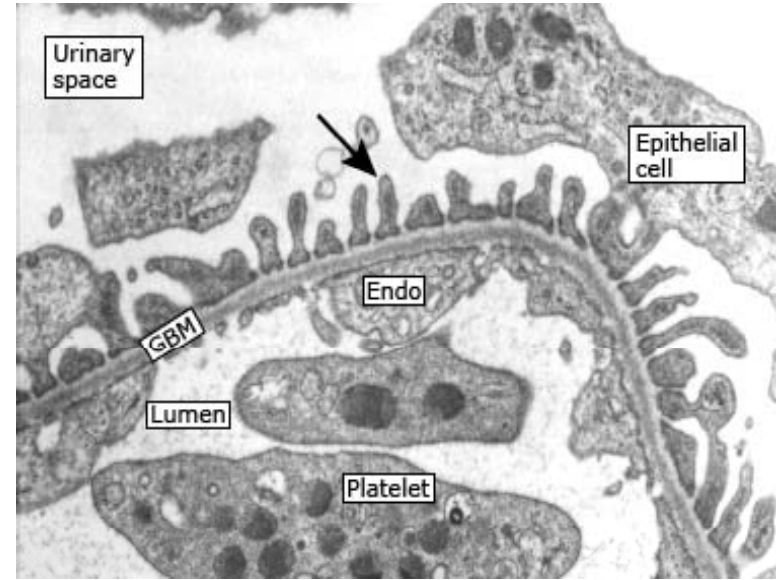
## “Tübüloretiküler inklüzyonlar”

**Ayırıcı tanı/**

HIV nefropati (  $\uparrow$  dolaşan  $\alpha$ -interferon, collapsing FS-GNF), alfa-INF tedavisi



Tübüloretiküler yapılanma (EM)



Normal glomerül (EM)

*J Clin Invest.* 1995;95(1):219.

## Lupus nefritinde progresyon ile ilişkili risk faktörleri

### Başlangıçta veya hastalığın seyrinde

- Serum kreatininde artış
- Hipertansiyon
- Nefrotik düzeyde proteinüri
- Anemi (Htc' in % 26'nın altında olması)
- Siyah ve hispanik ırk ve etnisite
- **Gecikmiş tedavi**
- Ciddi kronik tübulointerstisyel nefrit
- Kronik kresent varlığı
- **Biyopsiden önce, > 6 ay klinik tutulum bulgusunun olması**

*Am J Med.* 1987;83(5):877.

*Medicine (Baltimore).* 2010;89(5):300.

*Kidney Int.* 1994;45(2):544.

*Lupus.* 2005;14(11):890.

# İNDÜKSİYON TEDAVİSİ

**Klas I:** **Minimal Mezangial Lupus Nefriti**

**Klas II:** **Mezangial Proliferatif Lupus Nefriti**

**Klas III:** **Fokal Lupus Nefriti**

**Klas IV:** **Diffüz Lupus Nefriti**

**Klas V:** **Membranöz Lupus Nefriti**

**Klas VI:** **İleri Sklerozan Lupus Nefriti**  
≥%90 glomerülde global skleroz (rezidüel aktivite yok)



KDIGO Clinical Practice Guideline for Glomerulonephritis

VOLUME 2 | ISSUE 2 | JUNE 2012

<http://www.kidney-international.com>

**KDIGO, Kidney International Supplements (2012) 2, 221–232**



Annals of the Rheumatic Diseases

Ann Rheum Dis (2012) November, 71(11), 1771–1782  
Published online 2012 July 19, doi: 10.1093/rheumatism/kts049

CHESHIRE, ENGLAND

**Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis**

George R. Berthelot,<sup>1</sup> Maria Tzioumi,<sup>2</sup> Zahir Amoura,<sup>3</sup> Martin Aringer,<sup>4</sup> Inesora Espino,<sup>5</sup> Jo H M Barden,<sup>6</sup> John Borish,<sup>7</sup> Ruyard Cervera,<sup>8</sup> Thomas Chouh,<sup>9</sup> Andree Coma,<sup>10</sup> Fernando Fervenza,<sup>11</sup> Jürgen Floege,<sup>12</sup> Frederic A. Houssier,<sup>13</sup> John P A Isomaa,<sup>14</sup> David A Isenberg,<sup>15</sup> Cees G M Kosterberg,<sup>16</sup> Liu Lixia,<sup>17</sup> Stephan D Marks,<sup>18</sup> Alberto Masini,<sup>19</sup> Gabriela Moroni,<sup>20</sup> Ursula Neumann,<sup>21</sup> Manuel Plaza,<sup>22</sup> Mathias Schnitzler,<sup>23</sup> Argire Stancu,<sup>24</sup> Yasutaka Terao,<sup>25</sup> Carlos Vasconcelos,<sup>26</sup> Ronald C van Vollenhoven,<sup>27</sup> Yelena Zharava,<sup>28</sup> Marion Haubitz,<sup>29</sup> Carolina Gordon,<sup>30</sup> David Jayne,<sup>31</sup> and Gerardo J. Savigliani<sup>32</sup>

**EULAR/ERA-EDTA, Ann Rheum Dis 2012 November 71(11)-1771-1782**

**Table 39 | KDIGO nomenclature and description for grading recommendations**

Grade <sup>a</sup>	Implications		
	Patients	Clinicians	Policy
Level 1 "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

<sup>a</sup>The additional category "Not Graded" was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

**Table 37 | Final grade for overall quality of evidence**

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very Low	The estimate of effect is very uncertain, and often will be far from the truth.

**Table 38 | Balance of benefits and harm**

When there was evidence to determine the balance of medical benefits and harm of an intervention to a patient, conclusions were categorized as follows:

- **Net benefits** = the intervention clearly does more good than harm
- **Trade-offs** = there are important trade-offs between the benefits and harm
- **Uncertain trade-offs** = it is not clear whether the intervention does more good than harm
- **No net benefits** = the intervention clearly does not do more good than harm

## Klas I LN

Böbrek dışı bulguları (BDT) tedavi et **(2D)**

## Klas II LN

- ✓ **< 1 gr/gün proteinüri** varlığında BDT'a yönelik tedavi **(2D)**
- ✓ **> 3 gr/gün proteinüri** varlığında KS veya CNIs ile tedavi et (MDH için belirlenmiş olduğu gibi). **(2D)**

# PROLIFERATIF LN'DE İNDÜKSİYON TEDAVİSİ

GLUKOKORTIKOID (1A)

+

SIKLOFOSFAMİD (CYC) (1B) VEYA MIKOFENOLAT MOFETİL (MMF) (1B)

Geleneksel

Prednizon, 0.5 -1 mg/kg -gün p.o.

GLUKOKORTIKOID  
(1A)

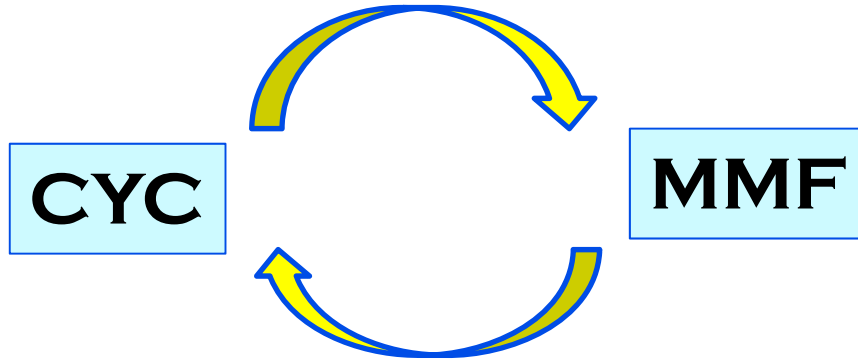
Ciddi aktif  
hastalık

Metil prednizolon, 500-1000 mg/gün, >30 dak. i.v.  
infüzyon , ardışık 3 gün

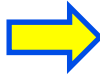
“Kortikosteridlerin doz ve süresi konusunda RKÇ yok”

# İNDÜKSİYON TEDAVİSİ

Tedavinin ilk 3 ayı boyunca renal klinik bozulma (kreatininde ve proteinüride artış) varsa



veya



Biyopsi tekrarla

2D

## KLASS III VE KLASS IV LN'DE BAŞLANGIÇ TEDAVİ MODELLERİ

REJİM	A NIH	B EURO-LUPUS	C PERORAL CYC	D MMF
<b>CYC</b>	i.v. CYC 0.5–1 g/m <sup>2</sup> , ayda 1, 6 ay	i.v. CYC 500 mg; her 2 haftada 1 kez, 3 ay	P.O. CYC 1.0–1.5 mg/kg/gün (maksimum doz 150 mg/g), 2–4 ay	—
<b>MMF</b>	—	—	—	6 ay 3 gr/gün'e kadar doz artımı
<b>Proliferatif LN'de RKÇ ile yararlarının gösterilmesi</b>	Evet	Evet	Evet	Evet
<b>Ciddi proliferatif LN'de RKÇ ile yararlarının gösterilmesi</b>	Evet	Denenmemiş	Denenmemiş	Denenmemiş
<b>Yorumlar</b>	Beyaz, siyah, Hispanik ve Çinli'lerde etkili.	Beyazlarda etkili, siyah, Hispanik, ve Çinli'lerde denenmemiş.	Beyaz, siyah ve Çinli'lerde etkili, İ.V. CYC'den daha ucuz ve kolay alım.	Beyaz, siyah, Hispanik, ve Çinli'lerde etkili. Yüksek maliyet.

Tüm rejimler kortikosteroid (0.5-1 ng/kg/gün, klinik yanıtı göre 6-12 ay boyunca doz azaltımı); ciddi olgularda İ.V. metil prednizolon eklenmesi  
KDIGO, Kidney International Supplements (2012) 2, 221–232

If adverse clinical/histological prognostic factors are present: glucocorticoids plus

MPA	2	B
Low-dose intravenous CY	4	C
High-dose intravenous CY	1	A
Oral CY	3	B

Use of glucocorticoids

Three consecutive pulses of intravenous methylprednisolone 500-750 mg	3	C
Then, oral prednisolone 0.5 mg/kg/day for 4 weeks with subsequent tapering	-	C

Pure class V nephritis with nephrotic-range proteinuria: glucocorticoids plus

MPA	2	B
High-dose intravenous CY	2	A
Cyclosporin (increased rates of relapse of nephrotic syndrome)	2	A
Tacrolimus	3	B
Rituximab	4	C

Azathioprine (AZA) use in LN

In selected patients without adverse clinical or histological prognostic factors

Class III-IV nephritis	2	B
Class V nephritis (non-nephrotic-range proteinuria)	4	C
When MPA or CY are contraindicated, not tolerated, or unavailable	-	C
Associated with higher relapse risk	2	B

Subsequent immunosuppression in class III-IV or V nephritis

MPA or AZA, in combination with low-dose glucocorticoids	1	A
Successful induction with MPA followed by continuing MPA	-	C
AZA preferred if pregnancy planned	-	C
Duration of immunosuppressive treatment: at least 3 years	3	C
Gradual drug withdrawal, glucocorticoids first, can then be attempted	-	C
Calcineurin inhibitors can be considered in pure class V nephritis	4	C

Failure to treatment with MPA or CY

Switch from MPA to CY	4	C
Switch from CY to MPA	4	C
Add or switch to rituximab	4	C

Rejim A  
NIH

## İndüksiyon tedavisi ile ilgili RKÇ'lar

### NIH çalışmaları (1B)

“ İ.V. CYC tedavisi yük.doz kortikosteroid (KS) tedavisine göre daha etkili ”

1. Austin III HA, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986;314: 614–619
2. Boumpas DT, et al. Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet* 1992; 340: 741–745
3. Steinberg AD, Steinberg SC. Long-term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. *Arthritis Rheum* 1991; 34:945–950.
4. Gourley MF, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. *Ann Intern Med* 1996; 125:549–557

Survival in Lupus and Lupus Nephritis			
5-Year Survival (percent)*			
Period	All Lupus	Lupus Nephritis	Class IV Nephritis
1953–1969	49	44	17
1970–1979	82	67	55
1980–1989	86	82	80
1990–1995	92	82	82
2000–2010	95–100	95–100	90–95

**Mortalite ve morbiditenin bir kısmından yüksek doz CYC ve KS sorumlu**

**Relaps** ↑

**SDBY** ↑

**Rezistans** ↑

**Yan etki -toksisite** ↑

## İ.V. Yüksek Doz CYC ile Pulse metil prednizolon yan etki profili

	IV CYC + P.O. Prednizolon -Kombinoterapi-	I.V. Pulse Metil prednizolon -Monoterapi-
Amenore	% 43	% 7.4
Servikal displazi	% 7.1	% 0
Herpes zoster	% 21	% 3.7
İnfeksiyon	% 32	% 7.4
Ölüm	% 5.8	% 0
Avasküler nekroz	% 9.2	% 16

Gourley MF, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. *Ann Intern Med.* 1996;125:549-557.

## 2002 Euro-Lupus Nephritis Trial (ELNT)

### Rejim B Euro-Lupus

Düşük doz i.v. CYC  
500 mg; her 2 haftada 1 kez,  
6 doz (3 ay),

Ort. Küm.doz **3 gr**

90  
hasta

### NIH protokolü

i.v. CYC, 0.5–1 g/m<sup>2</sup>, ayda 1,  
6 doz, 2 kez 3 ayda 1,  
maksimal 1500 mg/ay

Ort. Küm.doz **8.5 gr**

Prednison 0.5 mg/kg 2 haftada bir 2.5 mg azaltılarak 5-7.5 mg/gün, 30 ay

CYC kürlerinden sonra Azatiyoprin 2 mg/kg/gün

**Ortalama 41 ay sonraki renal sonuçlar**  
**Ve 10 yıl sonraki sonuçlar**

**Yanıt ve Relaps oranları benzer**  
**Enfeksiyon NIH'da daha fazla**

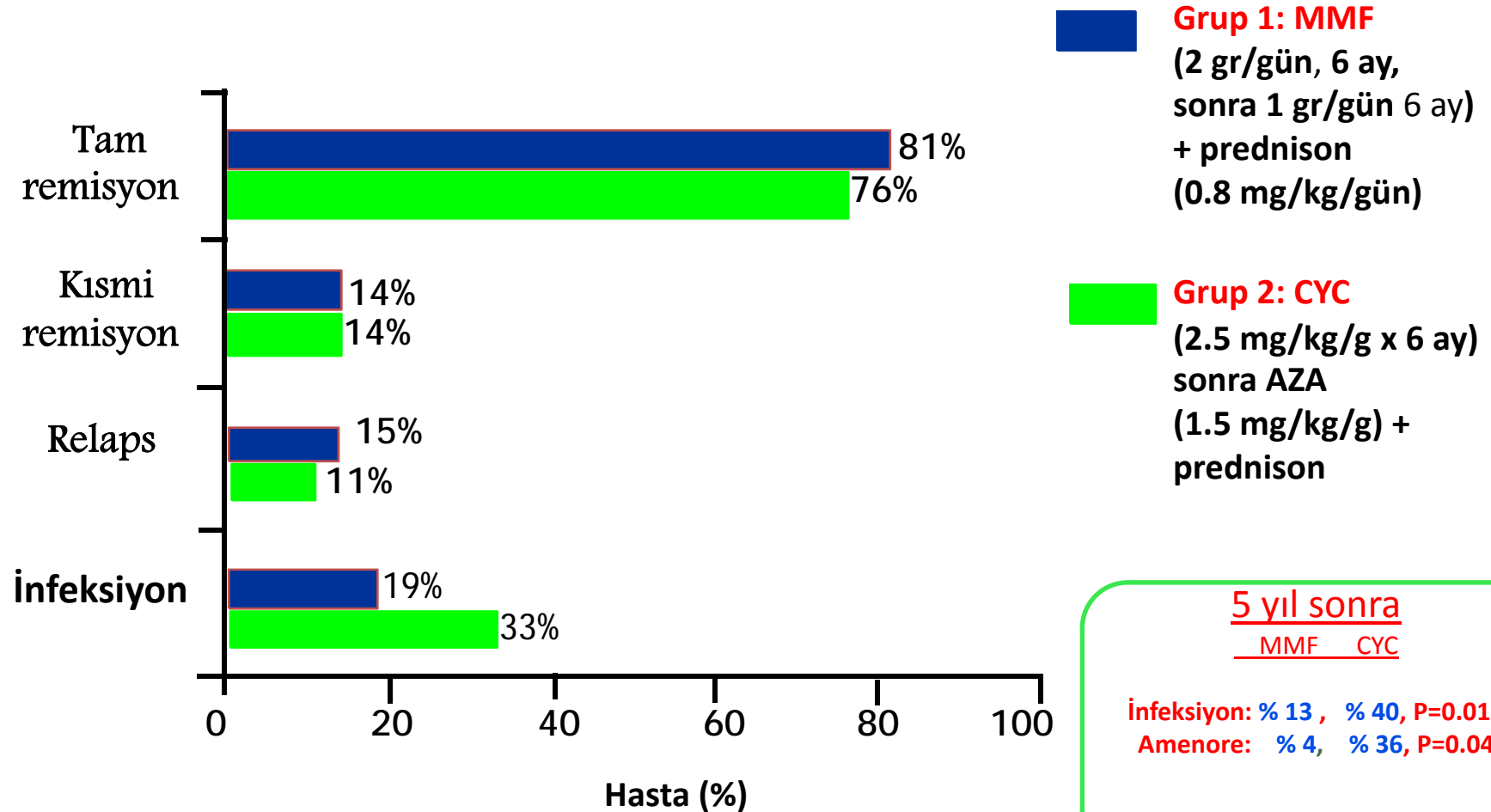
### Eksik yön:

Beyazlarda etkili, siyah, Hispanik, ve Çinli'lerde denenmemiş.  
Ciddi proliferatif lupusta denenmemiş

1. Houssiau FA, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002;46:2121–2131
2. Houssiau FA, et al. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. *Ann Rheum Dis* 2010; 69:61–64

# MMF ve Oral CYC'in 42 Diffuz Proliferatif Lupus Nefritli Hastada Etkinliđi

İlk RKÇ



Ölüm sadece CYC 'li grupta gözlenmiş (2 hasta %10)

# Şiddetli Lupus Nefritinin İndüksiyon Tedavisinde İ.V. CYC ve MMF (3 gr/gün)

2. RKÇ

140 hasta, çok merkezli, açık-etiketli, önceliksiz, randomize

(69 CYC, 71 MMF)

Klas IV, III, veya Miks III+V ve IV + V)

24 haftada

Primer sonuç:

Sekonder sonuç:

Tam remisyon

Kısmi remisyon(  $\geq 50\%$  iyileşme)

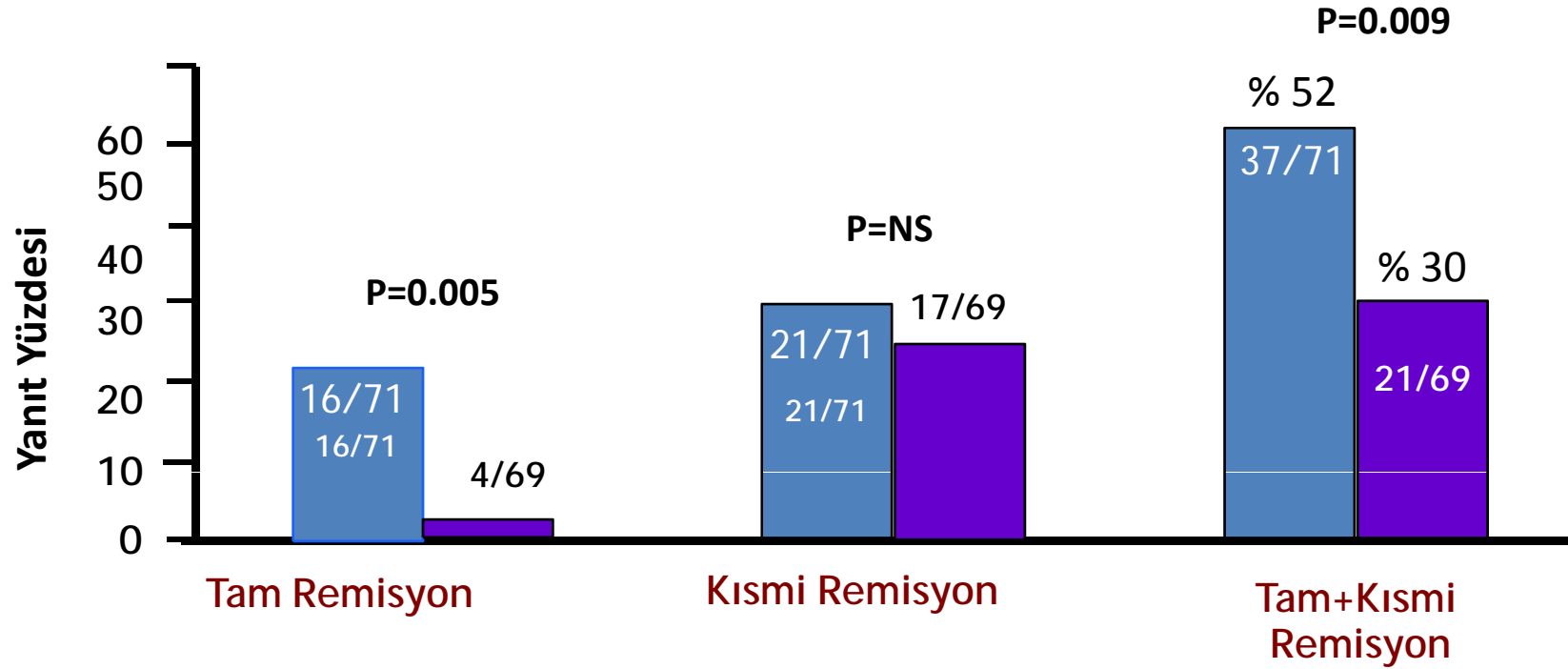
## Yan etki profili:

Piyojenik enfeksiyon **CYC** grubunda fdaha azla  
Diyare **MMF** grubunda daha fazla

Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. **N Engl J Med 2005; 353:2219–2228**

# Remisyon Oranı: MMF ve i.V. CYC

24. haftada



■ MMF ■ i.V. CYC

## Çalışmanın Geç Sonuçları

Ort. 37 ay izlem

	MMF	I.V. CYC
Renal Alevlenme	8	8
Renal Yetmezlik	4	7
Ölüm	4	8

p = NS

**Çalışmanın eksik yönü**

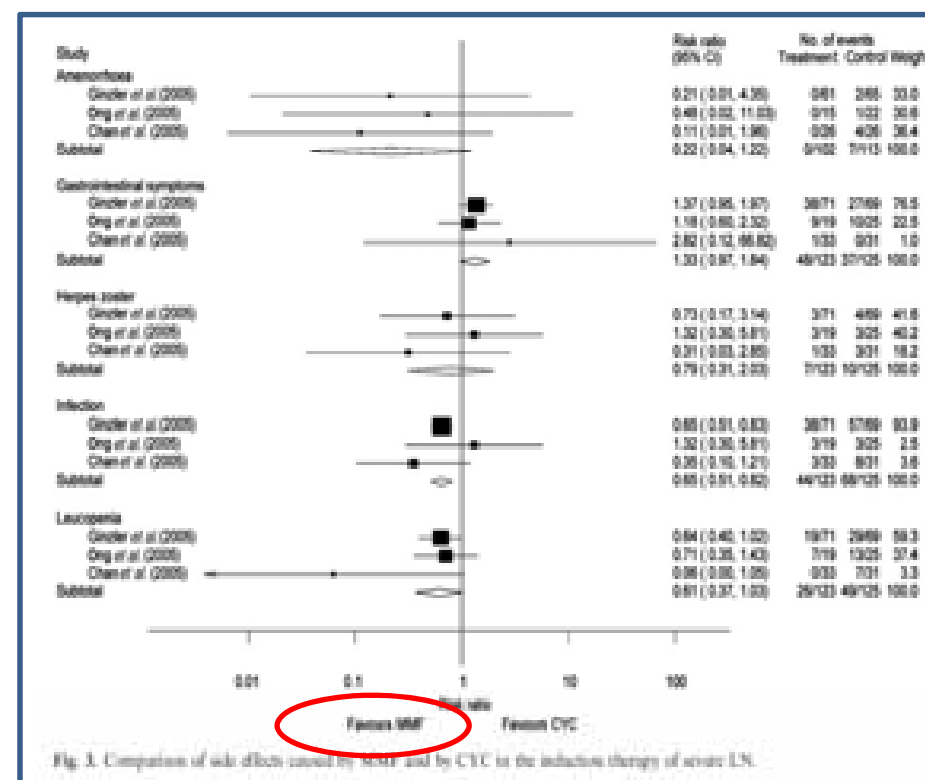
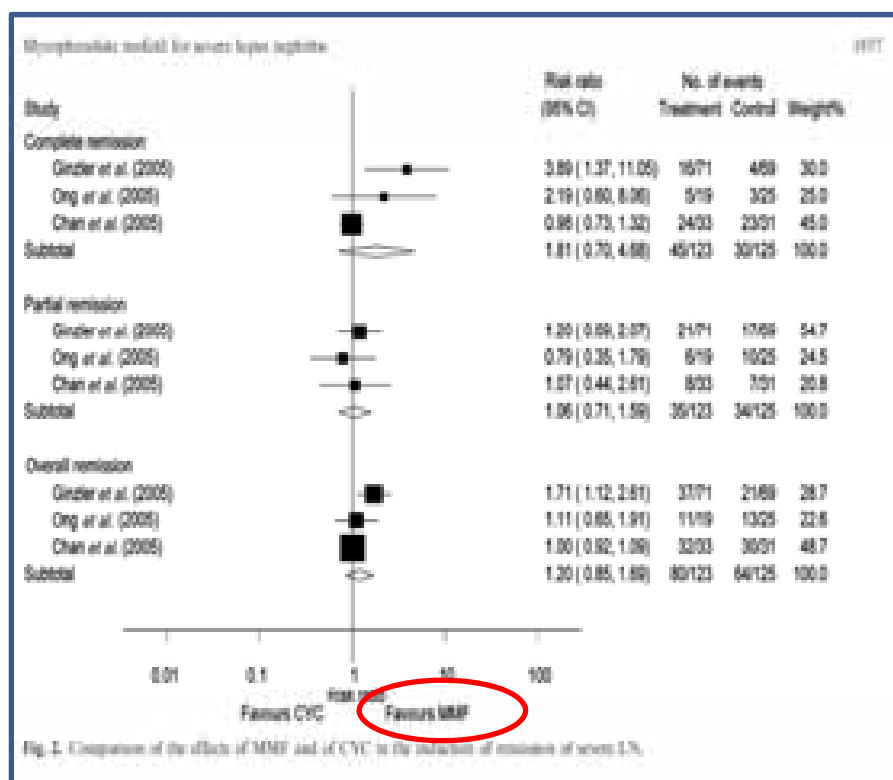


**Cross-over bir çalışma olması**

Original Article

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

Bin Zhu<sup>1,2</sup>, Nan Chen<sup>1</sup>, Yi Lin<sup>2</sup>, Hong Ren<sup>1</sup>, Wen Zhang<sup>1</sup>, WeiMing Wang<sup>1</sup>, XiaoXia Pan<sup>1</sup> and HaiJin Yu<sup>1</sup>



# ALMS indüksiyon tedavisi

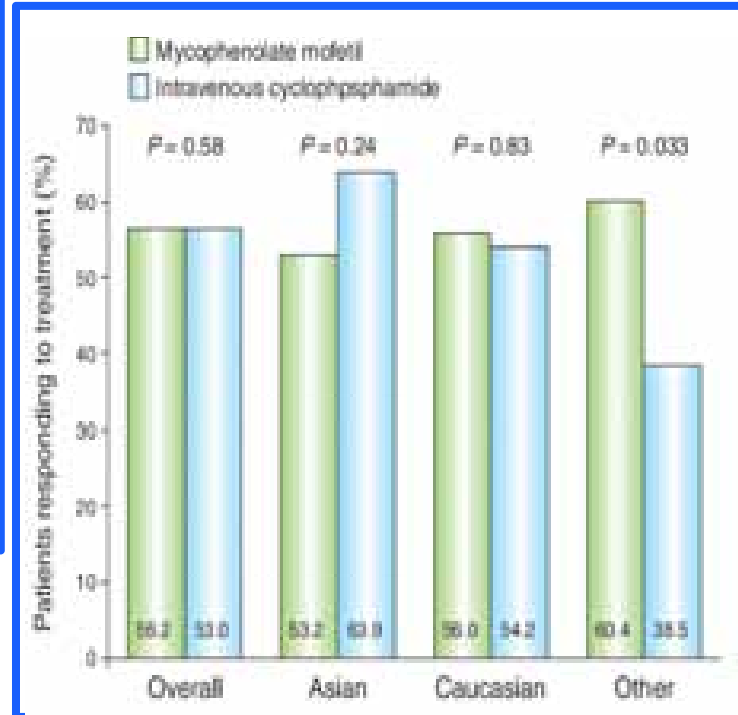
## Aspreva Lupus Management Study

**370 hasta, çok uluslu, RKC**

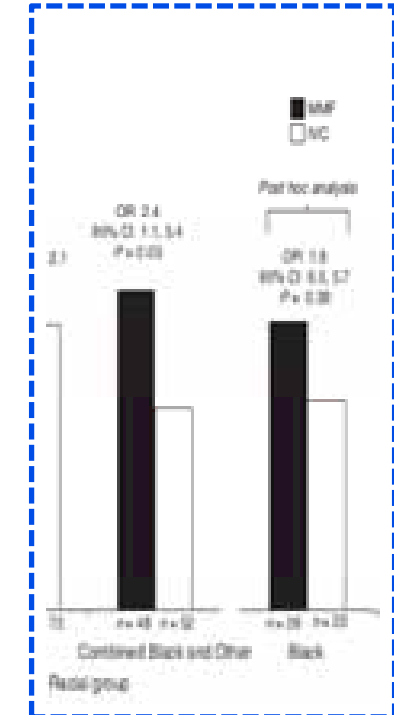
### Yan Etki

- Diyare** → MMF/CYC=%28/%12
- Bulantı** → CYC/MMF=%45/%37
- Kusma** → CYC/MMF=%14/%13
- Alopesi** → CYC/MMF=%35/%10
- Mortalite** → MMF/CYC=%5/%3 (NS)

### 24. Hafta indüksiyon tedavisi sonuçları



### İrk/etnisite yanıtı



Alt grup analizinde;

**KrKI < 30 ml/dak olanlarda MMF CYC'den daha az etkili**

## Klass V (membranöz) Lupus nefritinde tedavi

Proliferatif lezyonların eşlik ettiği Klass V LN tedavisi proliferatif LN gibi olmalıdır

- Sadece; SLE'nin böbrek dışı tutulumunda steroid + immünosüpresif tedavi (2D)
- Saf Klass V LN ve **kalıcı** nefrotik proteinüri ;  
**Kortikosteroid + ek immünosüpresif tedavi**  
**CYC (2C)**  
**CNI (2C)**  
**MMF (2D)**  
**AZA (2D)**

If adverse clinical/histological prognostic factors are present: glucocorticoids plus

MPA	2	B
Low-dose intravenous CY	4	C
High-dose intravenous CY	1	A
Oral CY	3	B

Use of glucocorticoids

Three consecutive pulses of intravenous methylprednisolone 500-750 mg	3	C
Three oral prednisolone 0.5 mg/kg/day for 4 weeks with subsequent tapering	4	C

Pure class V nephritis with nephrotic-range proteinuria: glucocorticoids plus

MPA	2	B
High-dose intravenous CY	2	A
Cyclosporin (increased rates of relapse of nephrotic syndrome)	2	A
Tacrolimus	3	B
Rituximab	4	C

Azathioprine (AZA) use in LN

In selected patients without adverse clinical or histological prognostic factors

Class III-IV nephritis	2	B
Class V nephritis (non-nephrotic-range proteinuria)	4	C
When MPA or CY are contraindicated, not tolerated, or unavailable	-	C
Associated with higher relapse risk	2	B

Subsequent immunosuppression in class III-IV or V nephritis

MPA or AZA, in combination with low-dose glucocorticoids	1	A
Successful induction with MPA followed by continuing MPA	-	C
AZA preferred if pregnancy planned	-	C
Duration of immunosuppressive treatment: at least 3 years	3	C
Gradual drug withdrawal, glucocorticoids first, can then be attempted	-	C
Calcineurin inhibitors can be considered in pure class V nephritis	4	C

Failure to treatment with MPA or CY

Switch from MPA to CY	4	C
Switch from CY to MPA	4	C
Add or switch to rituximab	4	C

# TİP V LUPUS NEFRİTİ

MMF 2-3 gm/gün, 6 ay



0.5-1 gr/gün Prednizon

Haftalar içerisinde en düşük etkili doz

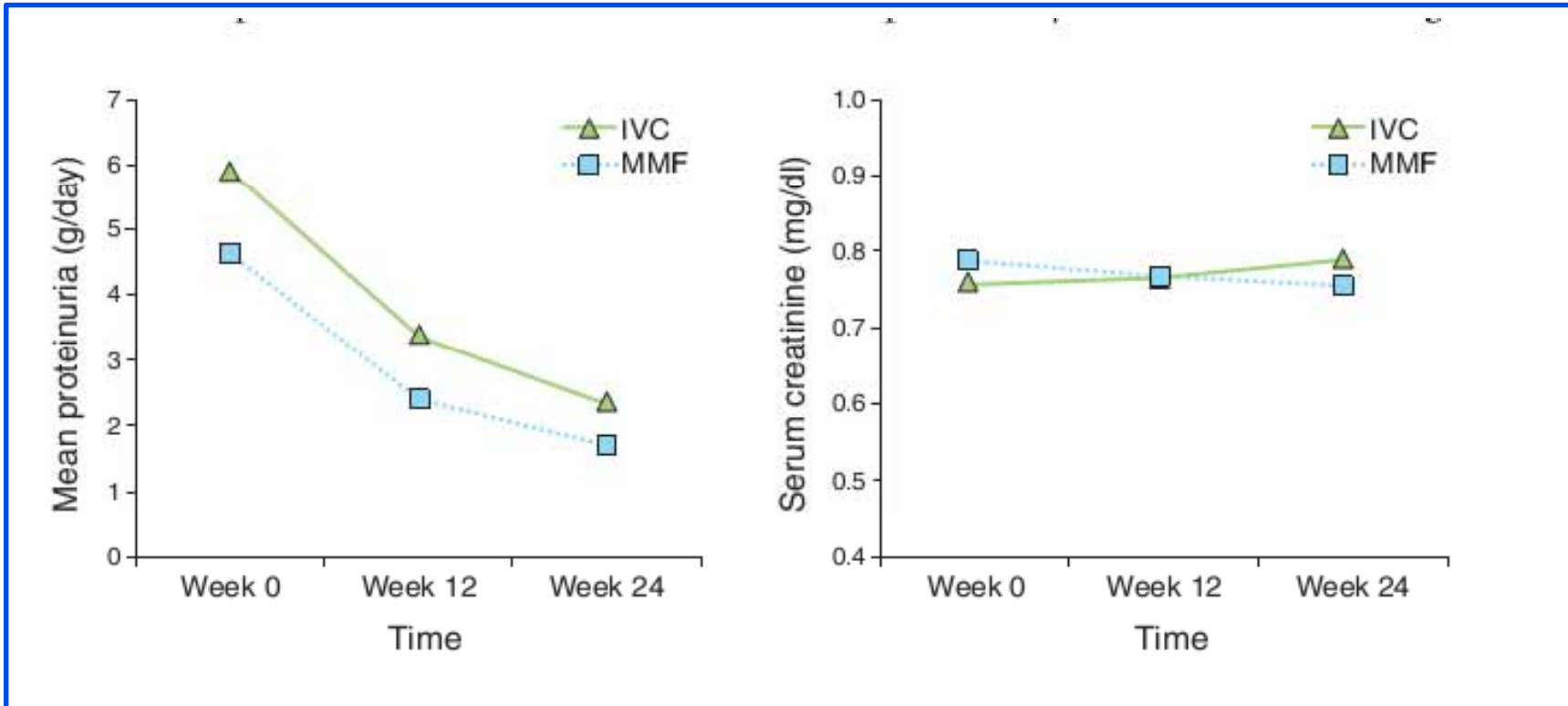
Düzelme var

MMF 1-2 gm/gün  
Veya  
AZA 2 mg/kg/gün  
+/- düşük doz prednizon

Düzelme yok

500-1000 mg/ m<sup>2</sup> CYC  
+  
GK i.V. puls 3 gün, ardından  
0.5-1 gm/gün Prednizon p.o.

**Ginzler (140) + ALMS (370) çalışmasındaki 510 hastadan  
84 saf membranöz LN hastasında**



Radhakrishnan J, et al: Mycophenolate mofetil and intravenous cyclophosphamide are similar as induction therapy for class V lupus nephritis. [Kidney Int 77: 152–160, 2010](#)

## **KDIGO,**

CYC toksisitesini azaltmak için;

**KrKI** → 25-50 ml/dak ise dozu **% 20** azaltılmalı  
10-25 ml/dak ise dozu **% 30** azaltılmayı önermektedir.

**Ref./** Haubitz M, et al. Cyclophosphamide pharmacokinetics and dose requirements in patients with renal insufficiency. *Kidney Int* 2002; 61: 1495–1501.

## **KDIGO,**

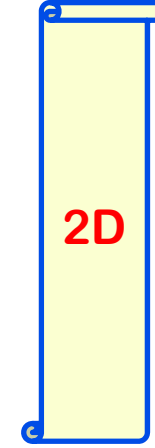
Malignite riskinden dolayı;

**SLE hastalarında siklofosfamidi bir ömür boyunca en fazla 36 gram almalarını önermektedir.**

**Ref./** Faurischou M, et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. *J Rheumatol* 2008;35: 100–105

## Başlangıç tedavilerine yanıt vermeyenlerde

- Rituksimab
- İ.V. İmmünglobulin
- CNIs
  - > Siklosporin (2.5 mg/kg/gün)
  - > Takrolimus (3 mg/gün)



Ref./Küçük gözlemsel çalışmalar

**KDIGO: Kidney International Supplements (2012) 2, 221–232**

### **DİĞER TEDAVİLER:**

Çoklu hedef tedavisi (MMF + Takrolimus + steroids)

Plazmaferezis / Tüm lenfosit ışınlama / İmmünablasyon ( anti-timosit globulin + yüksek doz İ.V. CYC) ± Otolog kemik iliği transplantasyonu

If adverse clinical/histological prognostic factors are present: glucocorticoids plus

MPA	2	B
Low-dose intravenous CY	4	C
High-dose intravenous CY	1	A
Oral CY	3	B

Use of glucocorticoids

Three consecutive pulses of intravenous methylprednisolone 500-750 mg	3	C
Then, oral prednisolone 0.5 mg/kg/day for 4 weeks with subsequent tapering	-	C

Pure class V nephritis with nephrotic-range proteinuria: glucocorticoids plus

MPA	2	B
High-dose intravenous CY	2	A
Cyclosporin (increased rates of relapse of nephrotic syndrome)	2	A
Tacrolimus	3	B
Rituximab	4	C

Azathioprine (AZA) use in LN

In selected patients without adverse clinical or histological prognostic factors

Class III-IV nephritis	2	B
Class V nephritis (non-nephrotic-range proteinuria)	4	C
When MPA or CY are contraindicated, not tolerated, or unavailable	-	C
Associated with higher relapse risk	2	B

Subsequent immunosuppression in class III-IV or V nephritis

MPA or AZA, in combination with low-dose glucocorticoids	1	A
Successful induction with MPA followed by continuing MPA	-	C
AZA preferred if pregnancy planned	-	C
Duration of immunosuppressive treatment: at least 3 years	3	C
Gradual drug withdrawal, glucocorticoids first, can then be attempted	-	C
Calcineurin inhibitors can be considered in pure class V nephritis	4	C

Failure to treatment with MPA or CY

Switch from MPA to CY	4	C
Switch from CY to MPA	4	C
Add or switch to rituximab	4	C

# Siklosporin ile induksiyon tedavileri- 1

## 1. Randomize çalışma / 40 steroid dirençli proliferatif LN olguya

A-	Siklosporin (5 mg/kg/gün)	+	Prednizon (2 mg/kg/gün)
B-	Siklofosfamid p.o.(2 mg/kg/gün)	+	Prednizon (2 mg/kg/gün)

### SONUÇ: 1. Yıl sonunda benzer proteinüri ↘

Fu LW et al. Clinical efficacy of cyclosporin A neoral in the treatment of paediatric lupus nephritis with heavy proteinuria.

Br J Rheumatol 1998; 37:217–221.

## 2. Randomize çalışma -NIH/ Membranöz LN' li 42 hasta

A-	Siklosporin + Prednizon / 11 ay
B-	İ.V. Siklofosfamid (6 doz: 2 ayda 1 ) + Prednizon
C-	Gün aşırı prednizon tek başına

### SONUÇ: 1. Yıl sonunda kümülatif remisyonlar :

**Siklosporin % 83 (daha hızlı remisyon) , CYC % 60 ( daha az rölaps), Prednizon % 27**

Austin HA et al. Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. J Am Soc Nephrol 2009; 20:901–911.

## Siklosporin ile induksiyon tedavileri-2

**En son Randomize çalışma** / 40 yetişkin yeni tanı proliferatif LN olguya

A-Siklosporin (4-5 mg/kg/gün) + Prednizon / 9 ay

B-Siklofosfamid İ.V. (10 mg/kg/ay) + Prednizon / 9 ay

**SONUÇ:**

**1. Yıl sonunda tam remisyonlar :**

**Siklosporin % 69, İ.V. CYC % 38 ( p=0.06),**

**CYC durağan veya düzelmiş kreatinin açısından daha etkili  
( % 86'a % 47)**

Zavada J et al. Cyclosporine A or intravenous cyclophosphamide for lupus nephritis: the Cyclofa-Lune study.  
**Lupus 2010; 19:1281-1289.**

# Takrolimus ile indüksiyon tedavileri

## Çin ve Japon hastalarında yapılan açık etiketli pilot çalışmalar:

1--Mok CC, et al. Tacrolimus for induction therapy of diffuse proliferative lupus nephritis: an open-labeled pilot study.

*Kidney Int* 2005;68:813–817.

2-Tse KC,, et al. A pilot study on tacrolimus treatment in membranous or quiescent lupus nephritis with proteinuria resistant to angiotensin inhibition or blockade. *Lupus* 2007; 16:46–51.

3-Tanaka H,, et al. Effective treatment of young patients with pediatric-onset, long-standing lupus nephritis with tacrolimus given as a single daily dose: an open-label pilot study. *Lupus* 2007; 16:896–900.

4-Szeto CC,, et al. Tacrolimus for the treatment of systemic lupus erythematosus with pure class V nephritis. *Rheumatology (Oxford)* 2008; 47:1678–1681.

**RKÇ-1** / Çinli 81 hasta/Takrolimus+ Steroid/Yüksek doz İ.V. CYC+ Steroid

**SONUÇ: 6. AYDA Tam remisyon**

Takrolimus → % 58 ; İ.V. CYC → % 39

Chen W, et al. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: a multicenter randomized clinical trial. *Am J Kidney Dis* 2011; 57:235–244.

**RKÇ-2** / 60 hasta/Takrolimus+ Steroid / MMF+ Steroid/ Yüksek doz İ.V. CYC+ Steroid

**SONUÇ: 24. hafta**

**Tam remisyon** Takrolimus → % 45 ; MMF → %40 ; İ.V. CYC → % 30

**Kümülatif remisyon:** Takrolimus → % 75 ; MMF → %70 ; İ.V. CYC → % 60

**Yan etki profilleri istatistiksel olarak benzer**

**Takrolimus grubunda daha hızlı serum albumin düzelmesi ve proteinüri azalması**

Li X, et al. Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. *Nephrol Dial Transplant* 2012; 27:1467–1472.

# A Meta-Analysis of Randomized Controlled Trials Comparing Tacrolimus with Intravenous Cyclophosphamide in the Induction Treatment for Lupus Nephritis

Jin Deng,<sup>1</sup> Dongmei Huo,<sup>2</sup> Qiaoyuan Wu,<sup>2</sup> Zhenhua Yang<sup>2</sup> and Yunhua Liao<sup>2</sup>

Tacrolimus Versus Cyclophosphamide for Lupus Nephritis

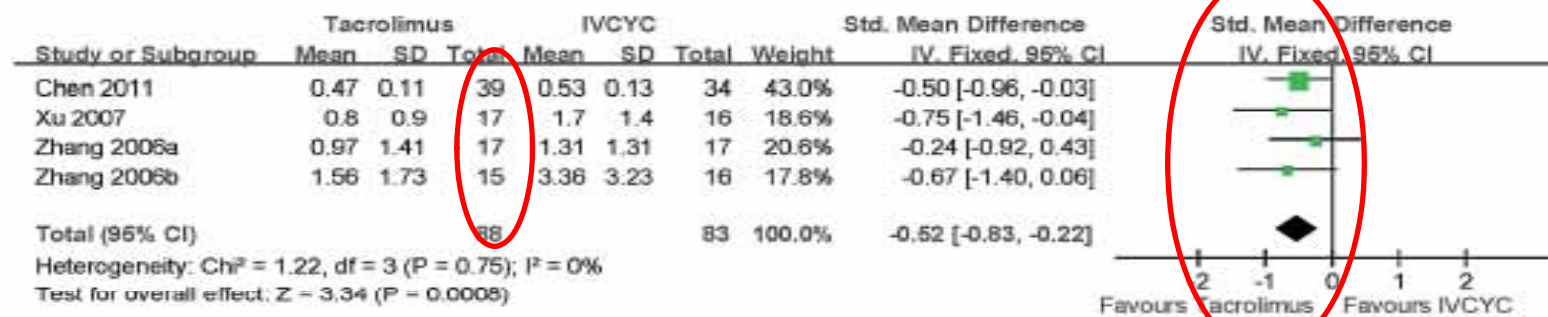


Fig. 3. Forest plot of studies comparing the effect of tacrolimus versus IVC on urine protein in LN.

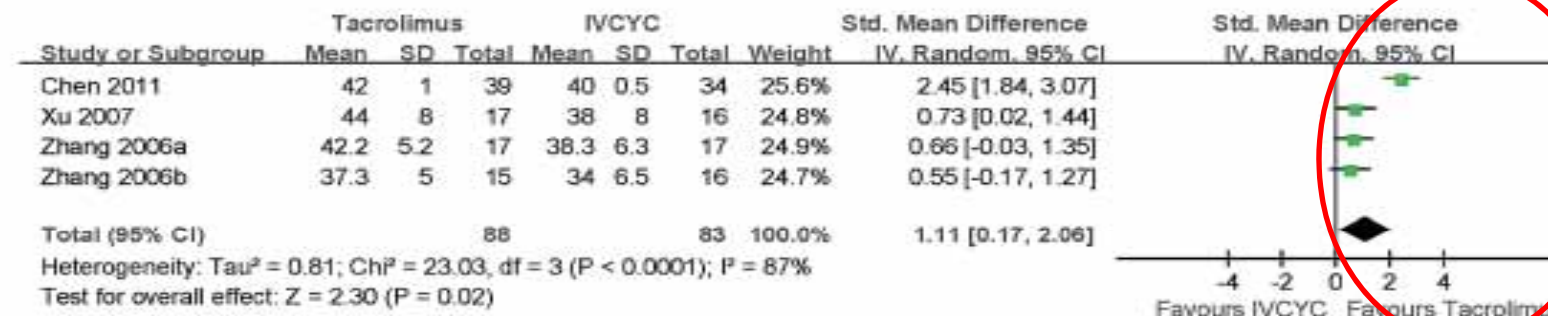


Fig. 4. Forest plot of studies comparing the effect of tacrolimus versus IVC on serum albumin in LN.

# LUPUS NEFRİTİ

## Tanı ve İndüksiyon tedavisi



*Dr. Mansur Kayataş*

Cumhuriyet Üniversitesi Tıp Fakültesi  
Nefroloji Bilim Dalı



## Recommendation

**Table 2** Category of evidence and strength of statements<sup>a</sup>

Statement/item	Level of evidence	Strength of statement
<b>1. Indications for first renal biopsy</b>		
Diagnostic value of urinary findings (proteinuria $\geq 0.5$ g/24 h especially with glomerular haematuria and/or cellular casts)	2	C
Clinical, serological or laboratory tests correlate modestly with renal biopsy findings	2	B
<b>2. Pathological assessment of kidney biopsy</b>		
International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification system preferred	2	C
Prognostic value of glomerular changes	1	A
Prognostic value of activity and chronicity indices	1	A
Prognostic value of tubulointerstitial lesions	2	B
Prognostic value of vascular lesions associated with anti-phospholipid antibodies	3	C
<b>3. Indications for immunosuppressive treatment and treatment strategy</b>		
Diagnostic renal biopsy required	–	C
Immunosuppression for class III <sub>A</sub> or III <sub>A/C</sub> ( $\pm$ V) and IV <sub>A</sub> or IV <sub>A/C</sub> ( $\pm$ V) nephritis	1	A
Immunosuppression for class V nephritis if proteinuria $> 1$ g/24 h	4	C
Target: preservation of renal function, prevention of disease flares, avoidance of treatment-related harms and improved quality of life and survival	–	C
Prognostic value of complete renal response (UPCR $< 50$ mg/mmol and normal or near-normal GFR)	1	B
Prognostic value of partial renal response ( $\geq 50\%$ reduction in proteinuria and normal or near-normal GFR)	1	B
<b>4. Treatment of adult lupus nephritis (LN)</b>		
Class III <sub>A</sub> or IV <sub>A/C</sub> ( $\pm$ V) and class IV <sub>A</sub> or IV <sub>A/C</sub> ( $\pm$ V): glucocorticoids plus		
Mycophenolic acid (MPA)	1	A†
Low-dose intravenous cyclophosphamide (CY)	1	B

If adverse clinical/histological prognostic factors are present: glucocorticoids plus

MPA	2	B
Low-dose intravenous CY	4	C
High-dose intravenous CY	1	A
Oral CY	3	B

Use of glucocorticoids

Three consecutive pulses of intravenous methylprednisolone 500-750 mg	3	C
Three oral prednisolone 0.5 mg/kg/day for 4 weeks with subsequent tapering	4	C

Pure class V nephritis with nephrotic-range proteinuria: glucocorticoids plus

MPA	2	B
High-dose intravenous CY	2	A
Cyclosporin (increased rates of relapse of nephrotic syndrome)	2	A
Tacrolimus	3	B
Rituximab	4	C

Azathioprine (AZA) use in LN

In selected patients without adverse clinical or histological prognostic factors

Class III-IV nephritis	2	B
Class V nephritis (non-nephrotic-range proteinuria)	4	C
When MPA or CY are contraindicated, not tolerated, or unavailable	-	C
Associated with higher relapse risk	2	B

Subsequent immunosuppression in class III-IV or V nephritis

MPA or AZA, in combination with low-dose glucocorticoids	1	A
Successful induction with MPA followed by continuing MPA	-	C
AZA preferred if pregnancy planned	-	C
Duration of immunosuppressive treatment: at least 3 years	3	C
Gradual drug withdrawal, glucocorticoids first, can then be attempted	-	C
Calcineurin inhibitors can be considered in pure class V nephritis	4	C

Failure to treatment with MPA or CY

Switch from MPA to CY	4	C
Switch from CY to MPA	4	C
Add or switch to rituximab	4	C

# *SLE'de böbrek bulguları*

Belirtiler	Prevalans (%)
<b>Proteinüri</b> Nefrotik sendrom	<b>100</b> <b>45-65</b>
<b>Hematüri</b> Mikrohematüri Eritrosit silendiri Makrohematüri	<b>80</b> <b>10</b> <b>1-2</b>
<b>Hücre silindirler</b>	<b>30</b>
<b>Renal fonksiyonlarda azalma</b> RPGN ABH	<b>40-80</b> <b>10-20</b> <b>1-2</b>
<b>Hipertansiyon</b>	<b>15-50</b>
<b>Hiperpotasemi</b>	<b>15</b>
<b>Tübüler anormallikler</b> (genellikle asemptomatik)	<b>60-80</b>

1. Appel GB, et al. Kidney Int. 2006;70:1403-1412.
2. Contreras G, et al. Clin Nephrol. 2002;57:95-107.
3. D'Agati V, et al. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2007, Chapter 55.
4. Appel GB. In: Brenner B, ed. The Kidney. Philadelphia: Saunders Elsevier; 2008:1067-1147.

## LN'de tedaviye yanıtın değerlendirilmesi

**Tam yanıt:** Serum kreatininin normale dönmesi

+

< 500mg/gün (50 mg/mmol) proteinüri

**Kısmi yanıt:** Serum kreatininde stabilizasyon ( $\pm$  % 25) veya düzelme, ancak normale gelememe + proteinüride  $\geq$  % 50 azalma ve NS varsa + proteinüri < 3 gr/gün

**Bozulma:** Tedavi yetersizliğinin kesin kriterleri belirlenmemiştir .

Serum kreatininde  $\geq$  % 25 yaygın kullanılır; ancak, geçerli olmamıştır.

## SLE tanısı için yönlendirilecek sorular

- ✓ 3 aydan daha fazla süren artrit veya romatizamal bir şikayetiniz var mı?
- ✓ Soğuğa maruz kalındığında parmaklarınızda solma, uyuşma veya bir rahatsızlık hissi oluyor mu?
- ✓ 2 haftadan daha uzun süren ağız yaranız oldu mu?
- ✓ Tam kan sayımınızda size hiç düşük değerlerinizin (anemi, düşük lökosit, düşük trombosit) olduğu söylendi mi?
- ✓ Yanaklarınızda 1 aydan daha fazla süren belirgin bir döküntünüz oldu mu?
- ✓ Güneşe çıktığınızda cildiniz kızarır mı ? (güneş yanığı değil)
- ✓ Hiç bir kaç gün süren derin nefes almakla göğüste batma hissiniz oldu mu (Plörezi)?
- ✓ Hiç size idrar tetkikinizde protein olduğu söylendi mi?
- ✓ Hiç çok hızlı saç kaybı yaşadınız mı?
- ✓ Hiç nöbet ,konvülsiyon veya buna benzer bir durum yaşadınız mı?

➤ Üç veya daha fazla soruya evet yanıtı varsa, SLE olasıdır ve ANA istenmelidir.

## Tam immünolojik remisyon

- İnaktif idrar sedimenti
    - $\leq 5$  eritrosit /BBA
    - $\leq 5$  lökosit /BBA
    - Dipstik 0-1+ heme
    - Eritrosit silendir (-)
  - Normal serum kreatinini
  - $< 500$  mg/gün proteinüri
- } İrreversibil hasarlanmada aranmaz

## The Lupus Nephritis Assessment with Rituximab trial

### LUNAR

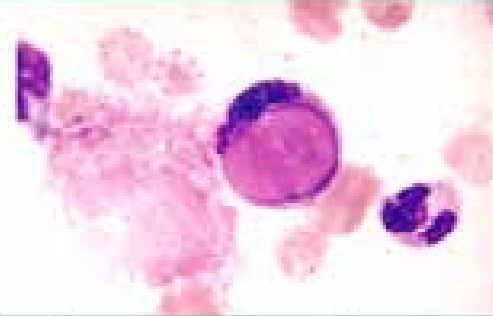
- Tam doz MMF (3 g/gün'e kadar) + Kortikosteroid alan Ciddi lupus nefritli 140 hastaya
- Rituksimab veya plasebo verildi
- 1 yıl sonra primer ve sekonder sonlanım sonuçları arasında fark yoktu

Merrill JT, et al. The randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum* 2010, 62: 222–233,

# Popülasyon taramalarında;

Bir kişide **ANA** negatif ise,  
**LUPUS** olasılığı < % 0.14

Circulating "LE Cell" in systemic lupus erythematosus



Blood smear from a patient with systemic lupus erythematosus showing a classical LE cell in which a viable neutrophil has ingested nuclear material. Note the nuclear debris and an adjacent normal neutrophil and the nuclear debris.  
Courtesy of the American College of Rheumatology.

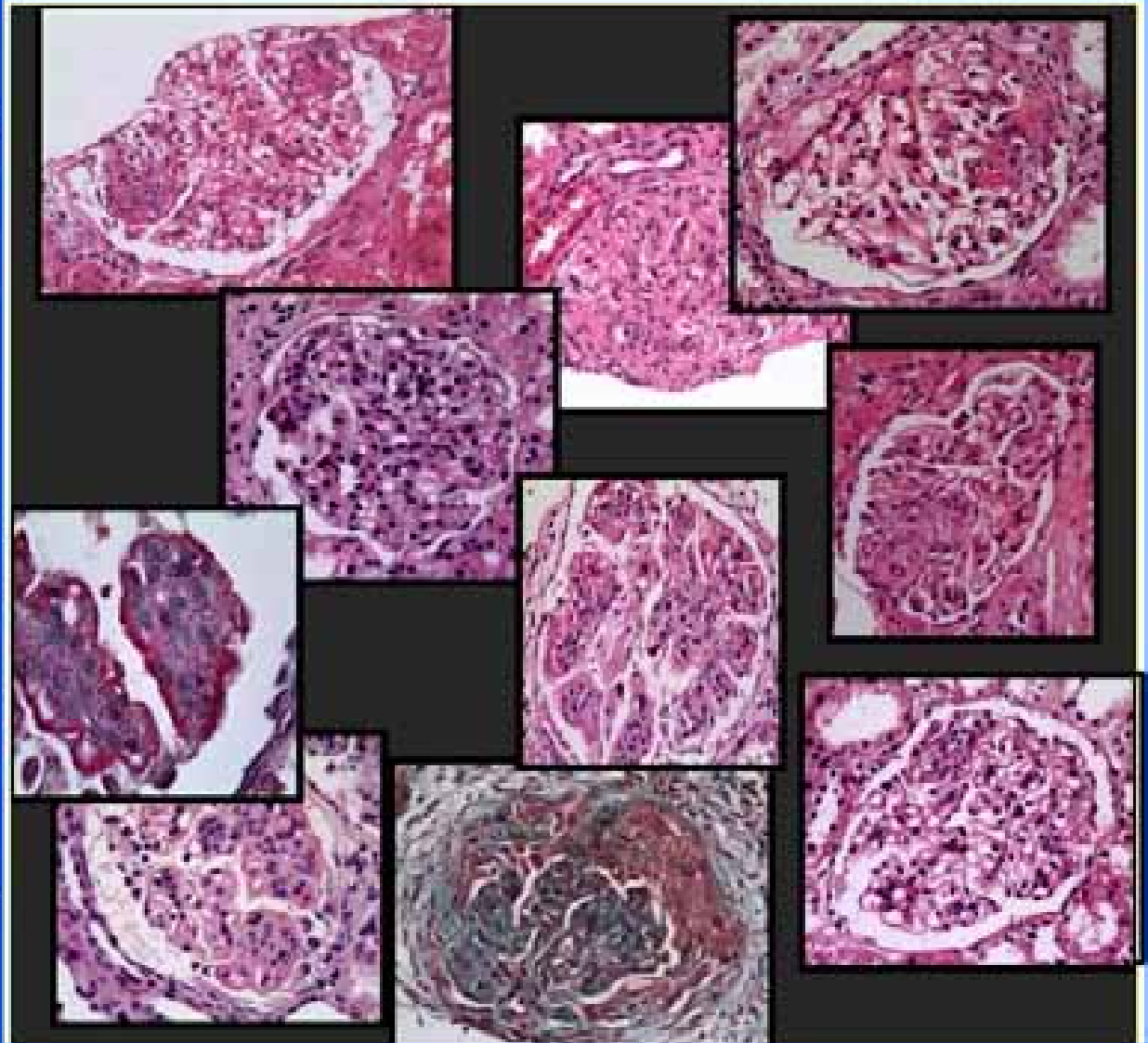
**Shiel WC Jr, Jason M.** The diagnostic associations of patients with antinuclear antibodies referred to a community rheumatologist. **J Rheumatol.** 1989;16(6):782.

# 2003 ISN / RPS Klasifikasyonu

## Işık Mikroskopi ve IFM bulgularına adapte edilen tanımlamalar

### Terminoloji

Diffüz
Fokal
Segmental
Global
Mezangial hiperselülarite
Endokapiller proliferasyon
Ekstrakapiller proliferasyon (selüler kresent)
Karyoreksis
Nekroz
Hyalin trombi
Etkilenen glomerül oranı



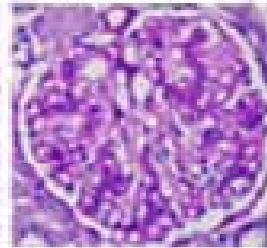
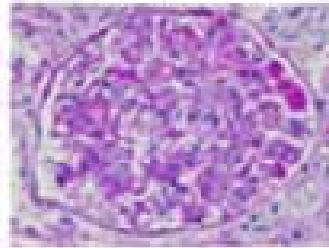
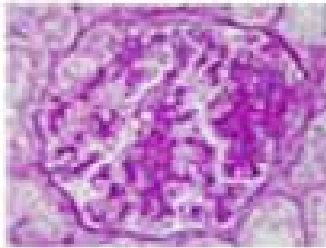
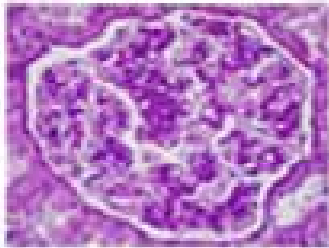
KLAS I

KLAS II

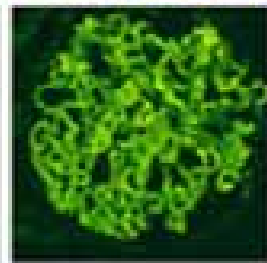
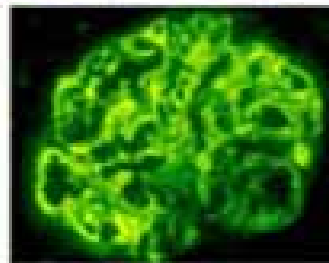
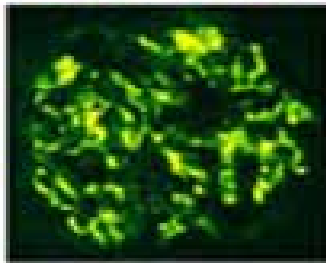
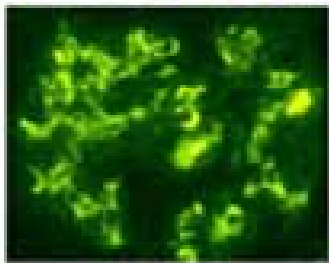
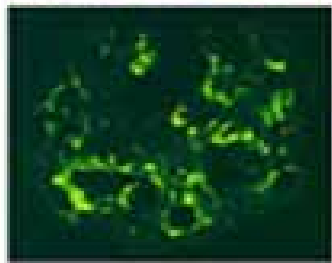
KLAS III

KLAS IV

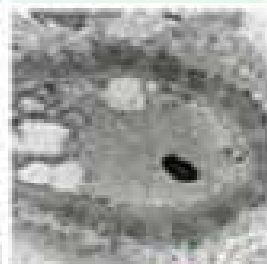
KLAS V



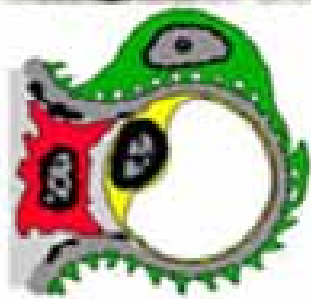
IM

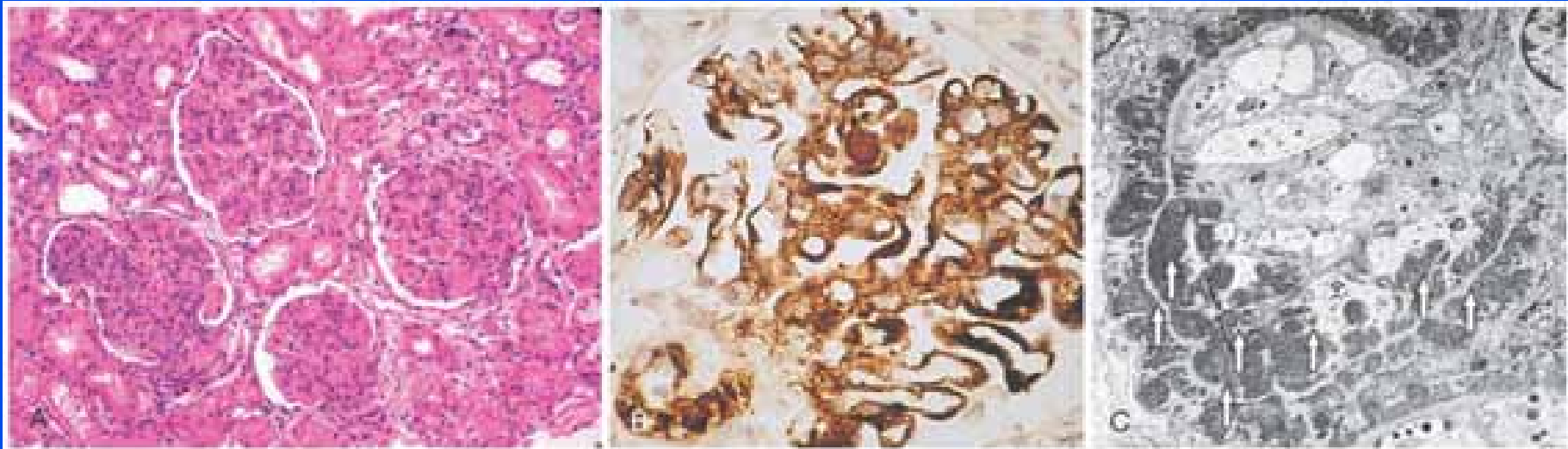


IFG IF

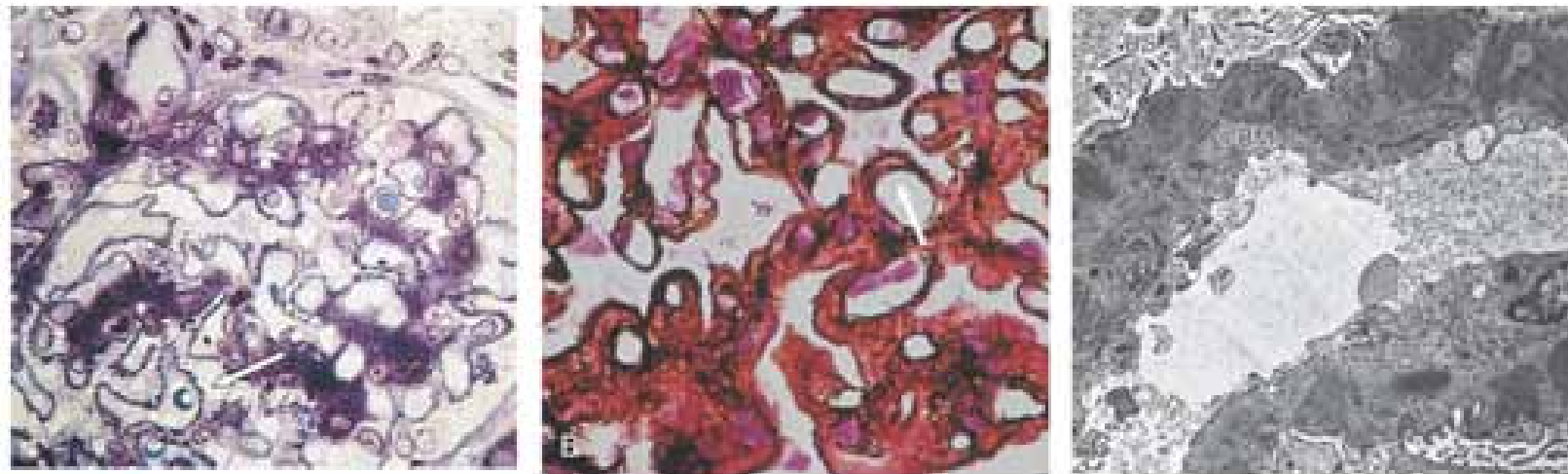


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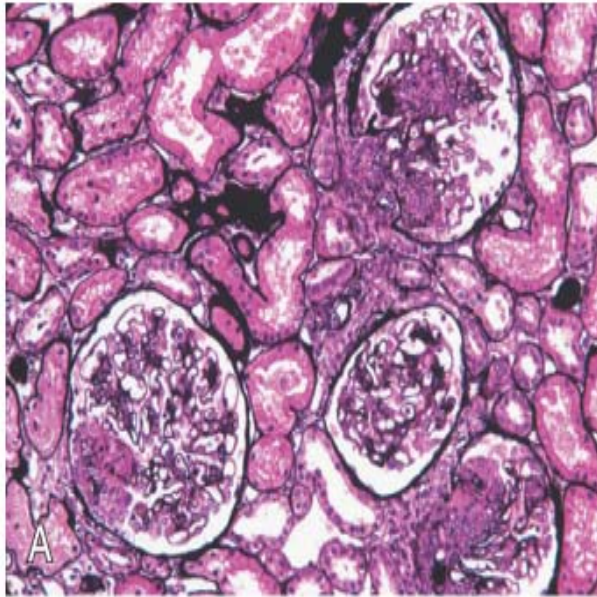




**Figure 25.7 ISN/RPS class IV: lupus nephritis.** **A,** Active diffuse proliferative lupus nephritis. **B,** By immunoperoxidase staining, there are dense irregular aggregates of IgG along the peripheral capillary walls. **C,** Electron microscopy reveals the immune aggregates as electron-dense deposits (arrows) predominantly in the subendothelial location.

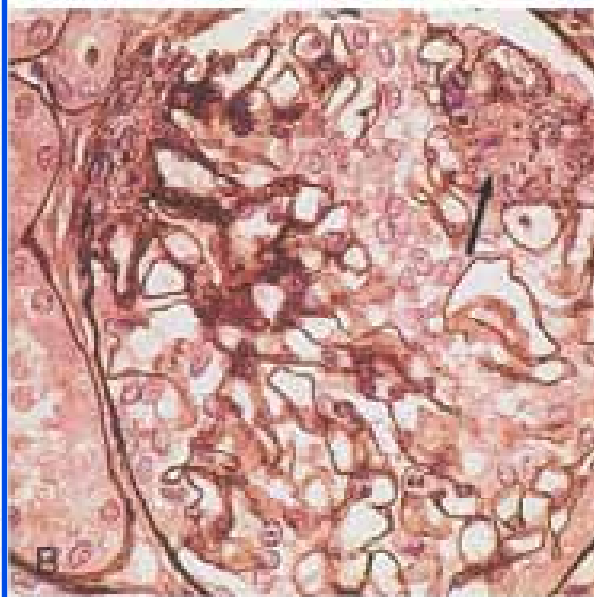


**Figure 25.8 ISN/RPS class V: membranous lupus.** **A,** A thick (~0.5 mm) araldite-embedded section stained with toluidine blue showing not only the extramembranous material in dark blue (arrow) but also the presence of mesangial deposits, which are common in lupus membranous nephropathy. **B,** A silver methenamine-stained section showing some double contouring of the silver-positive basement membrane (arrow) and subendothelium-deposited material as well as the characteristic silver-positive spikes of basement membrane-like material. **C,** An electron microphotograph showing the predominantly subepithelial electron-dense deposits (D) separated by protrusions of basement membrane material (spikes). Si, BM, basement membrane; US, urinary space.



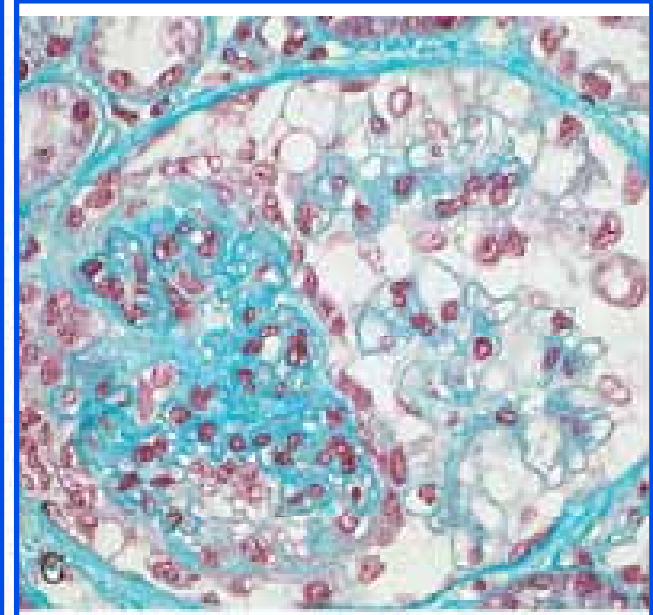
**A**

**A, Low power showing focal and segmental proliferative lesion—active (class III A) with less than 50% of glomeruli affected. (Hematoxylin-eosin.)**



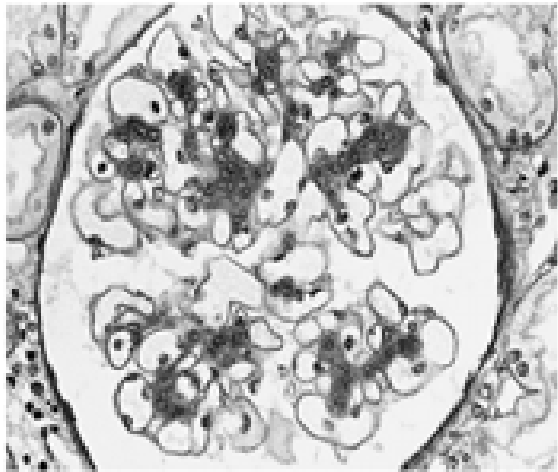
**B**

An area of focal necrosis containing cellular debris, karyorrhexis (arrow), is surrounded by an area of cellular proliferation. (Silver methenamine/hematoxylin-eosin.)

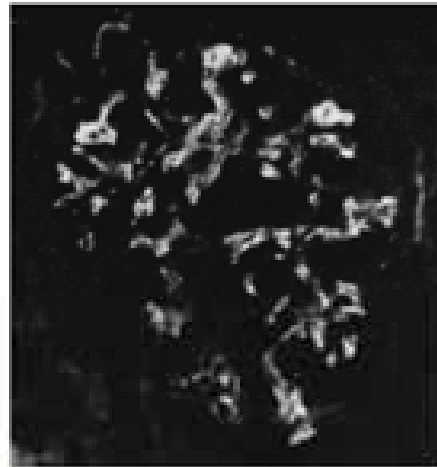


**C**

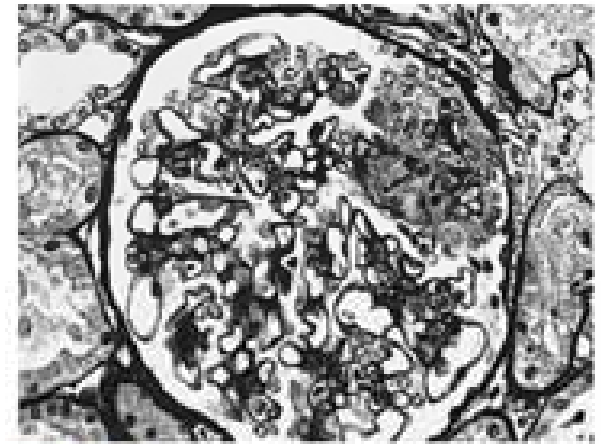
A major focal and segmental proliferative lesion affecting almost half of the glomerular capillary tuft. (Hematoxylin/lissamine green.)



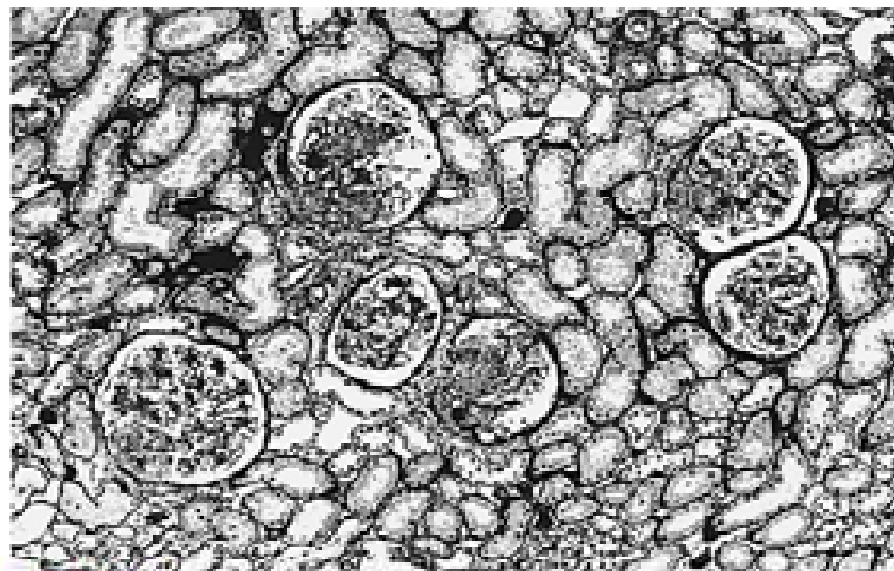
**FIGURE 32-1** Lupus nephritis class II. There is mild global mesangial hypercellularity (periodic acid-Schiff,  $\times 400$ ).



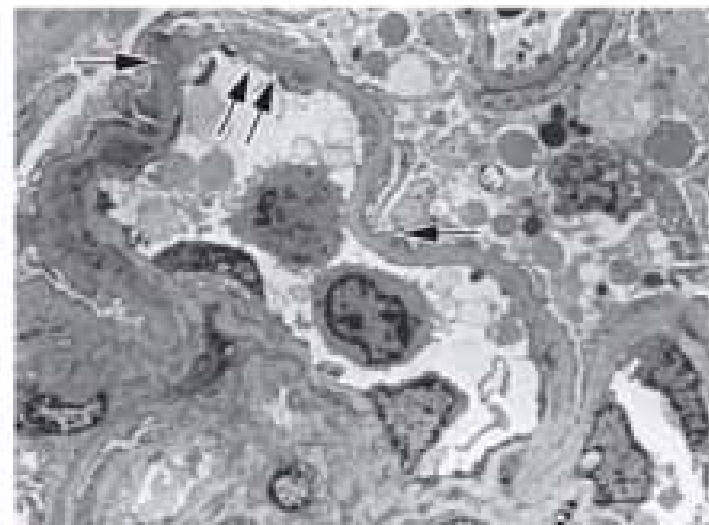
**FIGURE 32-2** Lupus nephritis class II. Immunofluorescence photomicrograph showing deposits of C1 restricted to the glomerular mesangium ( $\times 400$ ).



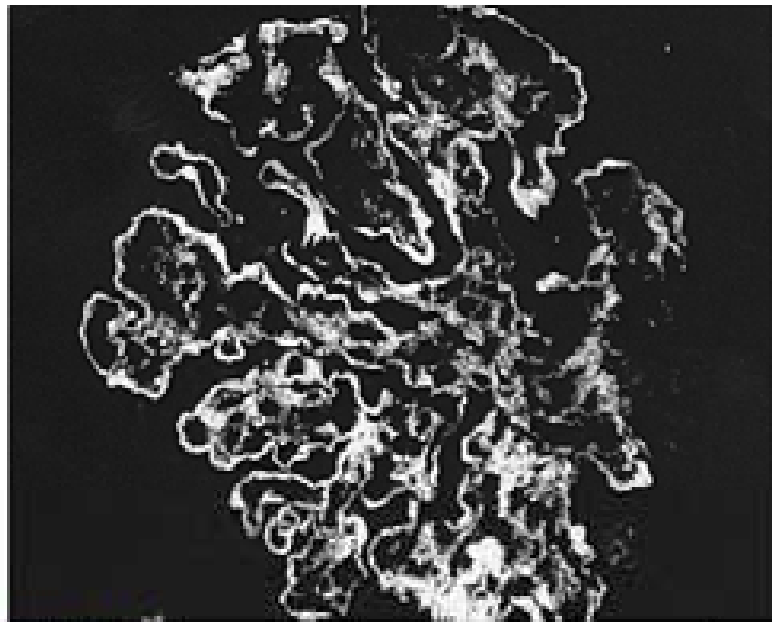
**FIGURE 32-3** Lupus nephritis class III. The glomerular endocapillary proliferation is discretely segmental with crescentic features and an early cellular crescent (Jones methenamine silver,  $\times 400$ ).



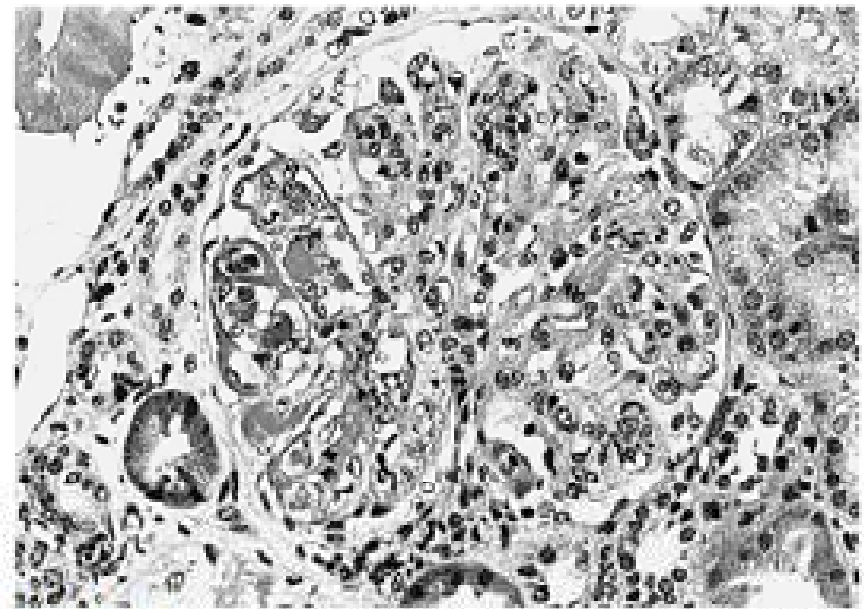
**FIGURE 32-4** Lupus nephritis class III. There is focal segmental endocapillary proliferation (Jones methenamine silver,  $\times 100$ ).



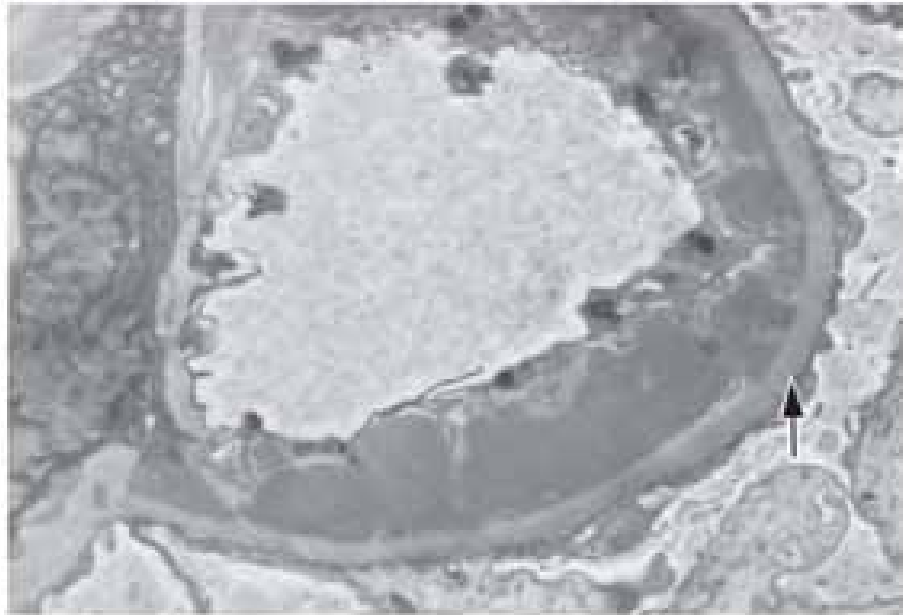
**FIGURE 32-5** Lupus nephritis class III. Electron micrograph showing deposits in the mesangium as well as involving the peripheral capillary wall in subendothelial (double arrow) and subepithelial (single arrow) locations. ( $\times 4900$ ).



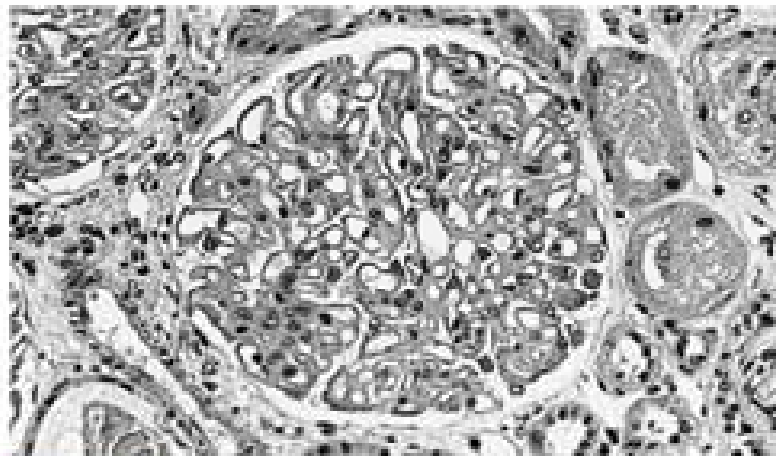
**FIGURE 32-8** Lupus nephritis class IV. Immunofluorescence photomicrograph showing global deposits of immunoglobulin G in the mesangial regions and outlining the subendothelial aspect of the peripheral glomerular capillary walls ( $\times 600$ ).



**FIGURE 32-7** Lupus nephritis class IV. There is global endocapillary proliferation with infiltrating neutrophils and segmental wire loop deposits (hematoxylin and eosin,  $\times 320$ ).



**FIGURE 32-9** Lupus nephritis class IV. Electron micrograph showing a large subendothelial electron-dense deposit as well as a few small subepithelial deposits (arrow) ( $\times 1200$ ).



**FIGURE 32-10** Lupus nephritis class V. There is diffuse uniform thickening of glomerular basement membranes accompanied by mild segmental mesangial hypercellularity (hematoxylin and eosin,  $\times 320$ ).



**FIGURE 32-11** Lupus nephritis class V. Silver stain highlights glomerular basement membrane spikes projecting outward from the glomerular basement membranes toward the urinary space (Jones methenamine silver,  $\times 800$ ).

## KORTİKOSTEROİDLER

- Ağızdan başlangıç dozu prednisone 1 mg/kg'a kadar, klinik yanıtı göre doz azaltma 6–12 ay.
- Methylprednizolon i.v. daha ağır olgularda
- Kortikosteroidlerin doz ve süresi konusunda RKÇ yok

## SİKLOFOSFAMİD (CYC)

- CYC (0.5–1 g/m<sup>2</sup>) i.v. 6 ay aylık doz (Rejim A, “NIH rejimi”)
- CYC CrCl 25–50 ve 10–25 ml/dk olanlarda doz sırasıyla %20 veya %30 azaltılmalıdır
- Ağır Kas III/IV LN, CYC içeren başlangıç tedavisi tercih edilmelidir.

## SİKLOFOSFAMİD (CYC)

- Düşük doz CYC 500 mg her iki haftada bir 3 ay Rejim B, Euro-Lupus, özellikle beyazlarda Rejim A kadar etkili

## AĐIZDAN SİKLOFOSFAMİD (CYC)

- Ağızdan 1.0-1.5mg/kg/gün (en üst doz150 mg/gün) 2–4 ay (Rejim C)
- Damardan CYC kadar etkili

## Tedaviye Cevap Ölçütleri (ACR 2006)

### Renal Fonksiyon:

İyileşme:  $\geq 25\%$   $\square$  GFR bazalden (anormal ise)

Değişmeme: stabil değerler

Kötüleşme:  $\geq 25\%$   $\square$  GFR bazalden

### Proteinuri:

Kısmi cevap: protein/Kr  $> 50\%$   $\square$  0.2-2 arası

Tam cevap: protein/Kr  $< 0.2$

Kötüleşme: protein/Kr  $\geq 100\%$   $\square$

### Uriner sediment

İyileşme: aktif idrar sedimenti  $\rightarrow$  inaktif sediment  
( $< 5$  eritrosit ve lökosit ve/seluler silendir)

## Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis

LOKE MENG ONG,<sup>1</sup> LAI SEONG HOOI,<sup>2</sup> TECK ONN LIM,<sup>3</sup> BAK LEONG GOH,<sup>4</sup> GHAZALI AHMAD,<sup>4</sup> ROZINA GHAZALLI,<sup>1</sup> SUE MEI TEO,<sup>5</sup> HIN SENG WONG,<sup>6</sup> SI YEN TAN,<sup>7</sup> WAN SHAARIAH,<sup>8</sup> CHWEE CHOON TAN<sup>9</sup> and ZAKI MORAD<sup>6</sup>

<sup>1</sup>Department of Medicine, Penang Hospital, <sup>2</sup>Hemodialysis Unit Sultanah Aminah Hospital, Johor Bahru, <sup>3</sup>Clinical Research Centre, Kuala Lumpur Hospital, <sup>4</sup>Department of Nephrology, Selayang Hospital, <sup>5</sup>Hemodialysis Unit, Ipoh Hospital, <sup>6</sup>Department of Nephrology, Kuala Lumpur Hospital, <sup>7</sup>Department of Renal Medicine, University of Malaya Medical Centre, <sup>8</sup>Hemodialysis Unit, Seremban Hospital and <sup>9</sup>Hemodialysis Unit, Tengku Ampuan Rahimah Hospital, Malaysia

### **SUMMARY:**

**Background:** The aim of the present study was to evaluate the efficacy of mycophenolate mofetil in the induction therapy of proliferative lupus nephritis.

**Methods:** Forty-four patients from eight centres with newly diagnosed lupus nephritis World Health Organization class III or IV were randomly assigned to either mycophenolate mofetil (MMF) 2 g/day for 6 months or intravenous cyclophosphamide (IVC) 0.75–1 g/m<sup>2</sup> monthly for 6 months in addition to corticosteroids.

**Results:** Remission occurred in 13 out of 25 patients (52%) in the IVC group and 11 out of 19 patients (58%) in the MMF group ( $P = 0.70$ ). There were 12% in the IVC group and 26% in the MMF group that achieved complete remission ( $P = 0.22$ ). Improvements in haemoglobin, the erythrocyte sedimentation rate, serum albumin, serum complement, proteinuria, urinary activity, renal function and the Systemic Lupus Erythematosus Disease Activity Index score were similar in both groups. Twenty-four follow-up renal biopsies at the end of therapy showed a significant reduction in the activity score in both groups. The chronicity index increased in both groups but was only significant in the IVC group. Adverse events were similar. Major infections occurred in three patients in each group. There was no difference in gastrointestinal side-effects.

**Conclusions:** MMF in combination with corticosteroids is an effective induction therapy for moderately severe proliferative lupus nephritis.

## PAPER

# **Efficacy of enteric-coated mycophenolate sodium in patients with resistant-type lupus nephritis: a prospective study**

O Traitanon<sup>1</sup>, Y Avihingsanon<sup>1,2</sup>, V Kittikovit<sup>3</sup>, N Townamchai<sup>1</sup>, T Kanjanabuch<sup>1</sup>, K Praditpornsilpa<sup>1</sup>, J Wongchinasri<sup>4</sup>,  
K Tungsanga<sup>1</sup> and S Eiam-Ong<sup>1</sup>

<sup>1</sup>Division of Nephrology, Department of Medicine, Chulalongkorn University, Rama IV, Bangkok, Thailand; <sup>2</sup>Lupus Research Unit, Chulalongkorn University, Rama IV, Bangkok, Thailand; <sup>3</sup>Department of Pathology, Faculty of Medicine, Chulalongkorn University, Rama IV, Bangkok, Thailand; and <sup>4</sup>Nopparat Rachathani Hospital, Ministry of Public Health, Bangkok, Thailand

The role of mycophenolate mofetil (MMF) is still controversial in the treatment of cyclophosphamide-resistant proliferative lupus nephritis (PLN). Enteric-coated mycophenolate sodium (EC-MPS) has less gastrointestinal adverse effects than MMF and is, therefore, increasingly utilised in organ transplantation. The aim of this study was to compare the efficacy and safety of EC-MPS versus an extended-course of intravenous cyclophosphamide (ED-IVCY) in resistant-type PLN. Thirty-one, biopsy-proven PLN, patients who failed to respond to an induction of IVCY were enrolled in a prospective, open-labelled, historically controlled study. Patients received 6 month of EC-MPS (720 mg b.i.d.) treatment. The patients in the ED-IVCY group, collected from a database, received a repeated 6-month course of monthly IVCY 0.5–1 g/m<sup>2</sup> of body surface area. Both groups received 0.5–1 mg/kg/day of prednisolone. Primary outcomes were partial or complete responses. A repeated kidney biopsy was performed to evaluate the histological response. No serious adverse events or patient deaths were observed during the study. Both groups had comparable baseline characteristics. At 6 months, the EC-MPS group had a comparable response rate with the ED-IVCY group. There were significantly less adverse events in the EC-MPS group. Repeated biopsies showed significant improvement in the EC-MPS group. EC-MPS provides salutary efficacy and safety in the treatment of resistant-type PLN and can be a suitably alternative treatment to ED-IVCY. *Lupus* (2008) **17**, 744–751.

**Key words:** cyclophosphamide; enteric-coated mycophenolate sodium; lupus nephritis; mycophenolate

Original Article

## Efficacy of enteric-coated mycophenolate sodium in patients with active lupus nephritis

SIU-KA MAK, KIN-YEE LO, MAN-WAI LO, SHUK-FAN CHAN, GENSY MW TONG,  
PING-NAM WONG and ANDREW KM WONG

*Renal Unit, Department of Medicine and Geriatrics, Kwong Wah Hospital, Kowloon, Hong Kong*

**SUMMARY:**

**Background:** The ideal treatment of lupus nephritis has yet to be defined. Both cyclophosphamide and mycophenolate mofetil have been used with encouraging results, but adverse events are frequently seen. There are no data on the use of enteric-coated mycophenolate sodium.

**Methods:** We retrospectively reviewed 12 patients with active forms of lupus nephritis (1 class III, 7 class IV and 4 class V) treated with enteric-coated mycophenolate sodium combined with corticosteroids.

**Results:** The mean age of the patients was  $32.3 \pm 11.2$  years and the average length of follow up was  $25.9 \pm 8.9$  months. The mean serum creatinine clearance was  $93 \pm 30.1$  mL/min per  $1.73 \text{ m}^2$  and the mean proteinuria level was  $4.5 \pm 3.6$  g/day. All had features that warranted aggressive treatment. Mycophenolate sodium was given for  $12.9 \pm 9.7$  months with an averaged starting dose of  $1350 \pm 163$  mg/day. Six patients attained complete remission and six attained partial remission with treatment. The mean interval to attain first remission (complete or partial) was  $8.3 \pm 5.7$  weeks. At last follow up, all patients were in complete or partial remission. Apart from herpes zoster that developed in one patient, no other significant side-effects were encountered.

**Conclusion:** Enteric-coated mycophenolate sodium was effective and well-tolerated in the treatment of active lupus nephritis.

**KEY WORDS:** enteric-coated, lupus nephritis, mycophenolate sodium.

*Teşekkür ederim*

