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The European Rare Kidney Disease Reference Network

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Working Group on Inherited Kidney Disorders

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WELCOME TO

ERKNet/ESPN and Era-EDTA Educational Webinar on Nephrology & Rare Kidney Diseases

Date: 2 March 2021

Topic: Lupus nephritis in children

Speaker: Stephen Marks

Moderator: Marina Vivarelli

GREAT ORMOND STREET INSTITUTE OF CHILD HEALTH

ERKNet The European Rare Kidney Disease Reference Network

Great Ormond Street Hospital for Children NHS Foundation Trust

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Lupus nephritis in children

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ERKNet / ESPN and ERA-EDTA Educational Webinar

Tuesday 2 March 2021

Disclosures

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- Research funding
  - Astellas
  - Aurinia
  - GSK
  - Novartis

- Consultancy fees
  - Novartis


With Lupus
Every day is ...
A test for survival
Lupus And Me

SLE

- Childhood-onset vs adult-onset disease
- Epidemiology
- Lupus nephritis
- Management of SLE and lupus nephritis
- Conclusions

Question 1

- What proportion of children have abnormal renal function on presentation with SLE ?

A. 10%

B. 20%

C. 30%

D. 60%

E. 90%

Epidemiology of adult SLE

- Overt kidney disease at time of diagnosis of SLE
  - in 40-60%

- More common and more severe in non European ethnicity (% affected, incidence ESRD /million population attributable to LN):
  - Caucasians: 12-33%; 2.5/million
  - African-American/Caribbean: 40-69%; 17-20/million
  - Hispanic: 36-61%; 6/million
  - Asian–Indian/Chinese: 47-53%

Epidemiology of paediatric SLE

- Limited data on incidence of childhood SLE
  - incidence in a paediatric population varies
  - 0.28 - 2.1 per 100,000 children at risk per year
  - Malleson et al (1996),Gardner-Medwin et al (2001)

- Prevalence in children and adults from various epidemiological studies varies
  - 12.0 - 50.8 per 100,000

Background - 1

- Childhood-onset SLE
  - variable clinical manifestations
  - unpredictable natural history
- Epidemiological studies
  - progressive clinical course of SLE
  - significant morbidity and mortality rates
  - 10 - 17% of proven cases present in childhood with more severe organ involvement than adults

Background - 2

- Renal disease is a major determinant of the long-term outcome of SLE
  - influence management with immunosuppressive agents
- Haematological and renal disease
  - more severe in patients with childhood-onset (compared to adult-onset) SLE

Background - 3

- Different spectrum
  - cardiopulmonary involvement is rare
  - CNS presentation commoner
- Multisystem involvement
  - arthritis
  - autoimmune hepatitis
  - macrophage activation syndrome

Background - 4

- Paediatric issues
  - children and parents
  - growing skeleton
  - education
  - evolving identity
  - QOL
  - adolescents
  - adherence to treatment

Background - 5

- Same autoimmune processes
- Same ACR classification criteria
- Same disease markers
  - ESR, C3, lymphocyte count, dsDNA
- Same drugs
  - steroids, aza, MMF, HCQ
  - cyclophosphamide, IVIg
  - rituximab and newer agents…

Lupus nephritis

Question 2

- Which ISN/RPS class of lupus nephritis has subepithelial deposits ?

A. ISN/RPS Class I lupus nephritis

B. ISN/RPS Class II lupus nephritis

C. ISN/RPS Class III lupus nephritis

D. ISN/RPS Class IV lupus nephritis

E. ISN/RPS Class V lupus nephritis

Clinical presentation and histopathology of LN

- Presentation of renal involvement
  - proteinuria
  - microscopic (and rarely macroscopic) haematuria
  - nephrotic syndrome
  - hypertension
  - evidence of renal dysfunction

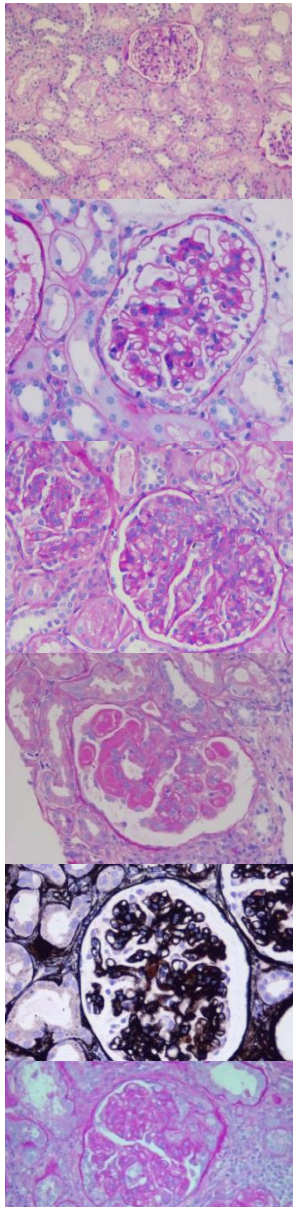
- Histopathology of LN cannot be accurately predicted from clinical and serological markers

History of LN histopathology

- Original WHO classification (1974 - 1975)
  - developed in Buffalo, New York and Geneva
- Modified WHO classification / ISKD (1982)
  - further subdivided the classes
- Modified WHO classification / Churg (1995)
  - minor adaptation for Class V LN
- ISN / RPS Working Group (2003)
  - current histopathological classification

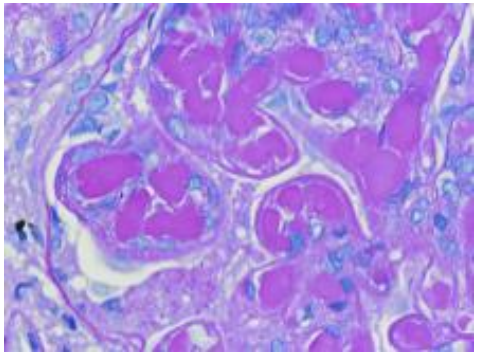
ISN / RPS classification of LN

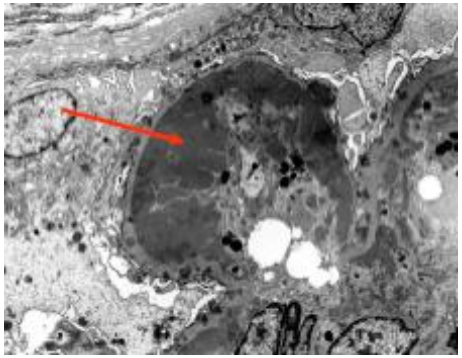
- **Class I:** Minimal mesangial LN
- **Class II:** Mesangial proliferative LN
- **Class III:** Focal LN (IIIA, IIIA/C, IIIC)
- **Class IV:** Diffuse segmental (IV-S) or global (IV-G) LN: A, A/C, C
- **Class V:** Diffuse membranous LN
- **Class VI:** Advanced sclerotic LN



Lupus nephritis biopsy ISN/RPS Classification

- No endocapillary hypercellularity
  - Mesangial deposits only Class I
  - Mesangial hypercellularity Class II
  - Subepithelial deposits Class V
- Endocapillary hypercellularity
  - Involving < 50% glom Class III*
  - Involving ≥ 50% glom
    - Segmental distribution Class IV S*
    - Global distribution Class IV G*



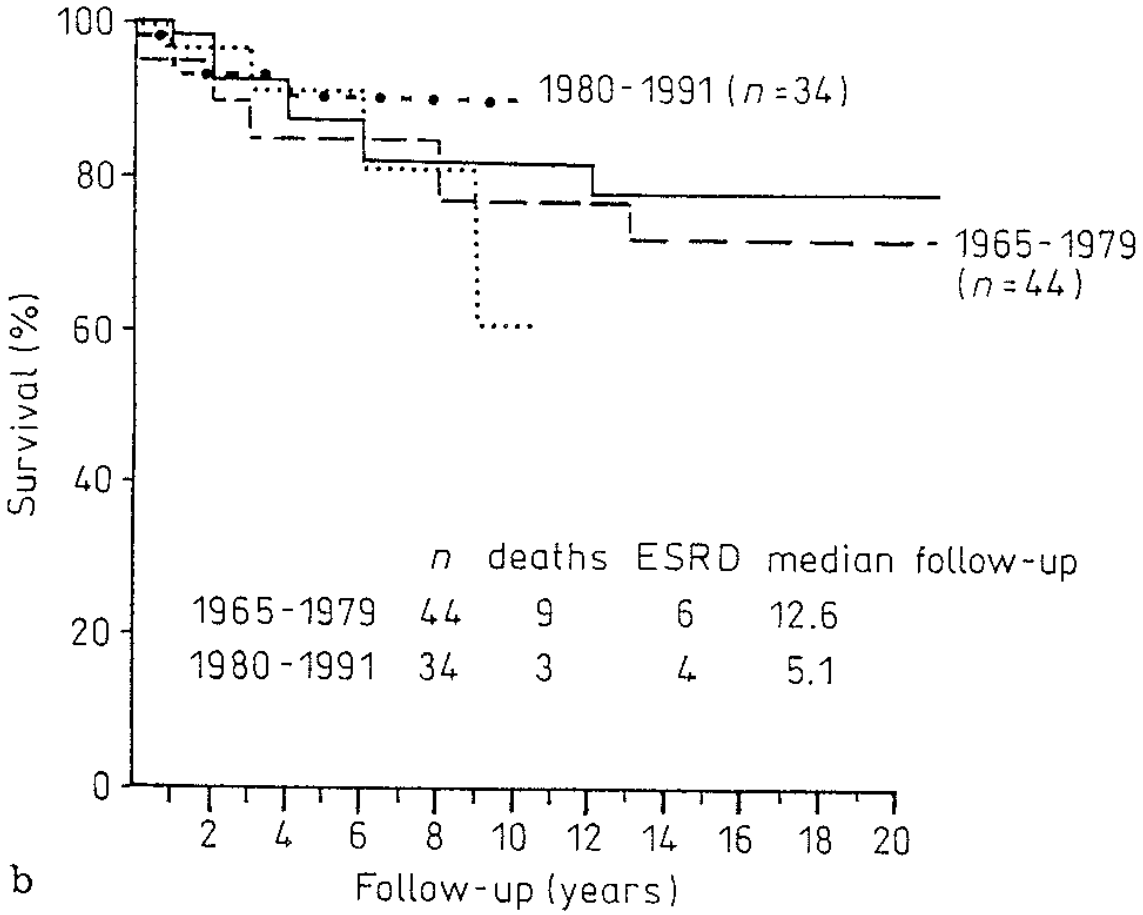


*Include proportion of glomeruli with active and chronic lesions, necrosis and crescents

Aims of treatment

- Aim to induce and maintain a remission
- Choose agents to minimise toxicity and maximise effectiveness
- Aim to reduce renal flares as associated with worse prognosis

London data



Cameron JS Pediatr Nephrol 1994;8:230-249

Introduction

- Conventional therapies
  - steroid-sparing agents
    - AZATHIOPRINE
    - INTRAVENOUS CYCLOPHOSPHAMIDE
    - MMF
    - OTHER IMMUNOSUPPRESSION
- Different management strategies should be considered in problematic patients

Question 3

- Which ethnic groups respond better to mycophenolate mofetil than intravenous cyclophosphamide ?

A. Asian

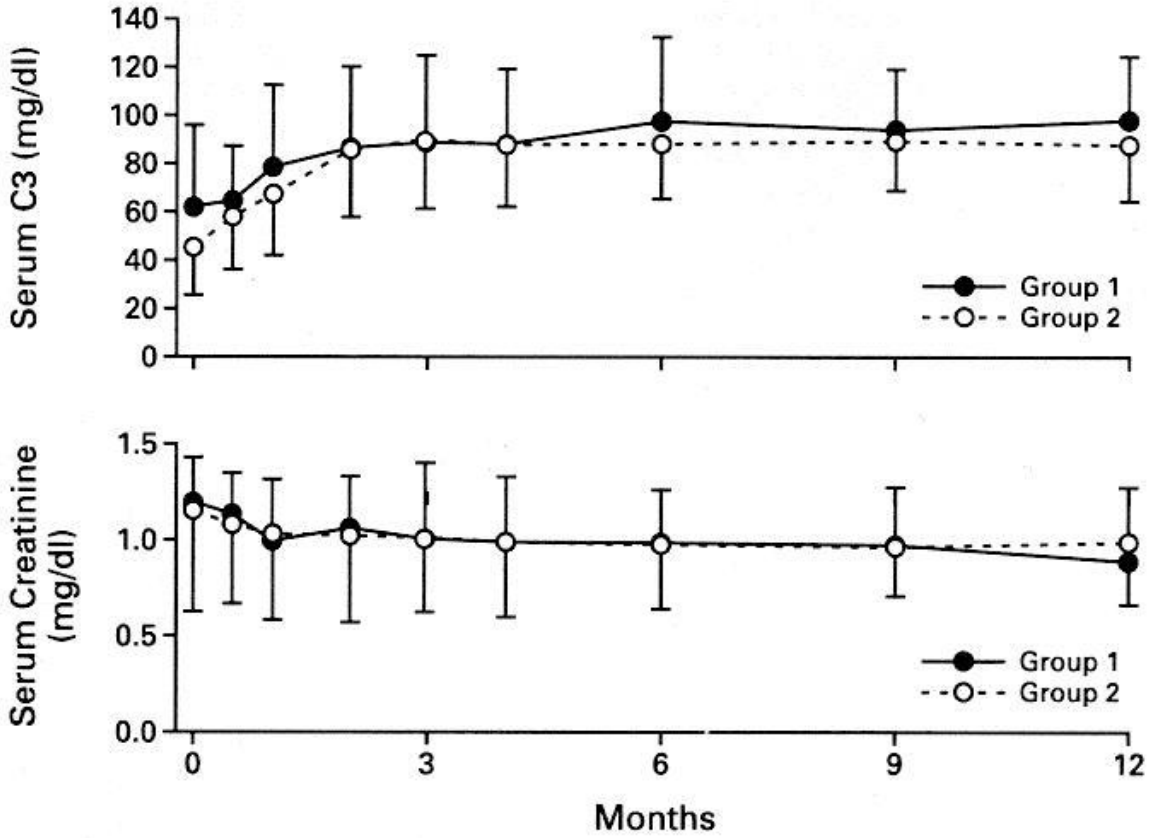
B. Black

C. Caucasian

D. Hispanic

E. No difference

MMF versus cyclophosphamide



No. of Patients					
Group 1	21	20	20	20	17
Group 2	21	20	20	17	16

MMF 1g bd

6m of CYC 2.5mg/kg/d

Chan et al NEJM 2000;343:1156-62

MMF versus cyclophosphamide

	MMF	CYC
• Complete remission	17	16
• Treatment failure	1	2
• Relapse	3	2
• Death	0	2
• Infections	4	7
• Amenorrhoea	0	3
• Hair loss	0	4
• Leucopenia	0	2

Has patient responded without flares ?

- If remission achieved
  - renal survival and patient survival 94-95%
- If remission not achieved
  - renal survival 46% and 31% at 5 and 10 years
  - patient survival 69% and 60% at 5 and 10 years
- Risk of ESKD highest: diffuse proliferative disease

Korbet *et al Am J Kid Dis* 2000;35(5):904-14

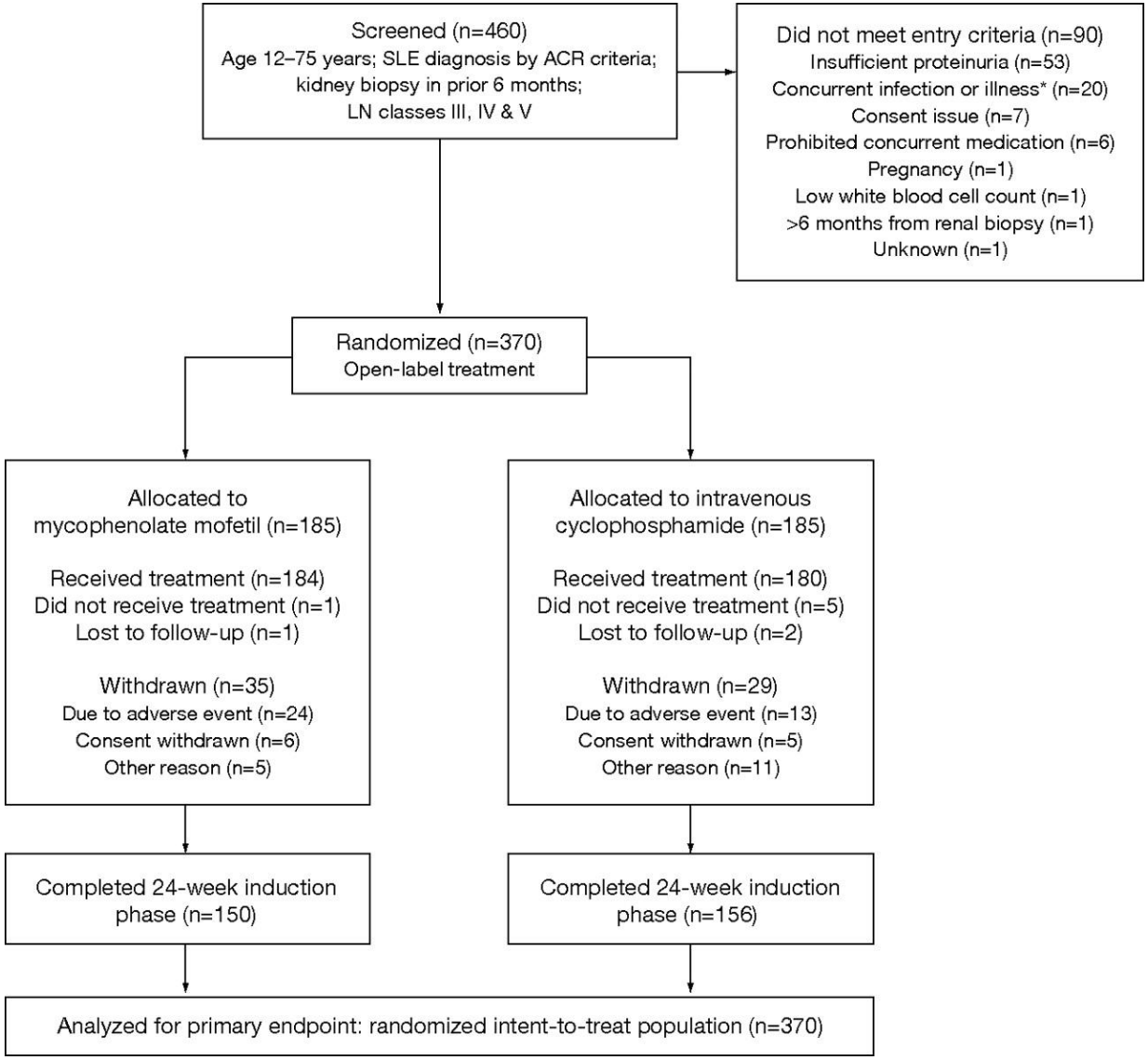
- Recent data, analysing ALMS data;
  - worse outcome if
    - baseline eGFR <30mls/min, low C4, LN > 1yr
  - good outcome if
    - normalisation of C3/C4 or >25% fall in proteinuria by 8 weeks

ALMS data

- Open label study 24 week induction phase
- ISN/RPS Class III to V LN
- MMF target dose 3g/day
- iv cyclophosphamide 0.5-1g/m^2/month
- Prednisolone 60mg/day tapered
- Primary end-points
  - decrease in urine protein : creatinine ratio
  - stable or improving plasma creatinine

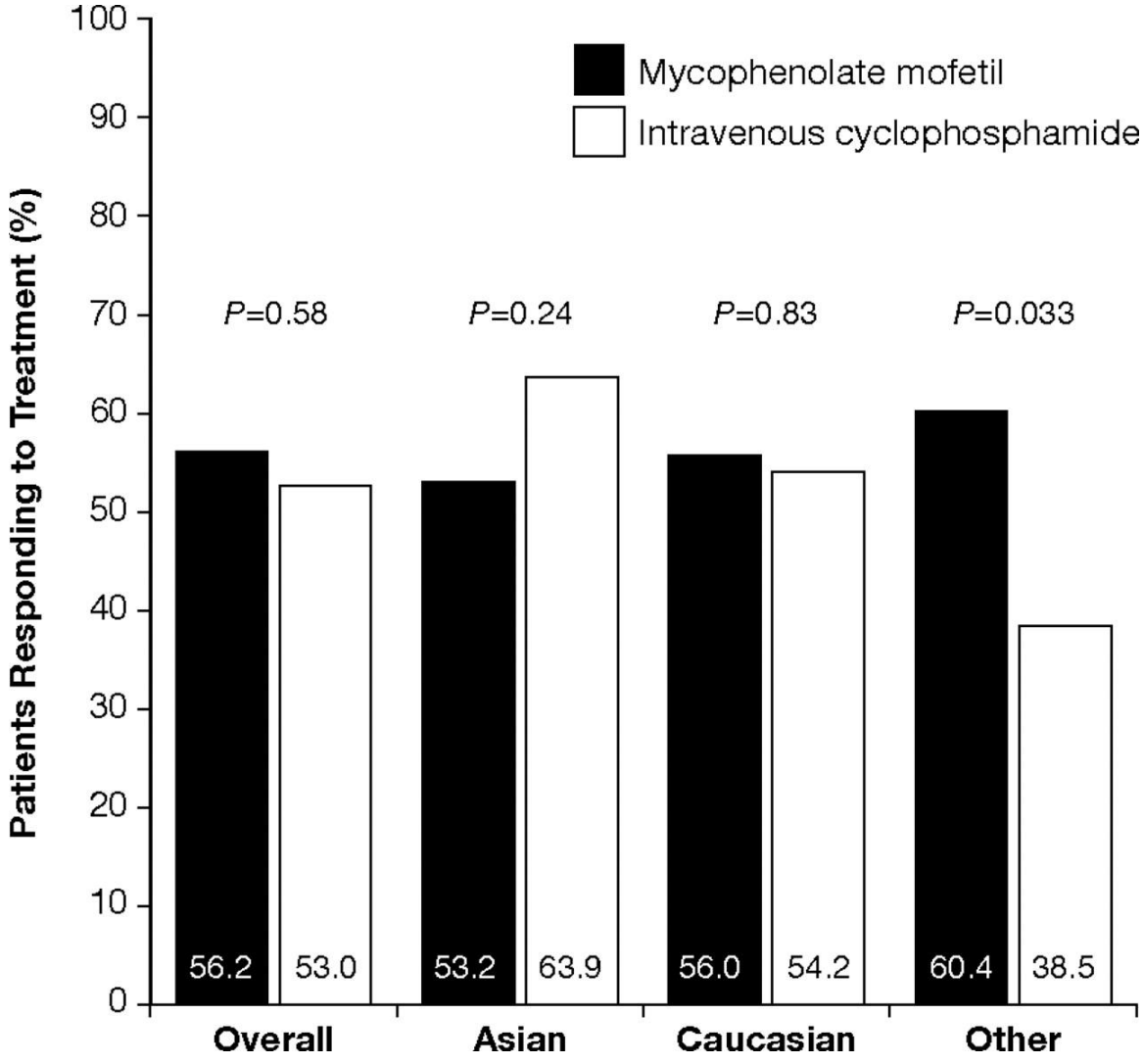
Appel, GB et al. J Am Soc Nephrol 2009;20:1103-1112

ALMS data

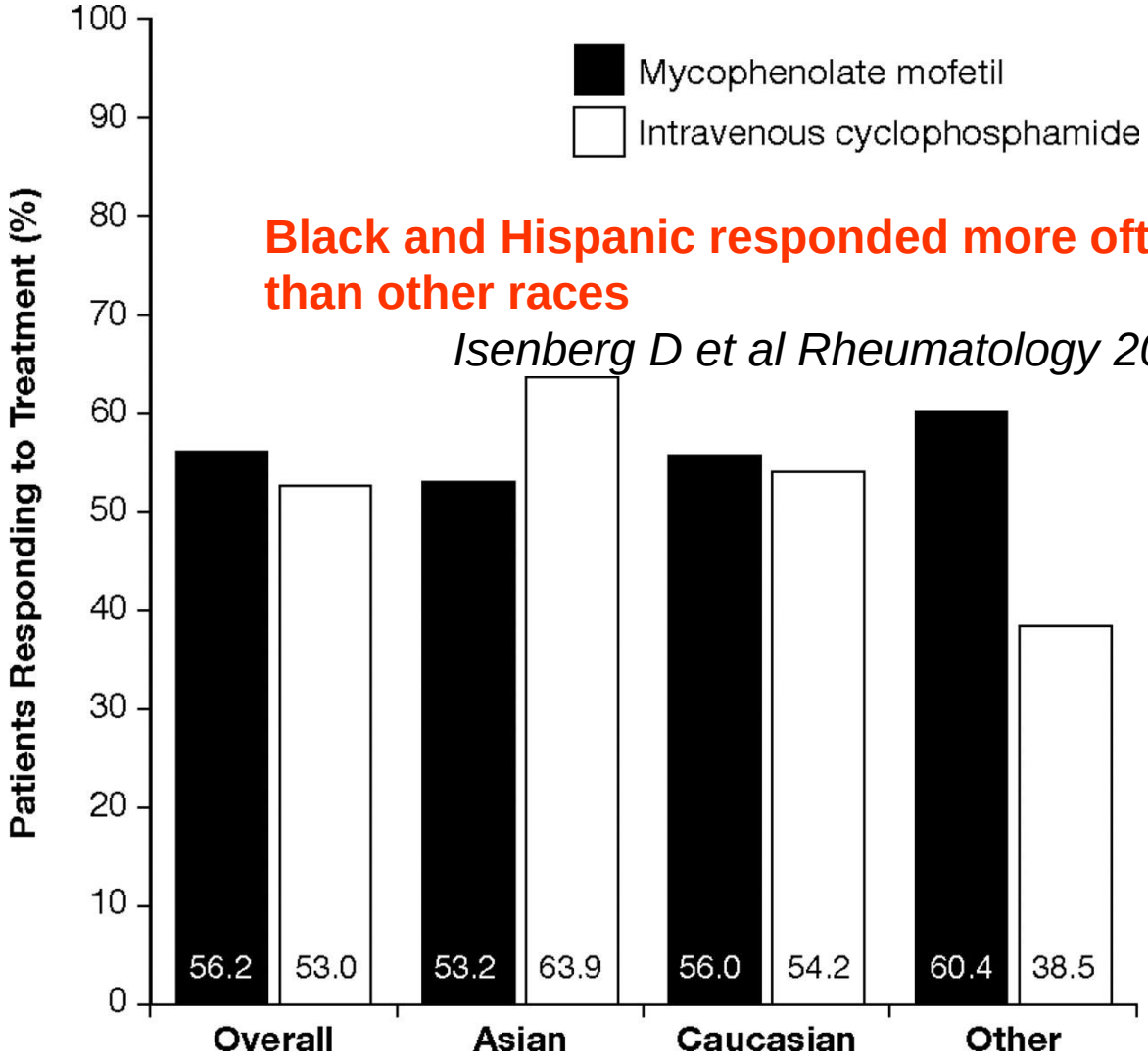


Appel, GB et al, J Am Soc Nephrol 2009;20:1103-1112

ALMS results



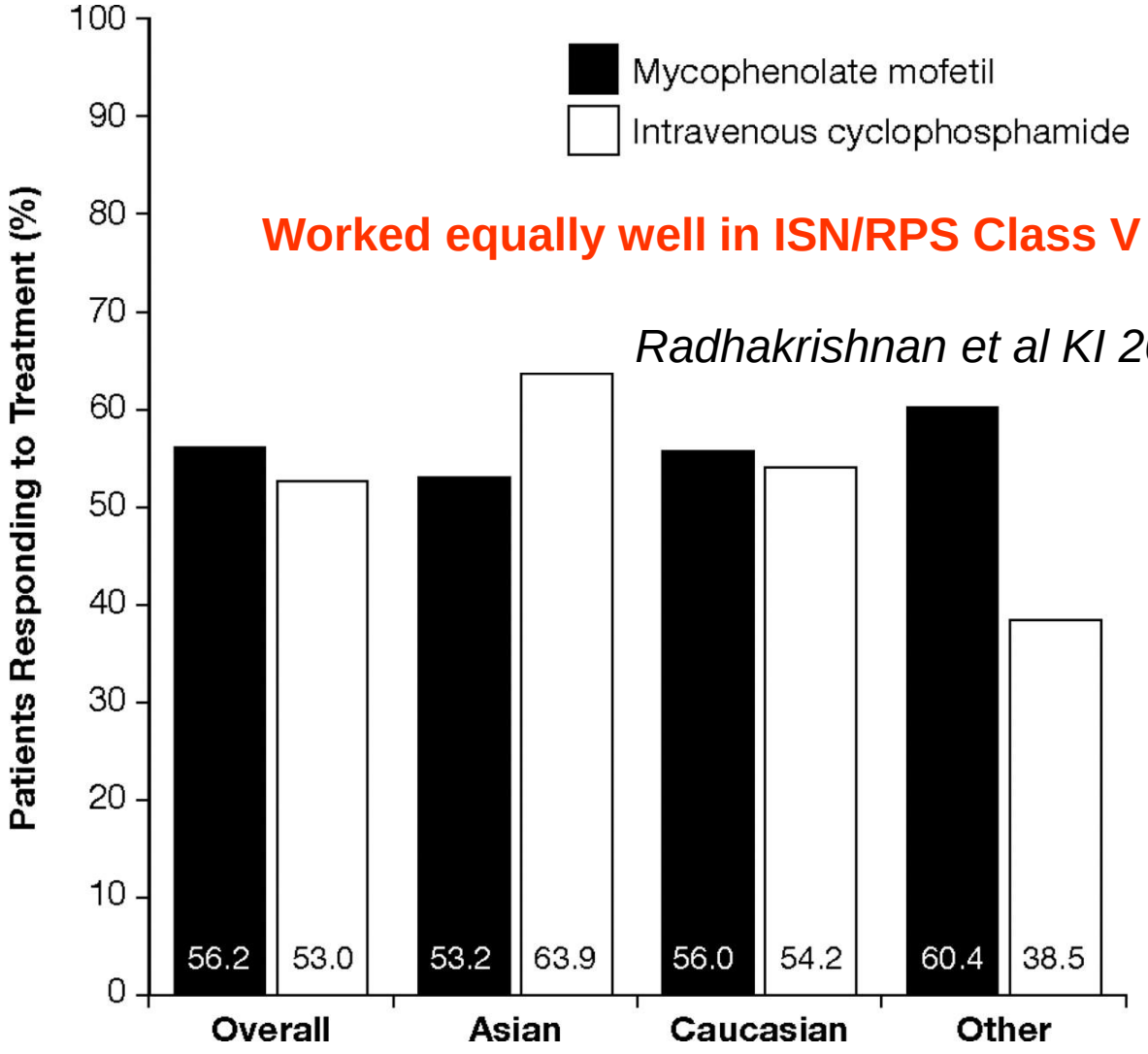
ALMS results



Black and Hispanic responded more often to MMF than other races

Isenberg D et al Rheumatology 2010;49:128

ALMS results



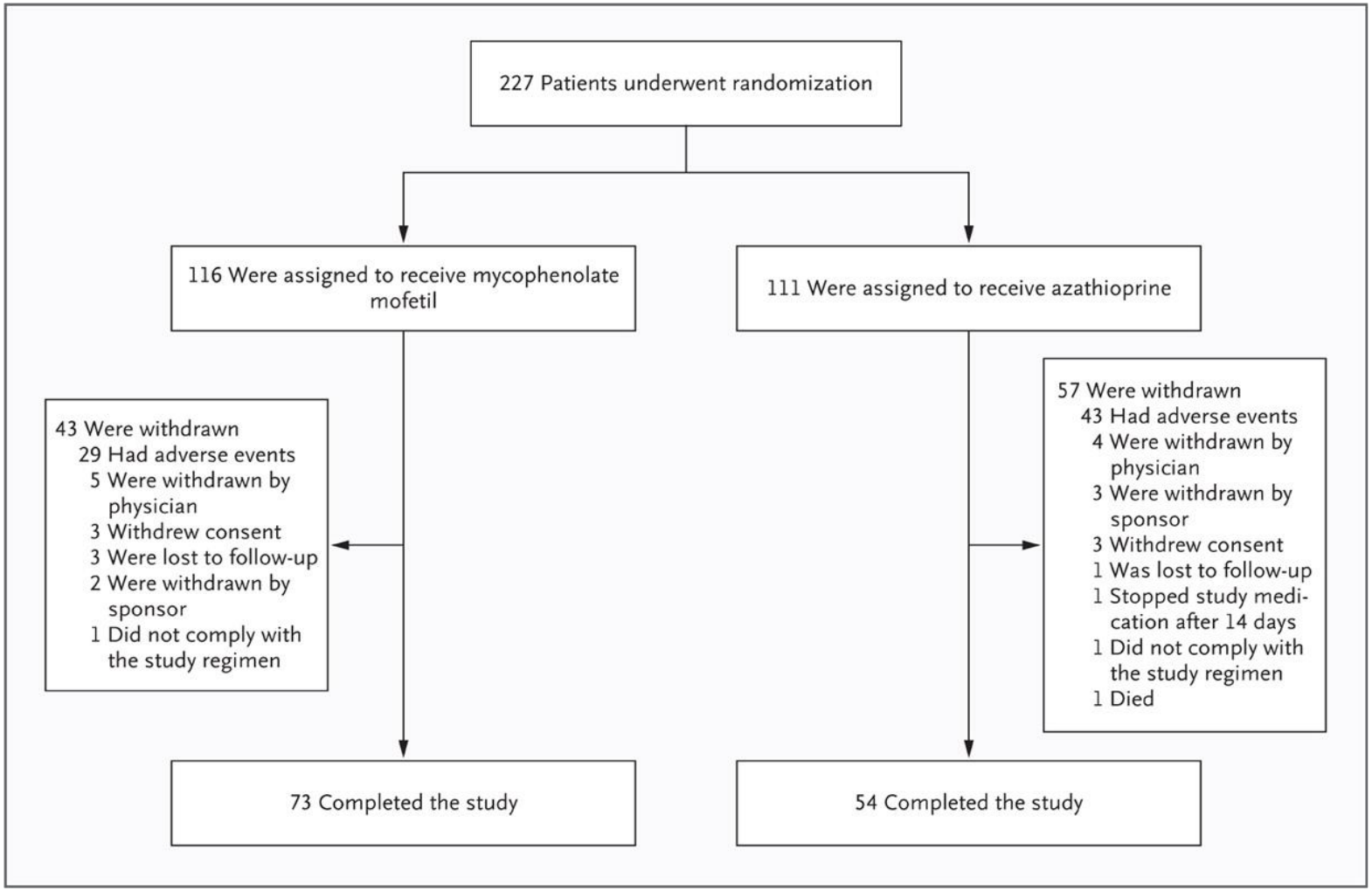
Worked equally well in ISN/RPS Class V LN

Radhakrishnan et al KI 2010;77:152

ALMS side-effects

	MMF	CYC
Death:	4.9%	2.8%
Diarrhoea:	28%	13%
Nausea:	15%	46%
Vomiting:	13%	38%
Alopecia	11%	36%

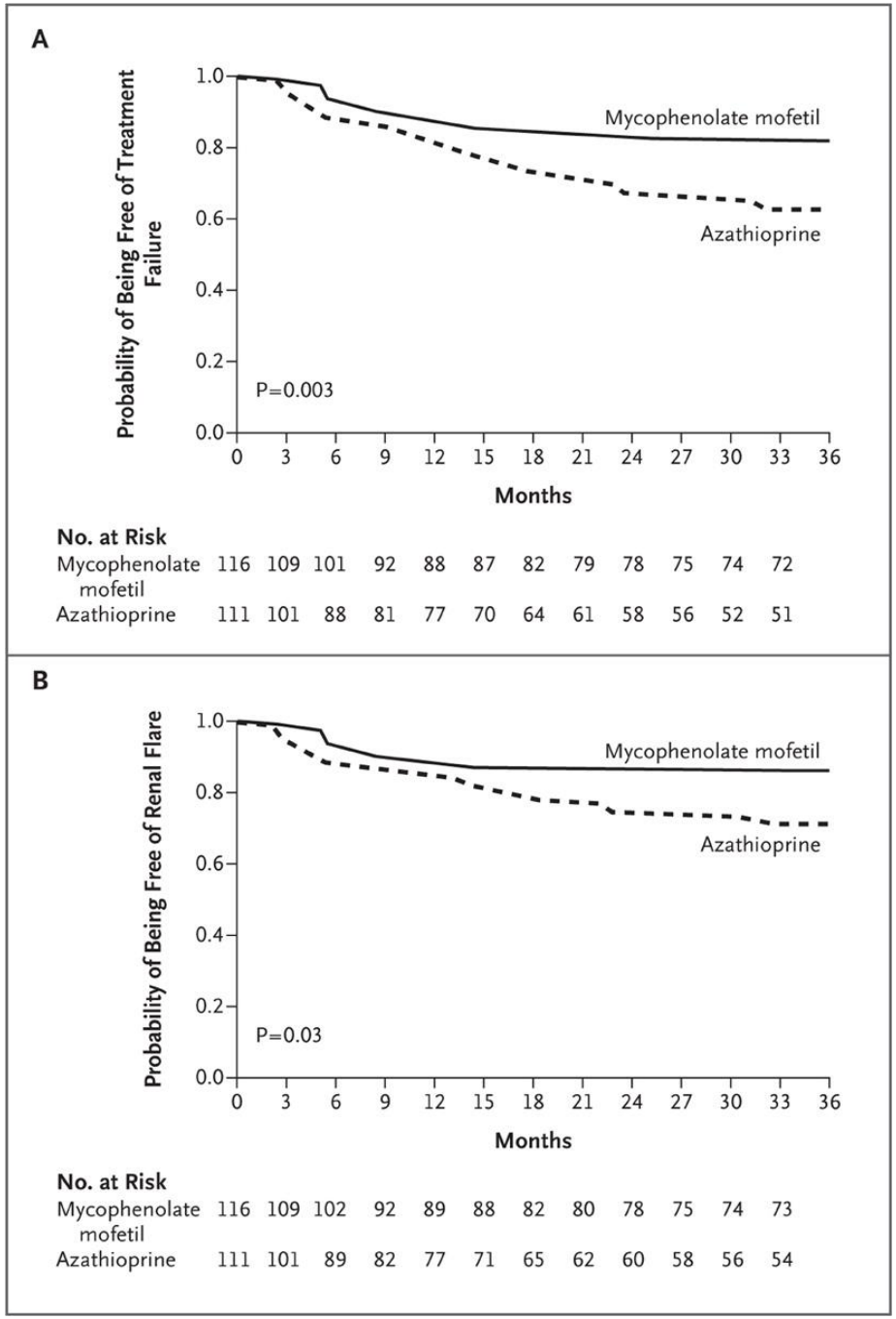
ALMS maintenance



Dooley MA et al. N Engl J Med 2011;365:1886-1895

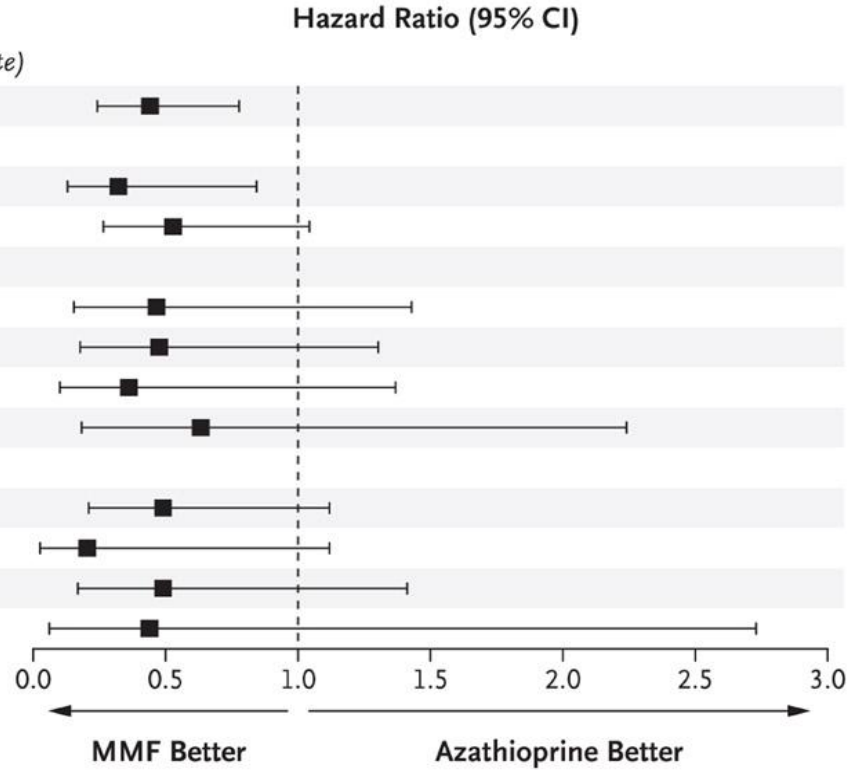
ALMS data

- Kaplan–Meier
  - curves for time to treatment failure and time to renal flare



Risk of treatment failure in subgroups of patients

Subgroup	MMF	Azathioprine
	no. of events/total no. of patients (incidence rate)	
All patients	19/116 (7.4)	36/111 (17.3)
Induction treatment		
IV cyclophosphamide	6/54 (4.7)	15/53 (14.5)
MMF	13/62 (10.1)	21/58 (20.1)
Region		
Asia	5/37 (5.5)	8/35 (12.1)
Latin America	5/25 (10.2)	16/35 (23.2)
USA and Canada	3/22 (6.4)	8/25 (18.4)
Rest of world	6/32 (8.7)	4/16 (13.6)
Race		
White	9/48 (9.4)	18/51 (18.7)
Black	2/12 (7.0)	6/11 (34.3)
Asian	6/39 (6.5)	9/37 (12.8)
Other	2/17 (5.3)	3/12 (12.6)



MAINTAIN LN trial

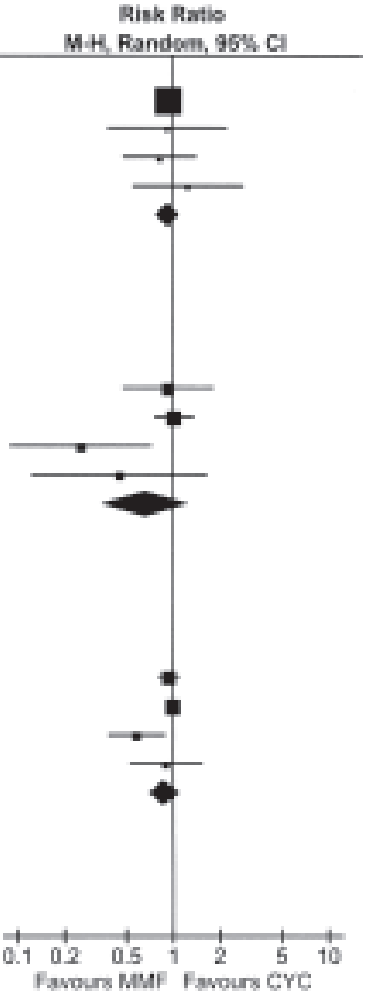
- 105 patients with proliferative LN
  - treated with steroids and 6 fortnightly iv CYC
  - after that randomised to MMF (2g/day) or azathioprine (2mg/kg/day)

- Renal flare
  - 19% MMF
  - 25% azathioprine (ns)

Houssiau FA et al Ann Rheum Dis 2010;69:2083

Meta-analysis of cyc vs MMF

Study or Subgroup	CYC Events	CYC Total	MMF Events	MMF Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Partial						
Appel 2009	98	185	104	185	82.6%	0.94 [0.78, 1.13]
Chan 2005	7	31	8	33	3.6%	0.93 [0.38, 2.26]
Ginzler 2005	17	69	21	71	9.6%	0.83 [0.48, 1.44]
Ong 2005	10	25	6	19	4.3%	1.27 [0.56, 2.87]
Subtotal (95% CI)		**310**		**308**	**100.0%**	**0.94 [0.80, 1.12]**
Total events	132		139			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.70$, df = 3 (P = 0.87); $I^2 = 0\%$						
Test for overall effect: Z = 0.68 (P = 0.49)						
2.1.2 Complete						
Appel 2009	15	185	16	185	28.0%	0.94 [0.48, 1.84]
Chan 2005	23	31	24	33	37.2%	1.02 [0.76, 1.37]
Ginzler 2005	4	69	16	71	19.6%	0.26 [0.09, 0.73]
Ong 2005	3	25	5	19	15.2%	0.46 [0.12, 1.68]
Subtotal (95% CI)		**310**		**308**	**100.0%**	**0.67 [0.35, 1.28]**
Total events	45		61			
Heterogeneity: $Tau^2 = 0.27$; $Chi^2 = 9.28$, df = 3 (P = 0.03); $I^2 = 68\%$						
Test for overall effect: Z = 1.21 (P = 0.23)						
2.1.3 Overall						
Appel 2009	113	185	120	185	33.8%	0.94 [0.81, 1.10]
Chan 2005	30	31	32	33	38.3%	1.00 [0.91, 1.09]
Ginzler 2005	21	69	37	71	16.2%	0.58 [0.38, 0.89]
Ong 2005	13	25	11	19	11.7%	0.90 [0.52, 1.54]
Subtotal (95% CI)		**310**		**308**	**100.0%**	**0.89 [0.71, 1.10]**
Total events	177		200			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 11.85$, df = 3 (P = 0.008); $I^2 = 75\%$						
Test for overall effect: Z = 1.09 (P = 0.28)						



Touma et al J Rheumatol 2011:38:69

What is difficult lupus ?

- Difficult disease
  - severity, lack of response
- Difficult patient
  - non-adherence
- Difficult confounding factors
  - non-attendance

Treatment options

- ?No treatment
- Corticosteroids
- Cyclophosphamide
- Azathioprine
- Hydroxychloroquine
- Plasma exchange
- Mycophenolate mofetil
- Rituximab (?new vs refractory cases)
- Newer biological agents

Drug treatments in lupus

- Corticosteroids form the basis of all regimens ?
- MMF for induction and remission
- iv cyclophosphamide for prolonged periods
  - previous gold standard
- Azathioprine is an effective drug for maintenance treatment of lupus nephritis
  - studies on efficacy in remission induction schedules are in progress
- Studies on 'conventional' immunosuppression show that RCT are needed
  - need large numbers of patients with long follow-up
    - Kuiper-Geertsma DG (2003), *Drugs* 63: 167-80.

Standard treatment

- Initial pulses of iv methylprednisolone
  - 600mg/m^2/day x 3 days followed by oral high dose prednisolone (wean rather quickly)
- Induction and maintenance MMF
  - 600 - 1200mg/m^2/day
- Consideration for monthly pulses of cyclophosphamide
  - 500-1000mg/m^2 for 6 months (?3 months)
  - followed by azathioprine 1.5-2.5 mg/kg/day

Introduction

- Evidence-based practice
- What do we know about therapies in 2021 ?
- How will we treat patients in the future ?

SLE management

ACR guidelines for screening, treatment and management of LN

OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY
ISN
kidney INTERNATIONAL supplements
KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES
KDIGO
KDIGO Clinical Practice Guideline for Glomerulonep
VOLUME 2 | ISSUE 2 | JUNE 2012
http://www.kidney-international.org

KDIGO clinical practice guideline GN

Arthritis Care & Research
Vol. 64, No. 6, June 2012, pp 797–808
DOI 10.1002/acr.21664

SPECIAL ARTICLE

American College of Rheumatology Guidelines for Screening, Treatment, and Management of Lupus Nephritis

BEVRA H. HAHN,[1] MAUREEN A. McMAHON,[1] ALAN WILKINSON,[1] W. DEAN WALLACE,[1] DAVID I. DAIKH,[2] JOHN D. FITZGERALD,[1] GEORGE A. KARPOUZAS,[1] JOAN T. MERRILL,[3] DANIEL J. WALLACE,[4] JINOOS YAZDANY,[2] ROSALIND RAMSEY-GOLDMAN,[5] KARANDEEP SINGH,[1] MAZDAK KHALIGHI,[1] SOO-IN CHOI,[1] MANEESH GOGIA,[1] SUZANNE KAFAJA,[1] MOHAMMAD KAMGAR,[1] CHRISTINE LAU,[1] WILLIAM J. MARTIN,[1] SEFALI PARIKH,[1] JUSTIN PENG,[1] ...FER M. GROSSMAN[1]

Annals of the RHEUMATIC DISEASES
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Ann Rheum Dis doi:10.1136/annrheumdis-2012-201940

Recommendation

Joint European League Against Rheumatism European Renal Association–European Dia and Transplant Association (EULAR/ERA-E recommendations for the management of a and paediatric lupus nephritis

OPEN ACCESS

George K Bertsias[1], Maria Tektonidou[2], Zahir Amoura[3], Martin Aringer[4], Inget Jo H M Berden[6], John Boletis[7], Ricard Cervera[8], Thomas Dörner[9], Andrea Do Franco Ferrario[11], Jürgen Floege[12], Frederic A Houssiau[13], John P A Ioannidi David A Isenberg[15], Cees G M Kallenberg[16], Liz Lightstone[17], Stephen D Mark Alberto Martini[19], Gabriela Moroni[20], Irmgard Neumann[21], Manuel Praga[22], Matthias Schneider[23], Argyre Starra[24], Vladimir Tesar[25], Carlos Vasconcelos[26], Ronald F van Vollenhoven[27], Helena Zakharova[28], Marion Haubitz[29], Caroline Gordon[30], David Jayne[31], Dimitrios T Boumpas[1]

EULAR and ERA-EDTA management LN

Arthritis Care & Research

Pediatrics

Consensus treatment plans for induction therapy of newly diagnosed proliferative lupus nephritis in juvenile systemic lupus erythematosus

Rina Mina[1,†], Emily von Scheven[2,†,*], Stacy P. Ardoin[3,‡], B. Anne Eberhard[4], Marilynn Punaro[5], Norman Ilowite[6], Joyce Hsu[7], Marisa Klein-gitelman[8], L. Nandini Moorthy[9], Eyal Muscal[10], Suhas M. Radhakrishna[11], Linda Wagner-weiner[12], Matthew Adams[13], Peter Blier[14], Lenore Buckley[15], Elizabeth Chalom[16], Gaëlle Chédeville[17], Andrew Eichenfield[18], Natalya Fish[19], Michael Henrickson[1], Aimee O. Hersh[20], Roger Hollister[21],

Issue

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Consensus Rx plans for induction

KDIGO Clinical Practice Guideline

for Glomerulonephritis

Caucasian

VOLUME 2 | ISSUE 2 | JUNE 2012

http://www.kidney-international.org

kidney INTERNATIONAL supplements

Nomenclature and description for rating guideline recommendations

- Strength of recommendation

Grade*	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.

*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.

- Supporting 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.

Adult lupus nephritis

Chapter 12: Lupus nephritis

12.1: Class I LN (minimal-mesangial LN)

12.1.1: We suggest that patients with class I LN be treated as dictated by the extrarenal clinical manifestations of lupus. (*2D*)

12.2: Class II LN (mesangial-proliferative LN)

12.2.1: Treat patients with class II LN and proteinuria <1 g/d as dictated by the extrarenal clinical manifestations of lupus. (*2D*)

12.2.2: We suggest that class II LN with proteinuria >3 g/d be treated with corticosteroids or CNIs as described for MCD (see Chapter 5). (*2D*)

12.3: Class III LN (focal LN) and class IV LN (diffuse LN)—initial therapy

12.3.1: We recommend initial therapy with corticosteroids (*1A*), combined with either cyclophosphamide (*1B*) or MMF (*1B*).

12.3.2: We suggest that, if patients have worsening LN (rising SCr, worsening proteinuria) during the first 3 months of treatment, a change be made to an alternative recommended initial therapy, or a repeat kidney biopsy be performed to guide further treatment. (*2D*)

Adult lupus nephritis

12.4: Class III LN (focal LN) and class IV LN (diffuse LN)—maintenance therapy

12.4.1: We recommend that, after initial therapy is complete, patients with class III and IV LN receive maintenance therapy with azathioprine (1.5–2.5 mg/kg/d) or MMF (1–2 g/d in divided doses), and low-dose oral corticosteroids (≤ 10 mg/d prednisone equivalent). (*1B*)

12.4.2: We suggest that CNIs with low-dose corticosteroids be used for maintenance therapy in patients who are intolerant of MMF and azathioprine. (*2C*)

12.4.3: We suggest that, after complete remission is achieved, maintenance therapy be continued for at least 1 year before consideration is given to tapering the immunosuppression. (*2D*)

12.4.4: If complete remission has not been achieved after 12 months of maintenance therapy, consider performing a repeat kidney biopsy before determining if a change in therapy is indicated. (*Not Graded*)

12.4.5: While maintenance therapy is being tapered, if kidney function deteriorates and/or proteinuria worsens, we suggest that treatment be increased to the previous level of immunosuppression that controlled the LN. (*2D*)

12.5: Class V LN (membranous LN)

12.5.1: We recommend that patients with class V LN, normal kidney function, and non–nephrotic-range proteinuria be treated with antiproteinuric and antihypertensive medications, and only receive corticosteroids and immunosuppressives as dictated by the extrarenal manifestations of systemic lupus. (*2D*)

12.5.2: We suggest that patients with pure class V LN and persistent nephrotic proteinuria be treated with corticosteroids plus an additional immunosuppressive agent: cyclophosphamide (*2C*), or CNI (*2C*), or MMF (*2D*), or azathioprine (*2D*).

12.6: General treatment of LN

12.6.1: We suggest that all patients with LN of any class are treated with hydroxychloroquine (maximum daily dose of 6–6.5 mg/kg ideal body weight), unless they have a specific contraindication to this drug. (*2C*)

12.7: Class VI LN (advanced sclerosis LN)

12.7.1: We recommend that patients with class VI LN be treated with corticosteroids and immunosuppressives only as dictated by the extrarenal manifestations of systemic lupus. (*2D*)

12.8: Relapse of LN

12.8.1: We suggest that a relapse of LN after complete or partial remission be treated with the initial therapy followed by the maintenance therapy that was effective in inducing the original remission. (*2B*)

12.8.1.1: If resuming the original therapy would put the patient at risk for excessive lifetime cyclophosphamide exposure, then we suggest a non–cyclophosphamide-based initial regimen be used (Regimen D, Table 28). (*2B*)

12.8.2: Consider a repeat kidney biopsy during relapse if there is suspicion that the histologic class of LN has changed, or there is uncertainty whether a rising SCr and/or worsening proteinuria represents disease activity or chronicity. (*Not Graded*)

12.9: Treatment of resistant disease

12.9.1: In patients with worsening SCr and/or proteinuria after completing one of the initial treatment regimens, consider performing a repeat kidney biopsy to distinguish active LN from scarring. (*Not Graded*)

12.9.2: Treat patients with worsening SCr and/or proteinuria who continue to have active LN on biopsy with one of the alternative initial treatment regimens (see Section 12.3). (*Not Graded*)

12.9.3: We suggest that nonresponders who have failed more than one of the recommended initial regimens (see Section 12.3) may be considered for treatment with rituximab, i.v. immunoglobulin, or CNIs. (*2D*)

12.10: Systemic lupus and thrombotic microangiopathy

12.10.1: We suggest that the antiphospholipid antibody syndrome (APS) involving the kidney in systemic lupus patients, with or without LN, be treated by anticoagulation (target international normalized ratio [INR] 2–3). (*2D*)

12.10.2: We suggest that patients with systemic lupus and thrombotic thrombocytopenic purpura (TTP) receive plasma exchange as for patients with TTP without systemic lupus. (*2D*)

12.11: Systemic lupus and pregnancy

12.11.1: We suggest that women be counseled to delay pregnancy until a complete remission of LN has been achieved. (*2D*)

Question 4

- What percentage of paediatric lupus recommendations are based on very low quality of evidence or lack of evidence ?

A. 10%

B. 20%

C. 30%

D. 60%

E. 90%

Paediatric lupus nephritis

Chapter 12: Lupus nephritis

12.12: LN in children

12.12.1: We suggest that children with LN receive the same therapies as adults with LN, with dosing based on patient size and GFR. (*2D*)

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 K Bertsias,[1] Maria Tektonidou,[2] Zahir Amoura,[3] Martin Aringer,[4] Ingeborg Bajema,[5] Jo H M Berden,[6] John Boletis,[7] Ricard Cervera,[8] Thomas Dörner,[9] Andrea Doria,[10] Franco Ferrario,[11] Jürgen Floege,[12] Frederic A Houssiau,[13] John P A Ioannidis,[14] David A Isenberg,[15] Cees G M Kallenberg,[16] Liz Lightstone,[17] Stephen D Marks,[18] Alberto Martini,[19] Gabriela Moroni,[20] Irmgard Neumann,[21] Manuel Praga,[22] Matthias Schneider,[23] Argyre Starra,[24] Vladimir Tesar,[25] Carlos Vasconcelos,[26] Ronald F van Vollenhoven,[27] Helena Zakharova,[28] Marion Haubitz,[29] Caroline Gordon,[30] David Jayne,[31] Dimitrios T Boumpas[1]

Ann Rheum Dis 2012;**71**:1771–1782. doi:10.1136/annrheumdis-2012-201940

Paediatric lupus nephritis

Statement	Mean (SD)	Median (IQR)*
10. Management of paediatric LN		
Compared to adult-onset disease, LN in children is more severe with increased damage accrual and more common at presentation but the diagnosis, management and monitoring is similar to that of adults. A coordinated transition programme to adult specialists is important in assessing concordance to treatments and optimising long-term outcomes.		

Paediatric lupus nephritis

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Paediatric lupus nephritis

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- Conclusions
  - evidence-based practice ?
  - 50% (15) Graded 2D and 13% (4) not graded
  - 3% (1), 13% (4), 10% (3) and 10% (3) graded Grade 1A, 1B, 2B and 2C respectively

2019 Update of the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) recommendations for the management of lupus nephritis

Antonis Fanouriakis ,[1,2] Myrto Kostopoulou,[3] Kim Cheema,[4] Hans-Joachim Anders,[5] Martin Aringer ,[6] Ingeborg Bajema,[7] John Boletis,[8] Eleni Frangou,[9] Frederic A Houssiau ,[10] Jane Hollis,[11] Adexandre Karras,[12] Francesca Marchiori,[13] Stephen D Marks,[14] Gabriella Moroni ,[15] Marta Mosca,[16] Ioannis Parodis ,[17] Manuel Praga,[18] Matthias Schneider,[19] Josef S Smolen,[20] Vladimir Tesar,[21] Maria Trachana,[22] Ronald F van Vollenhoven ,[23] Alexandre E Voskuyl,[24] Y K Onno Teng,[25] Bernadette van Leew,[26] George Bertsias,[27] David Jayne,[4] Dimitrios T Boumpas [1,28]

Management of paediatric LN

Kidney involvement is more common in childhood compared with adult-onset SLE, often as a presenting manifestation, while renal flares are observed in more than 50% of patients.[120 121] Since the 2012 EULAR/ERA—EDTA recommendations, American and European groups of experts in paediatric SLE and LN have published recommendations for the management of childhood-onset LN; both are largely based on data extrapolation from the studies in adults.[122 123] Notwithstanding differences between children and adults, the respective statements from the 2012 recommendations remained unchanged; diagnosis, treatment (paediatric doses of drugs, online supplementary table 3) and monitoring should follow the same principles as in adult disease. For children in adolescence, a transition programme is recommended to ensure adherence and optimal outcomes.

Management of paediatric LN

Kidney involvement is more common in childhood compared with adult-onset SLE, often as a presenting manifestation, while renal flares are observed in more than 50% of patients.[120 121] Since the 2012 EULAR/ERA—EDTA recommendations, American and European groups of experts in paediatric SLE and LN have published recommendations for the management of childhood-onset LN; both are largely based on data extrapolation from the studies in adults.[122 123] Notwithstanding differences between children and adults, the respective statements from the 2012 recommendations remained unchanged; diagnosis, treatment (paediatric doses of drugs, online supplementary table 3) and monitoring should follow the same principles as in adult disease. For children in adolescence, a transition programme is recommended to ensure adherence and optimal outcomes.

Treatment for lupus nephritis (Review)

Henderson L, Masson P, Craig JC, Flanc RS, Roberts MA, Strippoli GFM, Webster AC

THE COCHRANE COLLABORATION®

Management of Class III, IV LN

Induction phase

Corticosteroids
IV 30mg/kg (max 1g) x3, PO ≈1mg/kg/day
plus
Cyclophosphamide (0.5-0.75g/m2 IV x 6)
or
MMF 600mg/m^2 bd (max 1.5g bd)

6 months

No response

Swap induction therapy

Consider Rituximab

Maintenance phase

Corticosteroids (<0.5mg/kg/day)
plus
MMF *or* AZA (2mg/kg/day)

24$^+$ months

No response

2nd line: Rituximab
3rd line: Ciclosporin, *or* Tacrolimus, *plus* Corticosteroids

Abou-Raya et al. J Rheumatol 2013; 40(3): 265-72, Baca et al. Lupus 2006; 15(8):490-5

Other management options

Adjuvant therapy

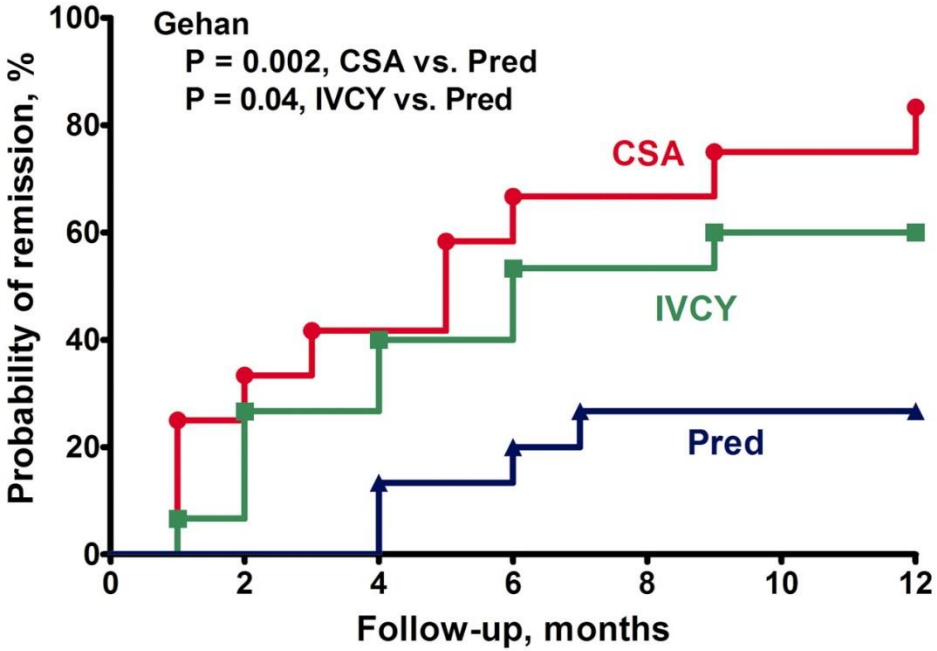
Hydroxychloroquine (up to 400mg/day)
Treat hypertension, proteinuria, hyperlipidaemia
Aspirin (if APL or ACL abs)
Anti-coagulate if APLS especially if nephrotic
Vaccines (non-live)
Treat vitamin D deficiency

Severe non-responding disease

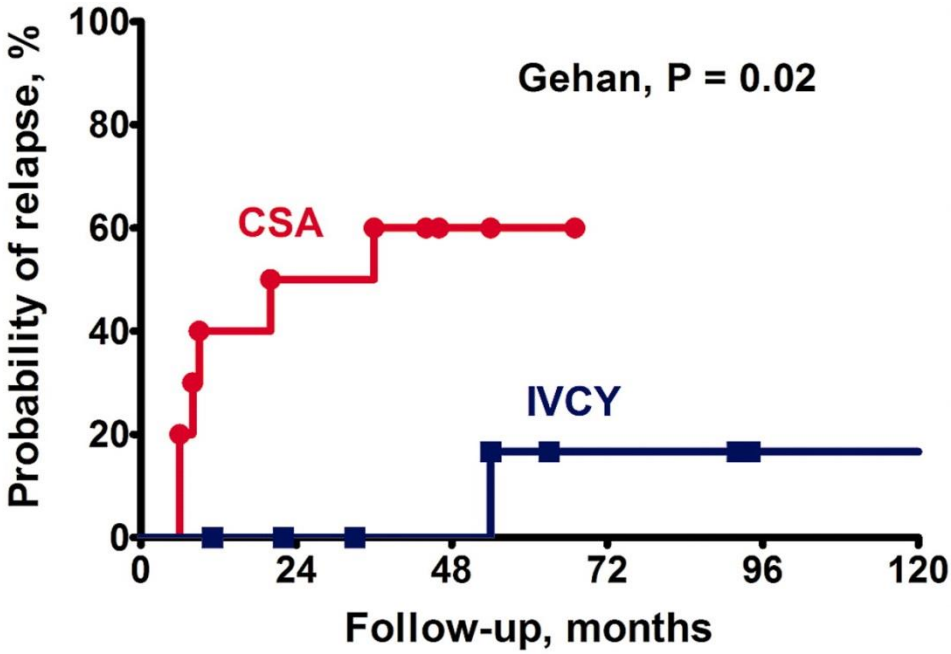
Immunoglobulin – 400mg/kg/day x 5 days then monthly
Plasma exchange – systematic review negative
Infliximab – case reports
Stem cell transplant – significant mortality/morbidity

Wenderfer et al, Autoimmune Dis 2012; sept 27 [epub], Casella, Lupus 2013;21 (12): 1335-42, Seck SM, Saudi J Kidney Dis Transpl 2011;22:219-24, Abou-Raya et al. J Rheumatol 2013; 40(3)

Membranous lupus nephritis



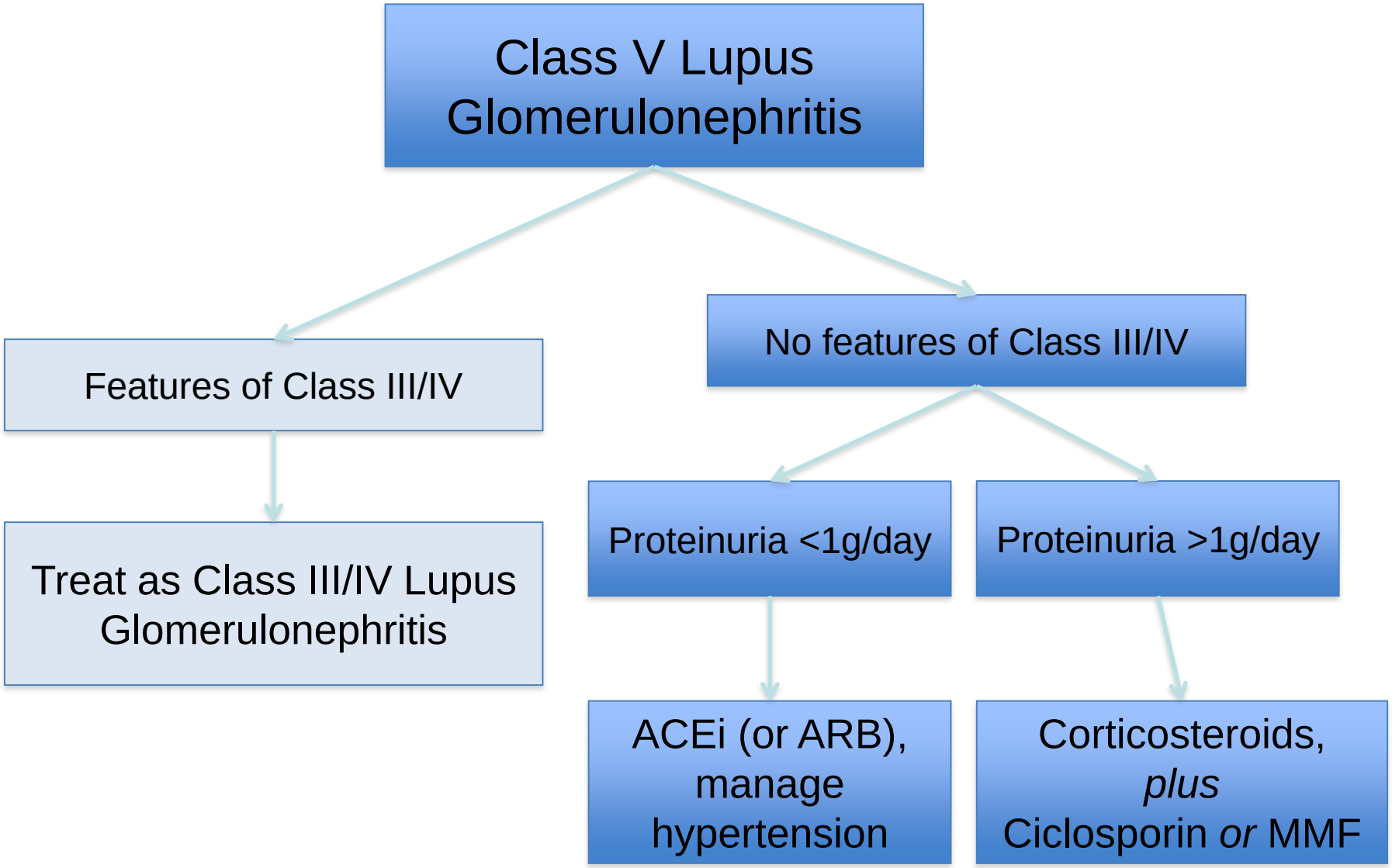
No. at Risk							
CSA	12	9	7	5	4	3	3
IVCY	15	14	11	9	7	6	6
Pred	15	15	15	13	11	11	11



No. at Risk						
CSA	10	5	2			
IVCY	9	7	6	4	2	2

Austin, HA et al, J Am Soc Nephrol 2009;20:901-911

Class V Lupus Nephritis



Autoantibodies and B cells in SLE

- ANA and anti-dsDNA
  - important diagnostic / prognostic markers
  - related to disease severity / renal damage
    - Foster MH et al (1999):*Semin Nephrol* 19(2):173-81
- Adults and children with active disease have profound B cell abnormalities
    - Tangye SG et al (1998) *J Exp Med* 188: 1691-703
    - Odendahl M et al (2003) *Ann Rheum Dis* 62: 851-8

Rituximab

- Monoclonal antibody
  - binds to CD20 Ag
    - located on pre-B and mature B lymphocytes
    - mediates B-cell lysis
  - clinical use
    - prophylaxis and treatment of lymphoma and EBV-driven LPD
    - autoimmune diseases
  - dose of 375mg/m^2 as slow iv infusion in PTLD
    - once weekly for 4 weeks

Reasons for treatment

- Multi-systemic presentation of SLE with life or organ-threatening disease
  - without response to iv methylprednisolone and/or plasma exchange
  - no time to wait for iv cyclophosphamide
- Active disease after previous treatment with iv cyclophosphamide
  - severe and continuous symptoms
    - eg. ACTIVE SKIN / KIDNEY, POOR GROWTH

Table II. Case series of pediatric systemic lupus erythematosus patients (pts) treated with rituximab

Reference	Number of pts	Rituximab regimen	Continued immunosuppression, including corticosteroid doses[a]	B-cell depletion achieved (% of pts)	Adverse effects (no. of pts)	Outcomes
Marks et al.[33,34]	7	750 mg/m^2 × 2 + CYC (if none previously)	AZA/MMF (n = 5 pts), median daily prednisolone dose of 0.35 (0.06–1.95) mg/kg reduced to 0.14 (0.05–0.39) mg/kg within 6mo (p = 0.0003) and maintained at 0.13 (0.05–0.25) mg/kg at follow-up at 12mos (p = 0.0014)	100 (7 of 7)	None reported	Median BILAG scores decreased from 22 at baseline to 6 at follow-up (p = 0.002)

a Corticosteroid dose documented where published with titration to the patient's disease activity.

AZA = azathioprine; **BILAG** = British Isles Lupus Assessment Group; **CYC** = cyclophosphamide; **MMF** = mycophenolate mofetil; **MTx** = methotrexate; **pts** = patients.

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Willems et al.[35]	11	350–450 mg/m^2 × 2–12 infusions + CYC (2)	AZA/MTx/MMF/CYC (6), 25–50% baseline prednisolone dose	88 (7 of 8 tested pts)	Septicemia (2), lymphopenia ± neutropenia ± thrombocytopenia (6) with rash (2), impetigo (1)	Complete hematologic remission in 100% (2 of 2 pts); complete renal remission in 25% (2 of 8 pts) and partial remission in 50% (4 of 8 pts)

a Corticosteroid dose documented where published with titration to the patient's disease activity.

AZA = azathioprine; **BILAG** = British Isles Lupus Assessment Group; **CYC** = cyclophosphamide; **MMF** = mycophenolate mofetil; **MTx** = methotrexate; **pts** = patients.

Patient population

- Safety and efficacy of rituximab
  - 21 treatment episodes
  - 19 children with refractory SLE
    - patients with severe multi-organ involvement
    - refractory to treatment
    - chronic active disease activity

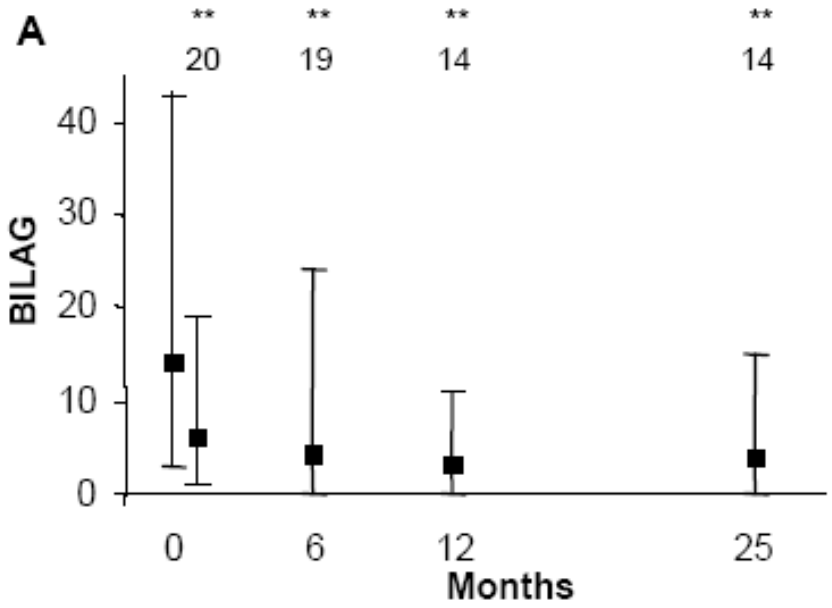
Patients

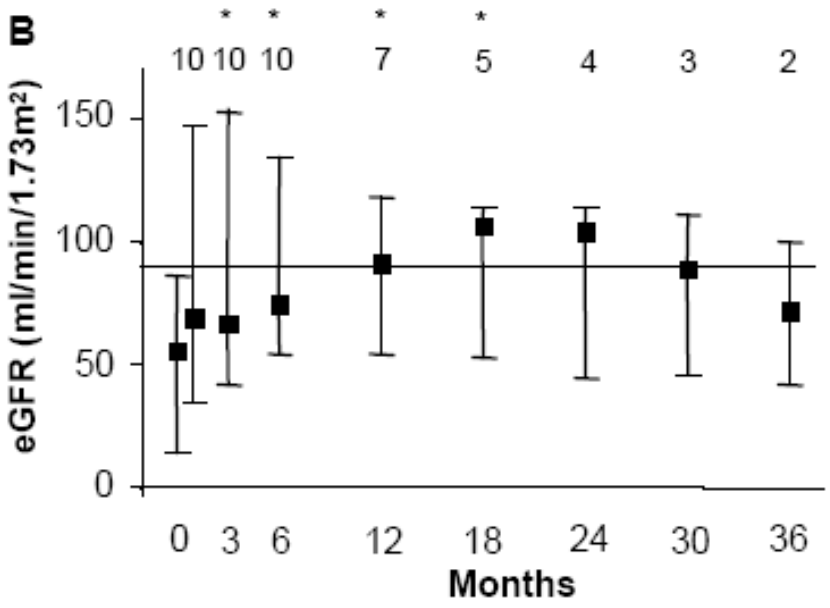
- Sex: 17 F : 2 M (89% F)
- Range of ages: 6.1 - 16.7 years
  Median 14.5y
- Disease duration: 0.1 - 9.4 years
  Median 3.1y
- Follow-up 0.5 - 3.2 years
  Median 1.7y
- Lupus nephritis 79% (n = 15: 60% Class IV)
  eGFR 14-85(median 54)mls/min/1.73m^2

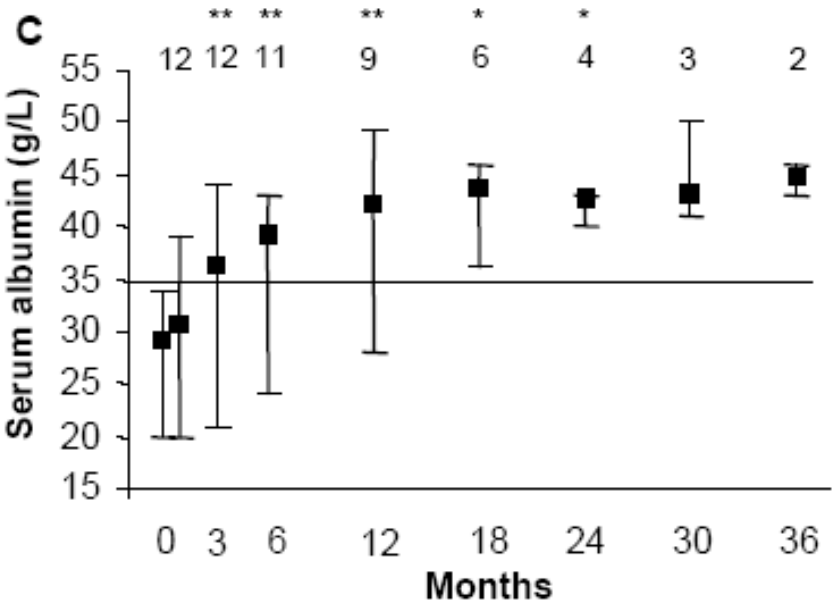
Patient / sex / age	Disease duration (years)	Follow-up duration (months)	Previous immunosuppressive therapy	Indication for rituximab	CYC **	Outcome
1A / male / 16.2	5.1	7	CS, AZA, MMF, CYC	GS, H	yes	FR
1B / male / 16.7	5.7	38	CS, AZA, MMF, CYC, RIT	GS	no	FR
2A / male / 15.0	7.9	18	CS, AZA, HC, MMF, CYC	GS, S	yes	FR
2B / male / 16.5	9.4	20	CS, AZA, HC, MMF, CYC, RIT	S	no	FR
3 / female / 15.9	5.9	36	CS, HC, MMF, CYC, IVIG	MSD (CNS)	yes	FR
4 / female / 12.8	2.7	34	CS, AZA, HC, MMF, CYC	MSD (CNS, R)	yes	FR
5 / female / 8.1	0.1	32	CS, CYC	MSD (CNS, R)	yes	FR
6 / female / 14.9	0.2	33	CS, CYC, IVIG	MSD (CNS, R)	yes	I
7 / female / 13.8	1.1	25	CS, AZA, HC, MMF, CYC	R	no	I
8 / male / 14.5	4.5	26	CS, AZA, MMF, CYC, MZ	GF	no	FR
9 / female / 10.3	0.2	24	CS, HC, CYC	MSD (R)	yes	FR
10 / female / 13.2	4.8	27	CS, AZA, HC, MTX, CYC, IVIG	S	yes	I
11 / female / 13.6	1.3	21	CS, HC, MMF, CYC	S, J	yes	FR
12 / female / 12.5	4.2	15	CS, AZA, HC, CYC	GS, R	no	I
13 / female / 14.0	0.8	14	CS, CYC	MSD (R)	yes	I
14 / female / 15.9	3.1	15	CS, AZA, CYC	GS, R	yes	I
15 / female / 14.5	6.4	10	CS, MMF, CYC	GS, R	no	I
16 / female / 15.7	1.9	7	CS, AZA, HC, CYC	GS, R	no	I
17 / female / 13.7	2.5	7	CS, AZA, HC, MMF	GS, S, J	yes	SI
18 / female / 6.1	2.8	6	CS, AZA, HC	GS, S	yes	FR
19 / female / 15.5	6.6	6	CS, HC, AZA	GS, S	yes	I

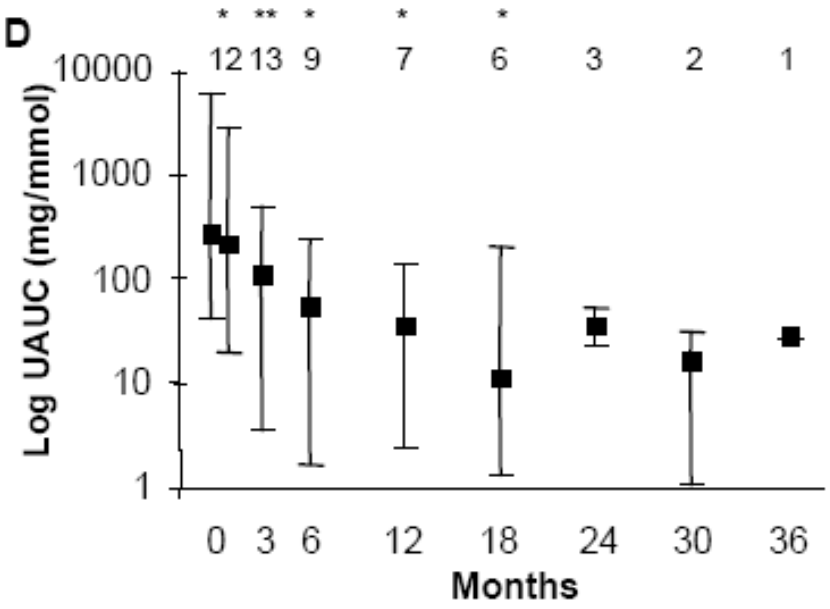
*CS, corticosteroids; AZA, azathioprine; HC, hydroxychloroquine; MMF, mycophenolate mofetil; CYC, cyclophosphamide; RIT, rituximab; IVIG, intravenous immunoglobulins; MTX, methotrexate; MZ, mizoribine; GS, generalised symptoms; H, haematological involvement; S, skin involvement; CNS, central nervous system involvement; R, renal involvement; GF, growth failure; J, joints involvement; FR, full recovery; I, improvement; SI, some improvement. In cases with multi-system disease (MSD) the most prominent symptoms are specified in brackets. **Information about addition of cyclophosphamide to the treatment with rituximab.

Disease activity and renal parameters

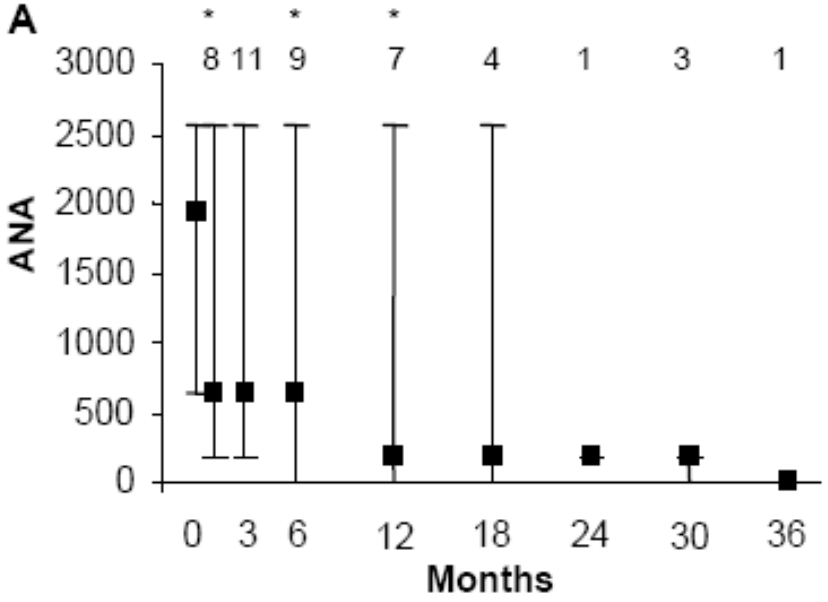


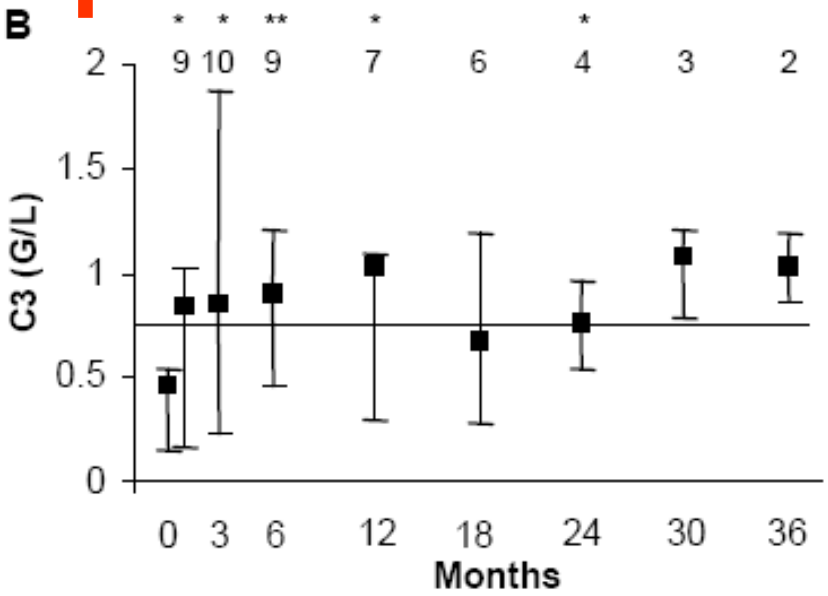


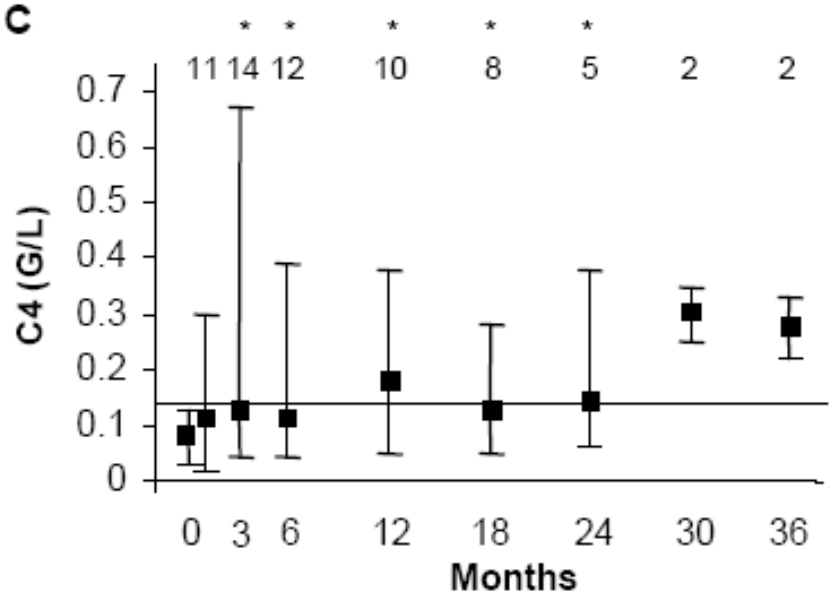


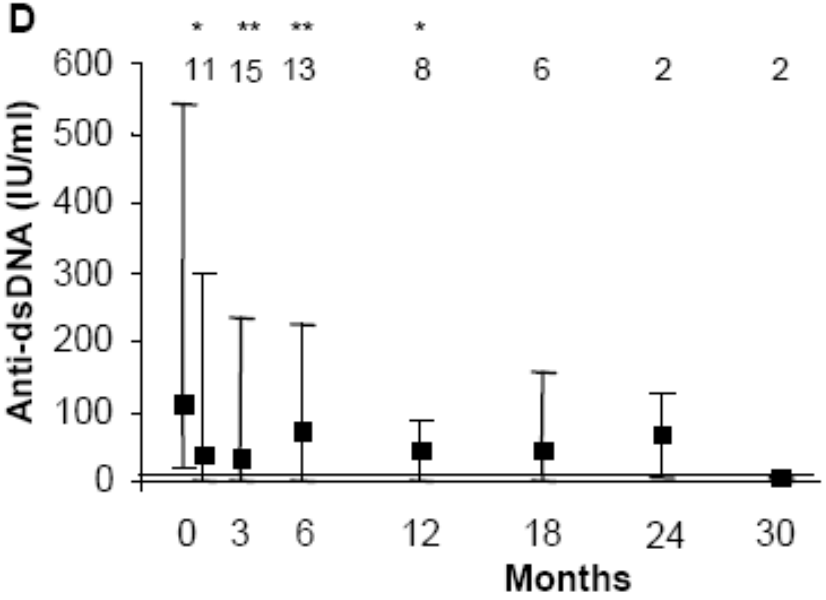


Immunological parameters

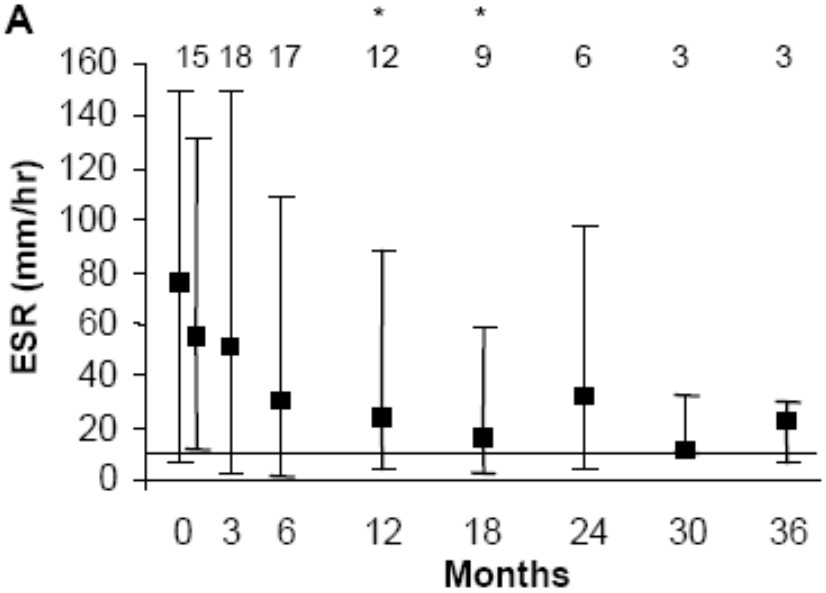


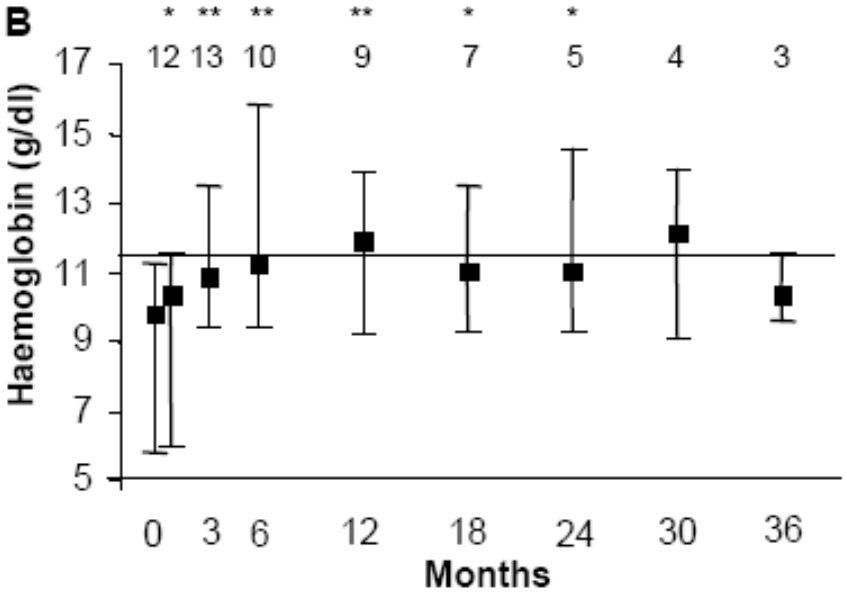


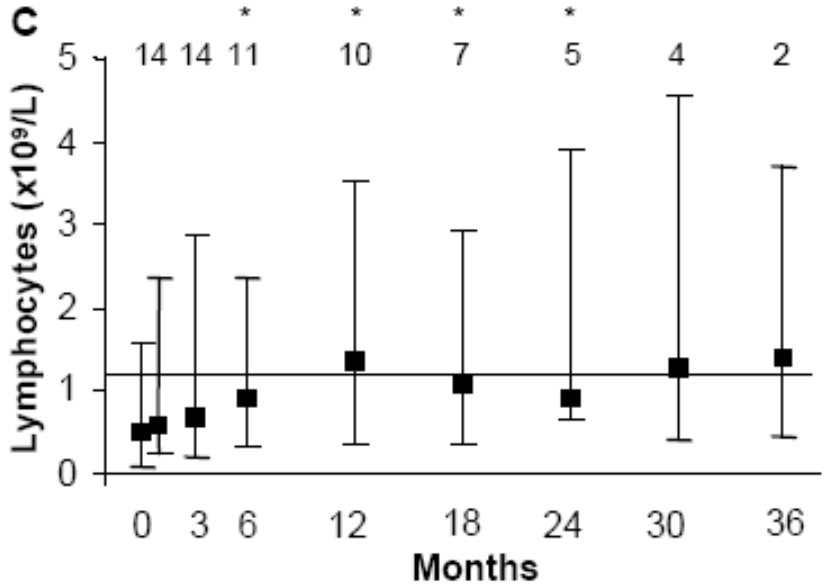


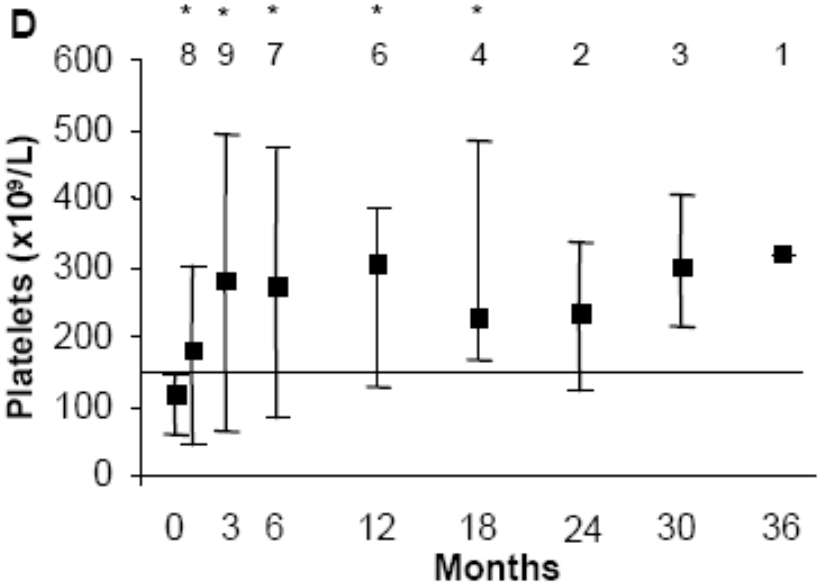


Haematological parameters

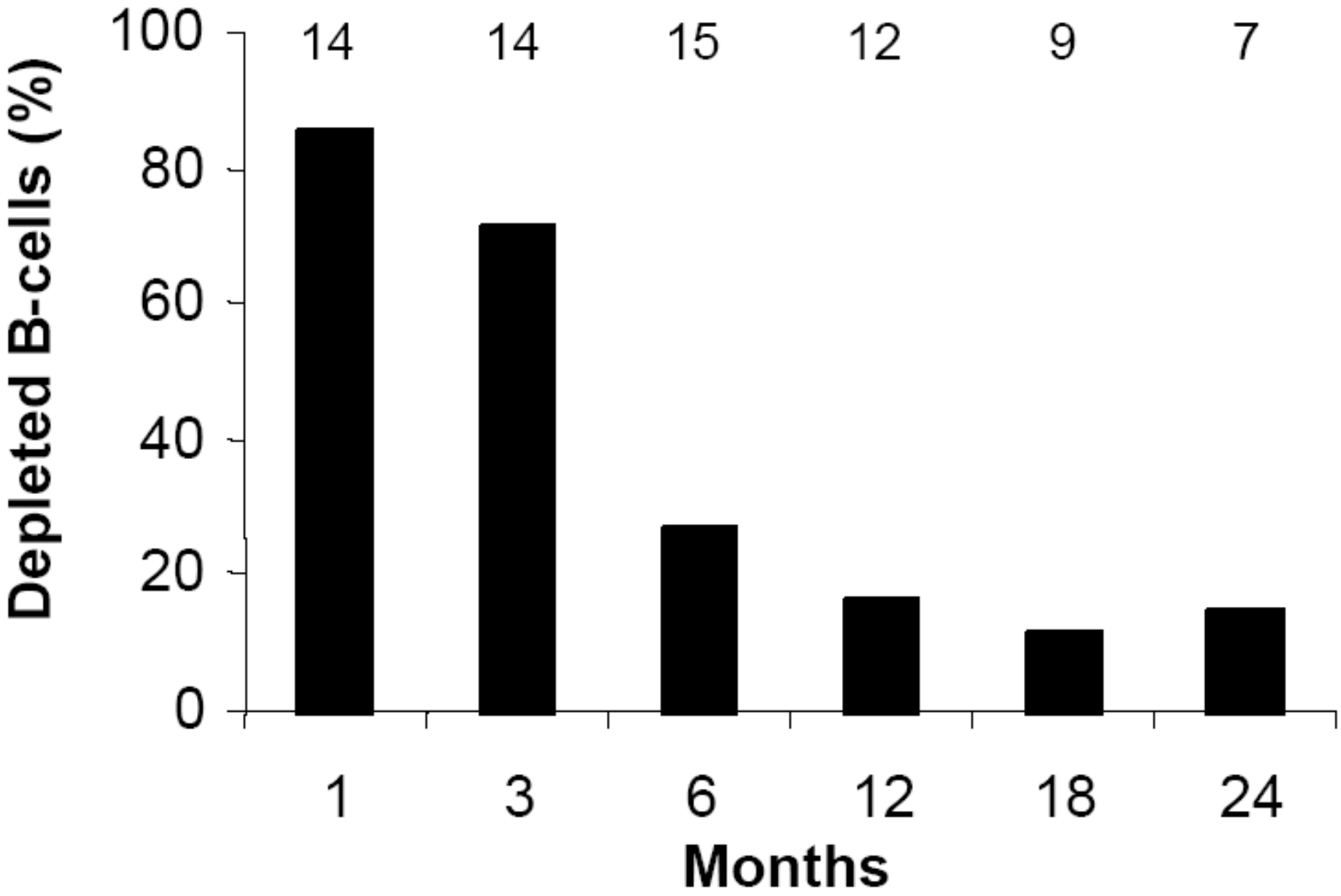








B cell depletion



Clinical outcome

- Patients had clinically significant improvement in symptoms and signs (as indication for therapy)
  - 52% full recovery and 43% improvement
- Anecdotal responses
  - “Never felt so good; I’ve had lupus for 11y”
  - “I have never had so much energy”
  - “My rash has gone and I feel fab”

Side-effects of rituximab

- 26% (5) patients developed herpes zoster
  - one recorded GI symptoms (nausea / vomiting)
  - one subsequent patient developed urticarial rash four days after infusion
  - CYTOKINE RELEASE SYNDROME in lymphoma treatment as greater cell numbers
    - FEVERS AND RIGORS WITHIN 2 HOURS
    - ALSO PRURITIS, RASHES, DYSPNOEA, BRONCHOSPASM, ANGIONEUROTIC OEDEMA AND TRANSIENT HYPOTENSION
  - in the event of an infusion-related adverse event, stop the infusion and recommence at half the previous rate once the symptoms have resolved

Conclusions

- This pilot study shows that B cell depletion therapy in childhood refractory SLE was safe and efficacious in 21 treatment episodes in 19 children

- There is a need for a multi-centre, randomised controlled trial for use of rituximab in treatment of childhood SLE

Dual centre paediatric cohort

Patients first episodes (n=63)

Laboratory marker	Before rituximab, median (IQR)	After rituximab, median (IQR)	p value
Haemoglobin (g/L)	10.9 (9.6-12.2)	11.7 (10.5-12.5)	<0.001*
WCC (x109/L)	5.8 (3.7-8.5)	5.1 (3.8-8.4)	0.819
Neut (x109/L)	3.9 (2.3-6.3)	3.5 (2.5-5.8)	0.433
Lymph (x109/L)	1.1 (0.8-1.5)	0.9 (0.6-1.3)	0.023*
Platelet (x109/L)	243 (161-328)	277 (209-351)	0.084
ESR (mm/hr)	60 (26-101)	37 (12-56)	<0.001*
C3 (g/L)	0.88 (0.52-1.03)	0.94 (0.70-1.20)	<0.001*
C4 (g/L)	0.11 (0.07-0.17)	0.17 (0.03-0.50)	0.001*
Albumin (g/L)	35 (25-41)	38 (33-43)	<0.001*
Creatinine (mmol/L)	58 (48-70)	53 (48-66)	0.004*
IgG (g/L)	11.9 (6.0-17.1)	9.7 (4.7-13.1)	<0.001*
IgA (g/L)	1.7 (1.1-2.5)	1.3 (0.8-2.5)	0.001*
IgM (g/L)	1.0 (0.5-1.3)	0.6 (0.3-0.8)	<0.001*
UACR (mg/mmol)	37 (2-351)	40 (2-142)	0.081
Anti-dsDNA (IU/L)	95 (13-283)	30 (5-91)	<0.001*

*statistically significant

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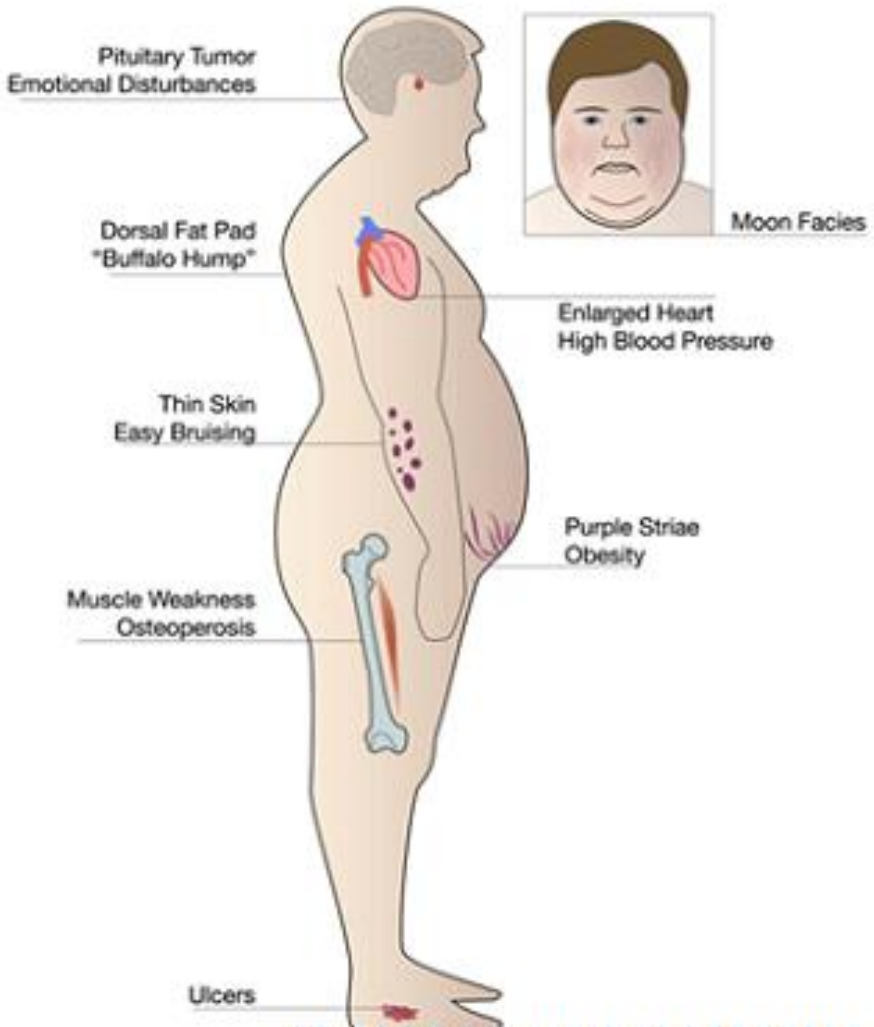
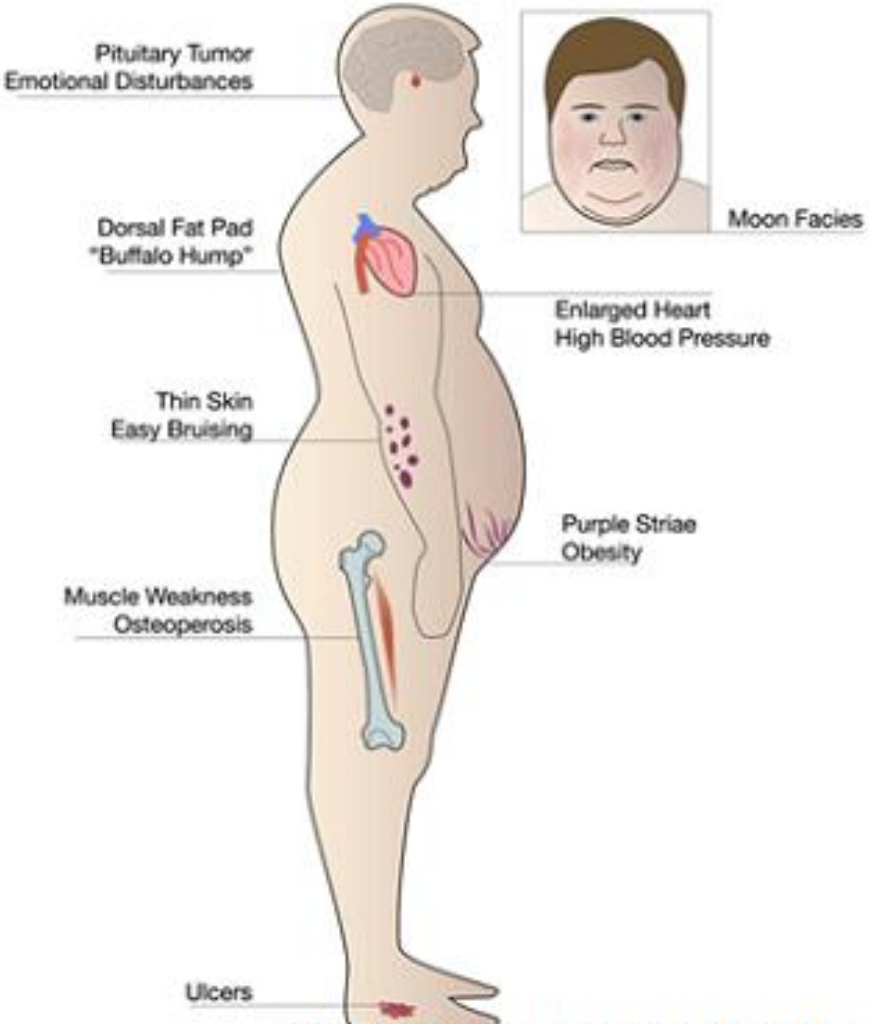
IgG (g/L)	11.9 (6.0-17.1)	9.7 (4.7-13.1)	<0.001*
IgA (g/L)	1.7 (1.1-2.5)	1.3 (0.8-2.5)	0.001*
IgM (g/L)	1.0 (0.5-1.3)	0.6 (0.3-0.8)	<0.001*
UACR (mg/mmol)	37 (2-351)	40 (2-142)	0.081
Anti-dsDNA (IU/L)	95 (13-283)	30 (5-91)	<0.001*

*statistically significant

Corticosteroid side-effects



Corticosteroid side-effects



SLE teenager

Patient photo

15 years and 10 months ♀

SLE (since age 9.6 years)

Sickle cell anaemia (HbSS)

Pulmonary hypertension

ISN/RPS class III (A/C) LN

Intra-articular right wrist and left ankle corticosteroid injections

Intravenous infusions

- 5 x iv cyc 1.875 g/m^2
- 10 x rituximab 750mg/m^2 q6m
- alternate day pred + MTx

SLE teenager

Patient photo

17 years and 7 months ♀

SLE (since age 9 years)

TTP requiring ivMP and PX

Steroid induced IDDM (GAD+)

Cutaneous lupus / folliculitis

ISN/RPS class III-S(C) LN (11.5y)

Intravenous infusions

- 5 x iv cyc 4.2g/m^2
- 4 x rituximab 750mg/m^2 q6m
- alternate day pred + aza

RITUXILUP trial – MP+MMF+Rituximab vs MMF+Steroids

- Rationale
  - steroids are associated with long term damage and premature mortality in patients with lupus nephritis.
  - little evidence to support correct dose and duration
    - evidence suggesting harm in long term use
  - pilot data suggest that, in patients not already on steroids, methylprednisolone 500mg and rituximab 1g on d1 and d14 with ONLY oral MMF thereafter, induces high rates of remission with few adverse events
- Goal
  - to demonstrate Rituxilup protocol is not inferior to MMF and steroids in efficacy AND has a better safety profile
- Significance
  - avoidance of oral steroids in majority of patients with LN

RITUXILUP trial – MP+MMF+Rituximab vs MP+MMF+Steroids (ALMS MMF regimen)

- Open label multi-centre RCT
  - UK: 18 adult and 4 paediatric centres
  - Europe: 3 networks and 5 other centres
  - USA: on board
- Designed as non-inferiority trial, asking the question whether combination of rituximab and no oral steroids is as effective as MMF and steroids in inducing renal remission
- Primary end-point of complete renal remission at 1 year
  - control group: CR 40% (trials suggest 18-40%)
  - inferiority margin 20%: CR of 30% in rituximab group would be non inferior
  - 87% power, require 228 patients; 252 assuming 10% drop out
- Key secondary EP: safety signals from lack of steroids
- Minimum follow-up 2 years with option of up to 4 years

Newer biological agents

Drug name	Actions	Studies
Epratuzumab	CD22 monoclonal antibody that inhibits B cells	Daridon, 2010
Atacicept	Recombinant fusion protein that binds with BAFF & APRIL receptors	Pena-Rossi, 2008
Tocilizumab	IL-6 monoclonal antibody	Illei 2010
Ocrelizumab	Targets CD20+ B cells	Hutas, 2008
Abatacept	Modulates CD80/CD86:CD28, controls regulatory & inhibitory factors	Merrill 2010
Abetimus	Induces B cell tolerance	Cardiel 2008
Rigeromid	Spliceosomal peptide P140; blocks recognition of IgG antibodies and CD4+ T cells	Muller, 2008

BAFF B cell activating factor; APRIL a proliferation-inducing ligand

Other treatments

- Long list of different agents in the pipeline
  - LJP 394 – anti-anti-DNA
  - anti-C5 complement Mab
  - other possibilities

- Stem cell transplantation

Stem cell transplantation

- March 2001, 34 patients were published
- 23 registered patients in Basle
  - 3 died
  - 1 worse
  - 5 improved but relapsed
  - 14 improved
    - Tyndall et al (2001) Ann Rheum Dis 60:702-707
- Current opinion

  - other available options so transplantation less appealing

Conclusions

- SLE is a multi-system disease
  - different spectrum from adults
  - various subspecialties
  - unpredictable course
- Various assessments
  - disease activity and damage
  - QOL assessments
- Rituximab has a role in treating active disease
- Chronic disease
  - collaboration with adult colleagues
  - for long-term outcomes and transition of care

Take home messages

- MMF has taken the role of cyclophosphamide and azathioprine
  - first line induction and maintenance therapy
- Rituximab is effective but not proven in RCT
  - positive case series so may be a problem with trials
- Belimumab is registered for the use in lupus
  - not tested in lupus nephritis
- Many drugs in the pipeline

Without it, I would not have learnt so much about myself and about life in general…

With support from friends, family, and clinicians,

dancing with the wolf is not all doom and gloom."

Jane Robinson, June 2006.

Quotation from adult patient with SLE

from published article in the British Medical Journal:

Robinson J. The patient's journey: systemic lupus erythematosus.

BMJ 2006 June;332(7554):1374-6.

Evidence-based medicine slides

1. Bertsias G et al (2012) “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.”
   Ann Rheum Dis; 71(11): 1771 - 1782.

2. Sag E, Tartaglione A, Batu ED, Ravelli A, Khalil AS, Marks SD, Ozen S (2014). “Performance of the new SLICC classification criteria in childhood systemic lupus erythematosus: a multicentre study.”
   Clin Exp Rheumatol; 32(3): 440 - 444.

3. Marks SD, Tullus K (2012). “Autoantibodies in systemic lupus erythematosus.” Ped Nephrol; 27(10): 1855 - 1868.

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European evidence-based recommendations for diagnosis and treatment of paediatric antiphospholipid syndrome: the SHARE initiative

Noortje Groot,[1,2] Nienke de Graeff,[1] Tadej Avcin,[3] Brigitte Bader-Meunier,[4] Pavla Dolezalova,[5] Brian Feldman,[6] Gili Kenet,[7] Isabelle Koné-Paut,[8] Pekka Lahdenne,[9] Stephen D. Marks,[10] Liza McCann,[11,12] Clarissa A. Pilkington,[10] Angelo Ravelli,[13] Annet van Royen-Kerkhof,[1] Yosef Uziel,[14] Sebastiaan J. Vastert,[1] Nico M. Wulffraat,[1] Seza Ozen,[15] Paul Brogan,[10] Sylvia Kamphuis,[2] Michael W. Beresford[11,12]

ARD Online First, published on June 19, 2017 as 10.1136/annrheumdis-2016-210960

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First, published on September 6, 2017 as 10.1136/annrheumdis-2017-211898

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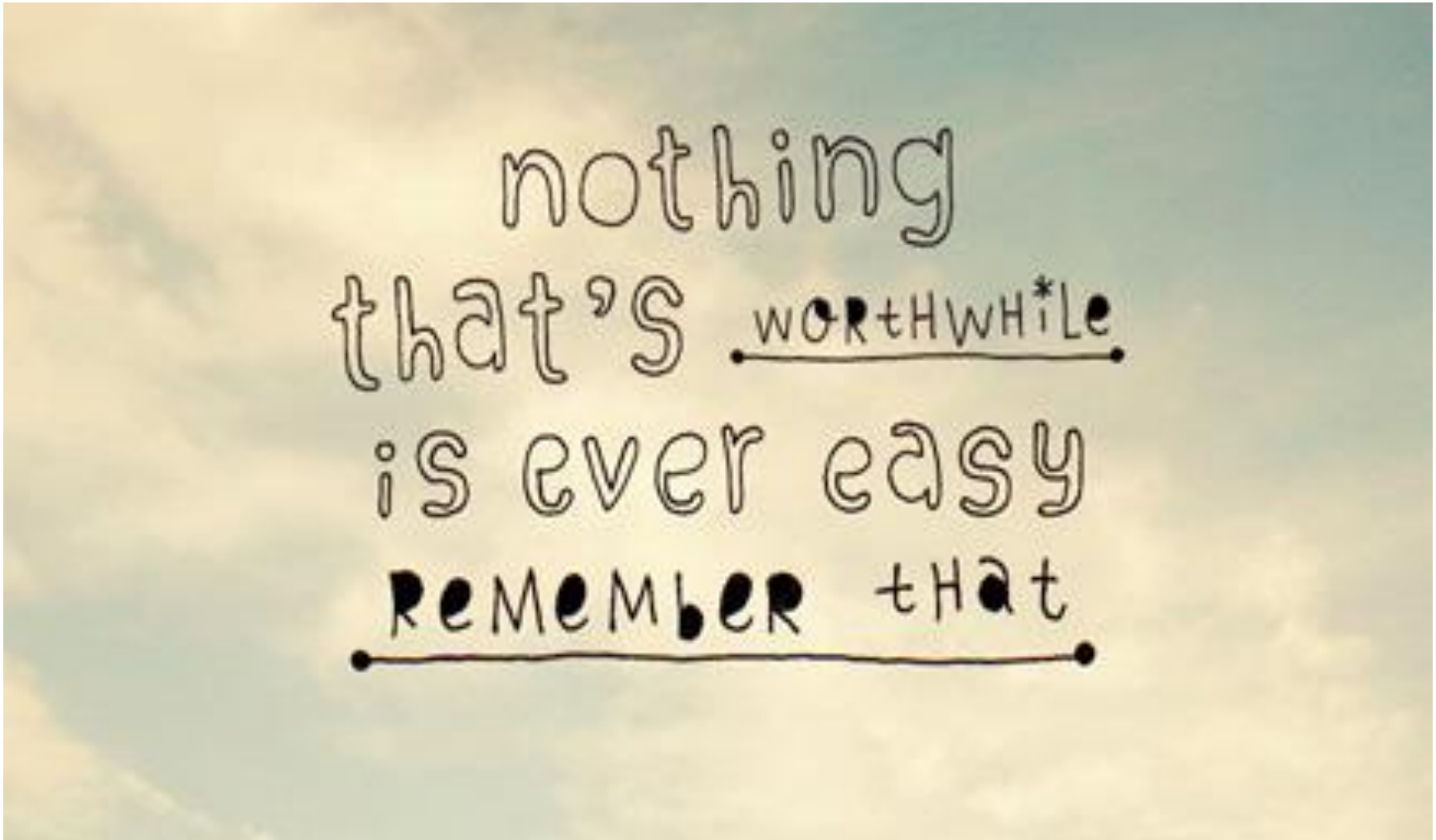
Any questions ?



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Speaker: **Olivier Devuyst**

Topic**: Uric acid disorders**

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Date: **30 March 2021**

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Topic**: Genetics of stones**

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