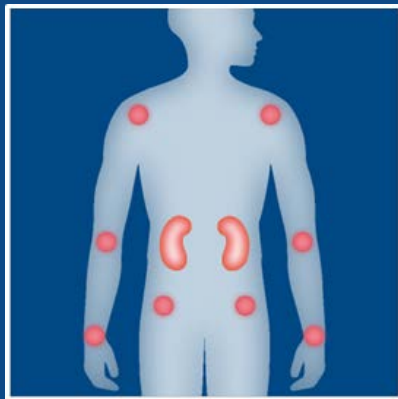


Nephro Update Europe 2018

5-6 October, Budapest

Systemic Autoimmune Diseases



Charles Pusey, UK

Conflicts of Interest

Research Support: Medical Research Council, National Institute for Health Research, Wellcome Trust, Kidney Research UK, Vasculitis UK, Imperial Health Charity

Lecturing: Nephro Update 2017

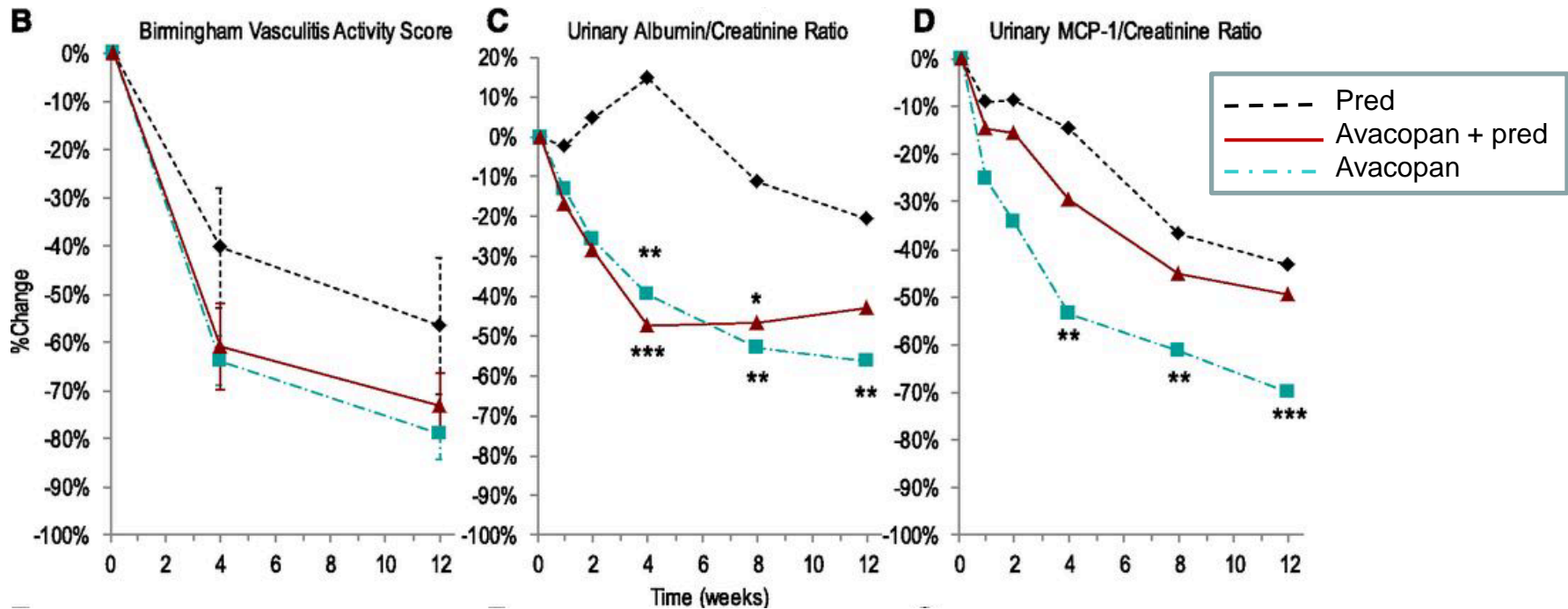
Consulting activities: Cell Medica

ANCA-associated vasculitis

State of the Art

- Induction treatment
 - Limited Pred + MTX (or MMF or AZA)
 - Generalised Pred + CYC(IV) or RTX \pm PE (\pm MP)
- Maintenance treatment
 - Standard Pred + AZA (or MMF or MTX)
 - Relapsing Pred + RTX 6 monthly
- Histopathological class of biopsy predicts outcome
- Anti-MPO/PR3 levels may be of value in monitoring disease (especially renal)
- 5 year patient survival 70-80%, renal survival 60-70%

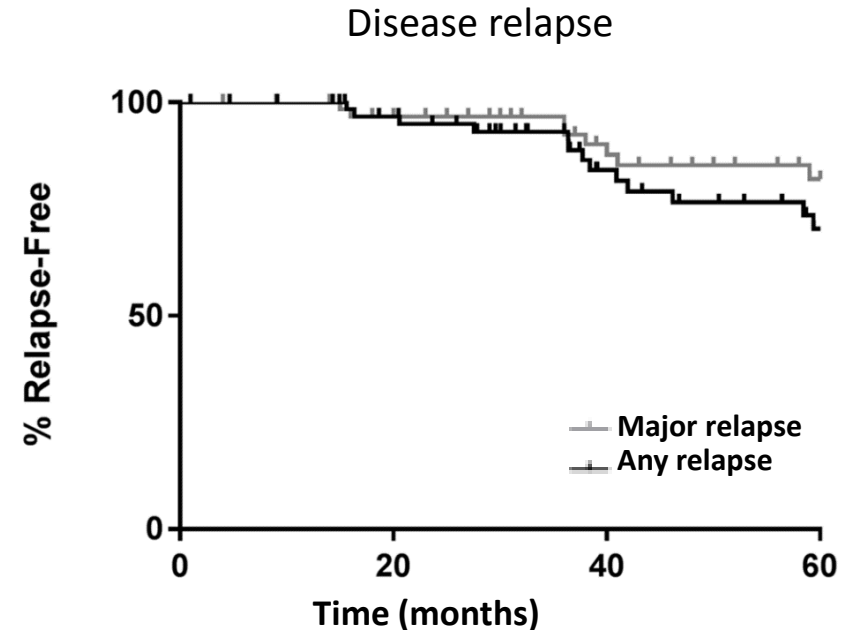
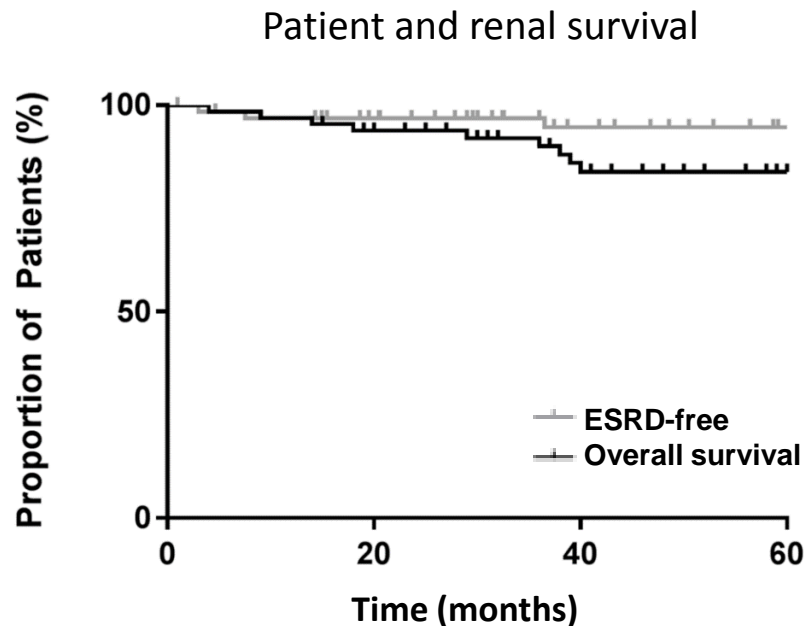
CLEAR – Randomised trial of avacopan versus prednisolone as induction therapy for AAV



- Replacement of pred by avacopan in 67 AAV patients
- Patients also received CYC or RTX at induction
- Avacopan was effective in replacing corticosteroids at 12 weeks

Jayne et al, J Am Soc Nephrol 2017; 28: 2756-2767

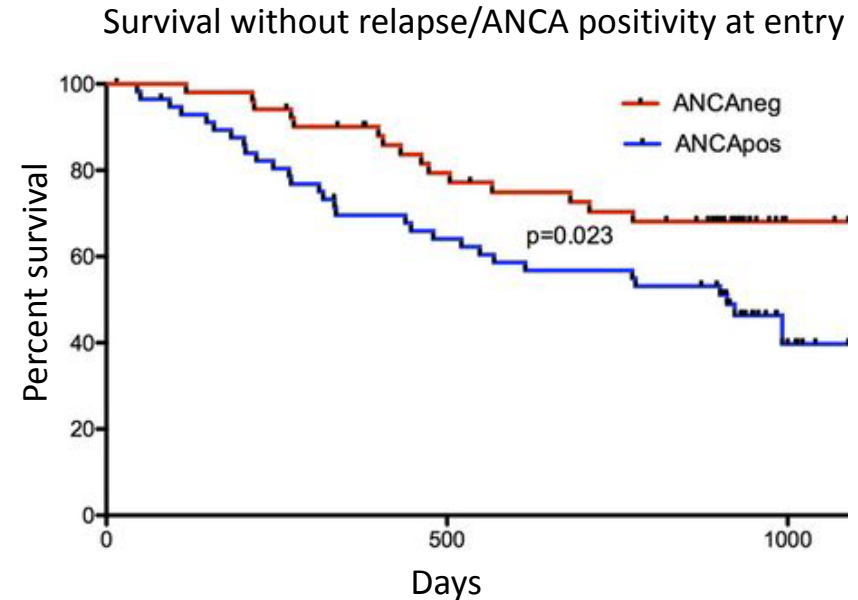
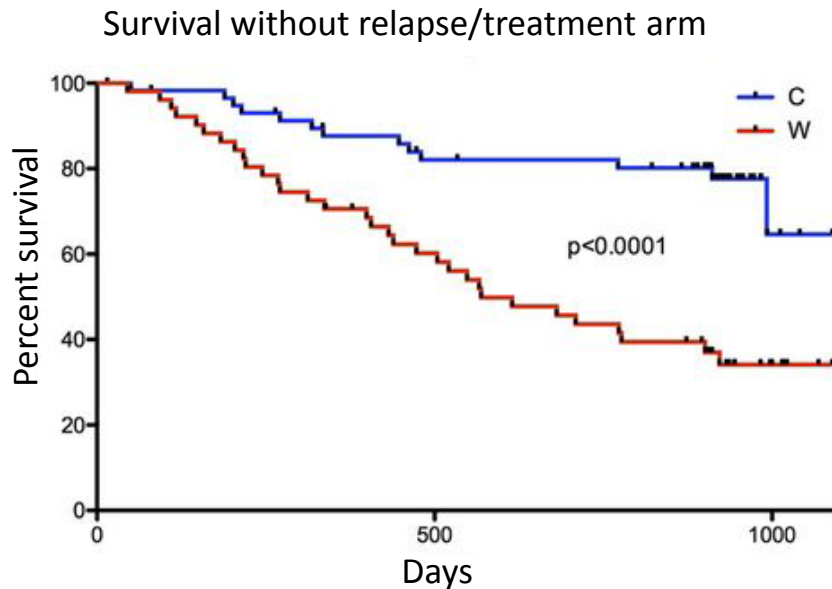
Combined rituximab and IV cyclophosphamide in renal AAV (CycLowVas)



- Study of 66 AAV patients in UK, treated with RTX, IV CYC and oral pred
- Remission in 94% at 6m, sustained fall in B cells and ANCA
- 5y patient survival 84%, renal survival 95%, major relapse 15%
- Compared with matched EUVAS cohort, CycLowVas showed reduced risk of death, ESRD, and relapse

McAdoo et al, Nephrol Dial Transplant 2018 (epub ahead of print)

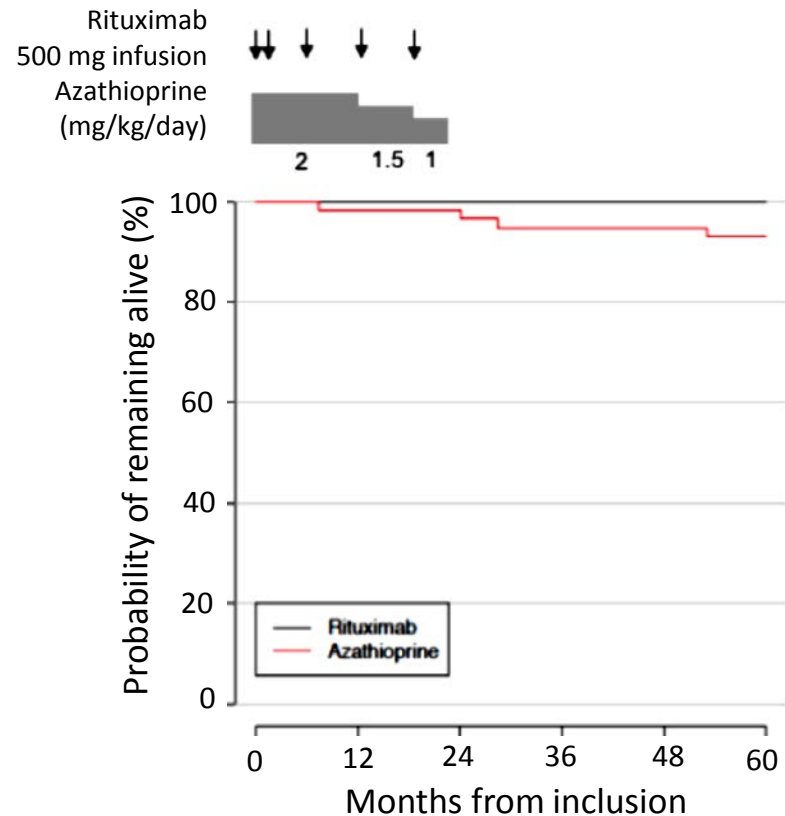
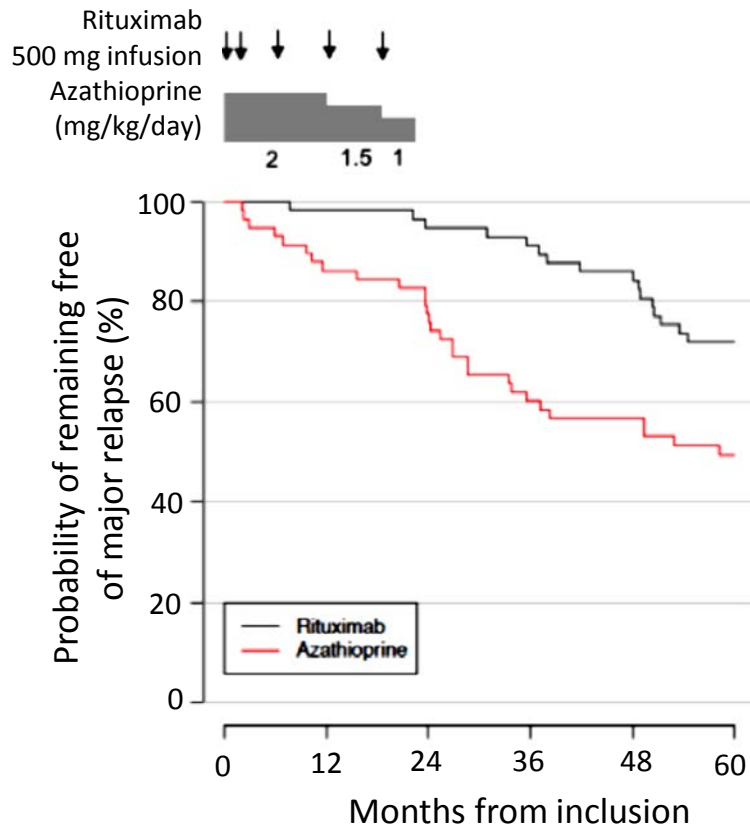
REMAIN – Randomised trial of prolonged treatment for remission maintenance in AAV



- Maintenance with AZA/pred for 24 vs 48 months after CYC induction
- Continuation group had less relapse and better renal outcome but more adverse events
- ANCA positivity at randomisation associated with relapse

Karras et al, Ann Rheum Dis 2017; 76: 1662-1668

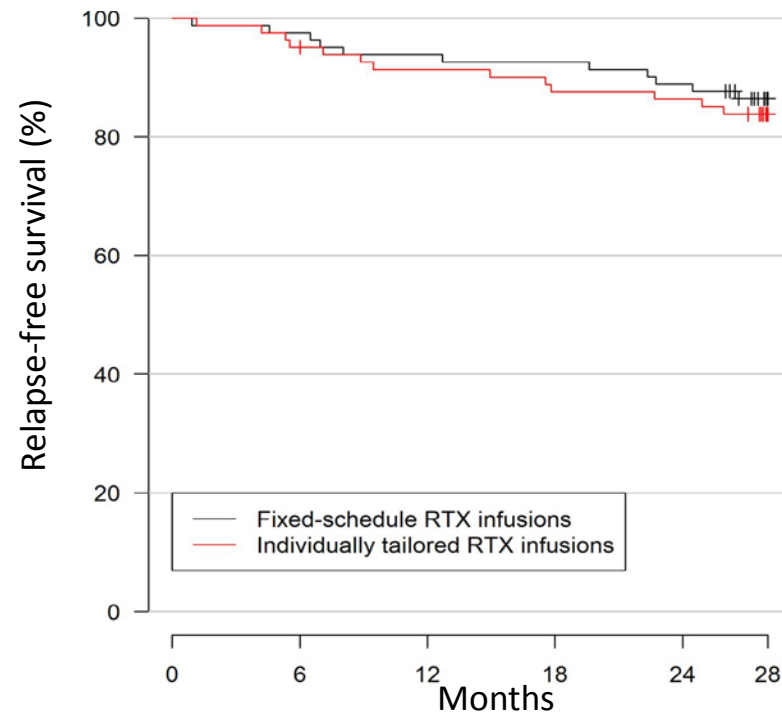
Long-term follow-up of MAINRITSAN trial of rituximab vs azathioprine maintenance in AAV



- 60 month follow-up of MAINRITSAN
- Major relapses fewer in RTX group
- Patient survival better in RTX group

Terrier et al, Ann Rheum Dis 2018; 77: 1151-1157

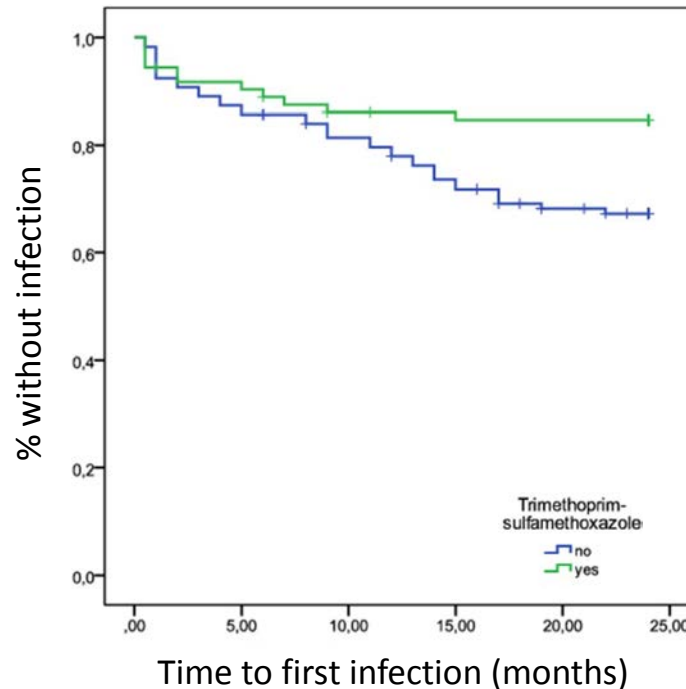
MAINRITSAN2 – Randomised trial of fixed schedule vs tailored rituximab maintenance in AAV



- Maintenance with RTX 500 mg 6 monthly vs RTX based on B cells/ANCA
- Relapse rates did not differ between groups
- Tailored RTX group received fewer infusions

Charles et al, Ann Rheum Dis 2018; 77: 1144-1150

Effect of cotrimoxazole on severe infections following rituximab in AAV



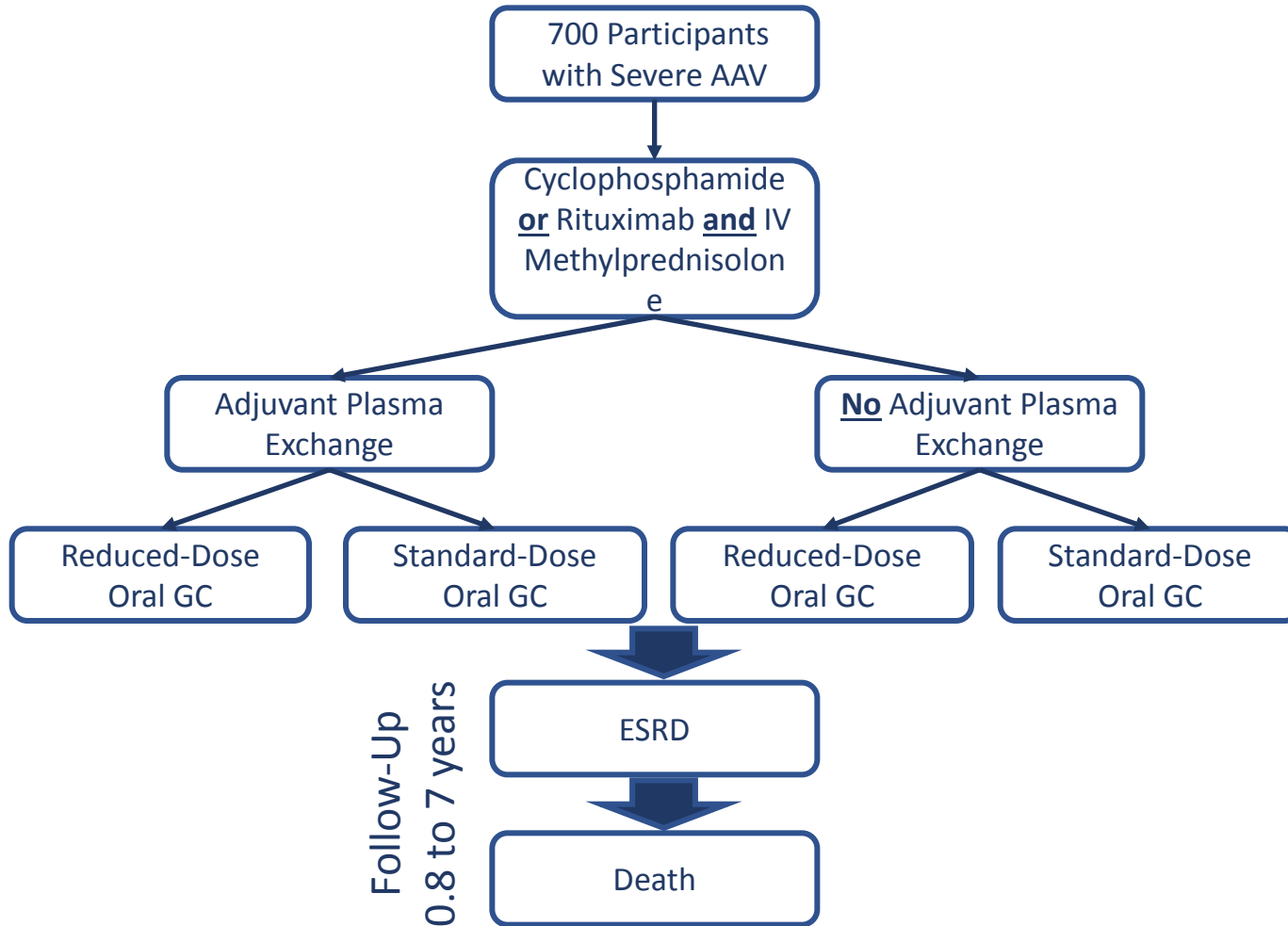
- Study of 192 AAV patients treated with RTX
- Severe infections in 49 patients
- Cotrimoxazole associated with lower frequency infections
- Risk increased by older age, bronchial lesions, COPD, alemtuzumab

Kronbichler et al, Ann Rheum Dis 2018 (epub ahead of print)

Take Home Message

- Avacopan (C5aR inhibitor) can substitute for corticosteroids in induction of MPA/GPA – but short-term, phase 2 study
- Combined rituximab and IV cyclophosphamide is effective for induction in AAV with reduced rate of relapse
- Continued azathioprine/low dose pred for 48m vs 24m reduces relapse and improves renal outcome in AAV – but more adverse events
- Long-term follow-up of MAINRITSAN trial shows fewer major relapses and better survival in rituximab group
- Fixed schedule vs tailored rituximab maintenance shows similar relapse rates with fewer infusions in tailored group
- Cotrimoxazole is associated with lower frequency of severe infections following rituximab treatment in AAV

PEXIVAS



Objectives

Does PLEX reduce death or ESRD?

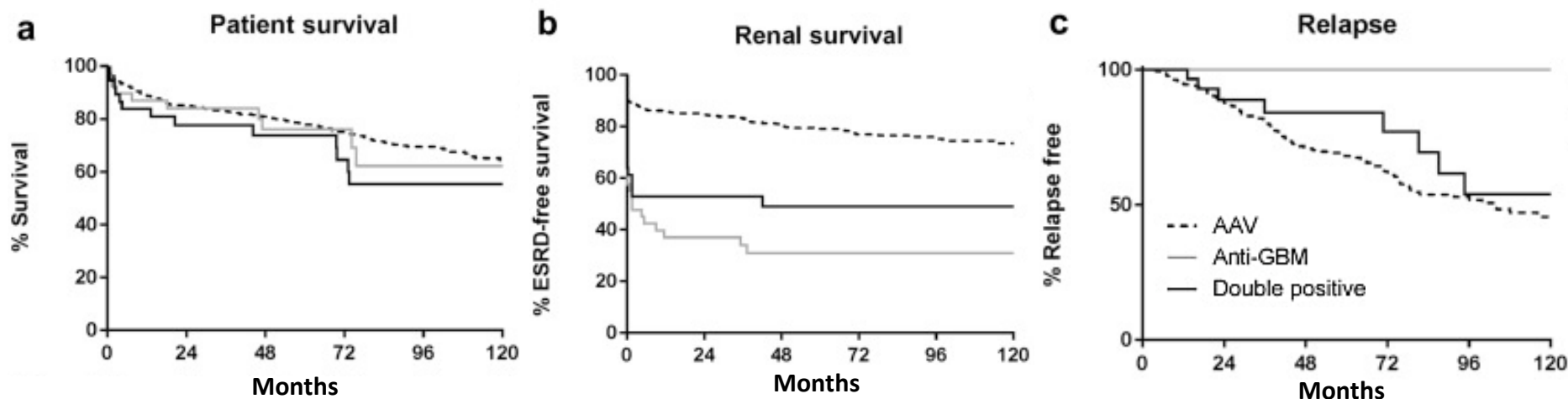
Is a “reduced” dose GC regimen non-inferior to a “standard” dose regimen in terms of death or end-stage renal disease?

Anti-GBM disease

State of the Art

- Treat with pred, CYC (oral) and PE x 14 – with anti-GBM ab monitoring
- Stop CYC at 3m, pred at 6m, no maintenance
- Dialysis dependent or oliguric patients with 100% crescents unlikely to recover renal function
- Alveolar haemorrhage an independent indication for treatment
- “Double-positive” anti-GBM ab and ANCA patients have renal outcome similar to (or better than) anti-GBM disease

Survival and relapse in anti-GBM ab and ANCA “double positive” patients

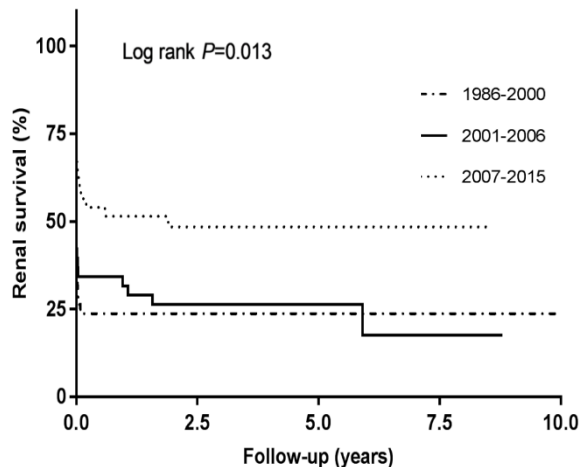


- Study of 41 anti-GBM, 37 double +ve, and 568 AAV patients
- Renal survival double +ve patients similar to anti-GBM
- Trend for more double +ve patients to come off dialysis
- Relapse in double +ve patients similar to AAV

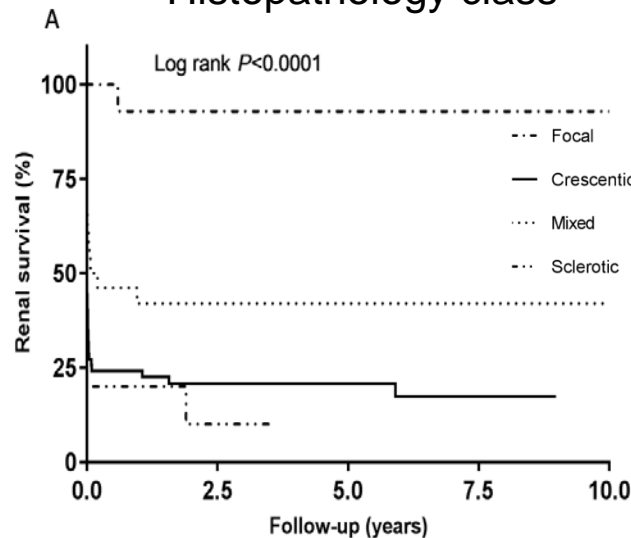
McAdoo et al, Kidney Int 2017; 92:693-702

Predicting outcome in anti-GBM disease

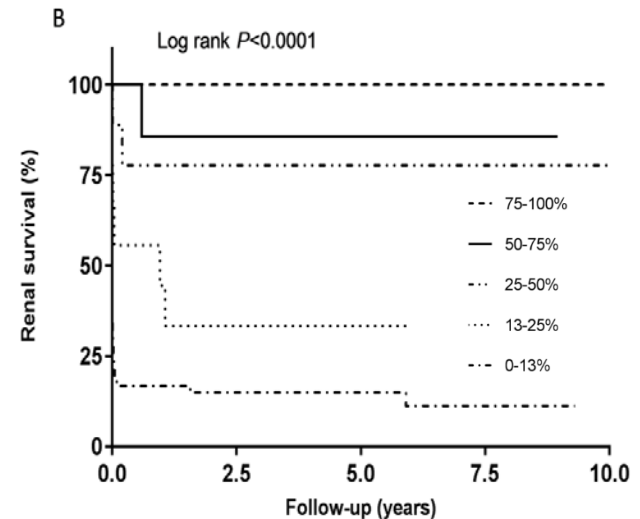
Year of diagnosis



Histopathology class



% normal glomeruli



- International study of 123 anti-GBM patients, 1986-2015
- Overall 5 y patient survival 83%, renal survival 34% (better after 2007 at 50%)
- Focal class (*Berden et al, JASN 2010*) show good renal outcome, sclerotic class poor outcome
- ESRD predicted by dialysis at presentation, % normal glomeruli, interstitial infiltrate

Van Daalen et al, Clin J Am Soc Nephrol 2018; 13: 63-72

Take Home Message

- Renal survival in double-positive patients similar to anti-GBM disease, but worse than AAV
- Double-positive patients show trend to better renal recovery from dialysis, and relapse similar to AAV
- Histopathologic class of biopsy in anti-GBM disease (as for AAV) shows good renal recovery in focal class
- Dialysis dependency at presentation, % normal glomeruli and interstitial infiltrate predict ESRD

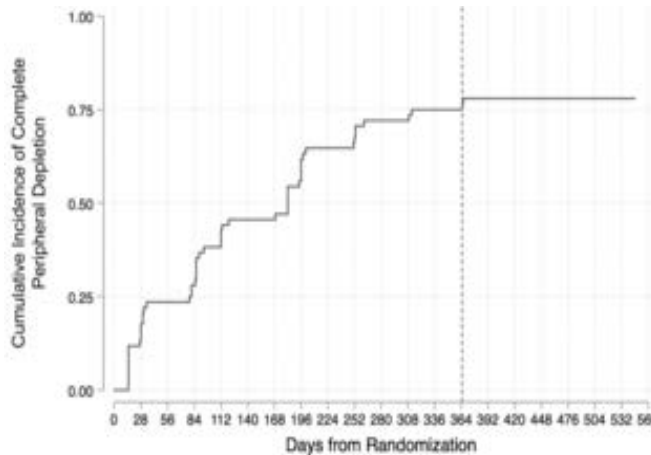
Lupus nephritis

State of the Art

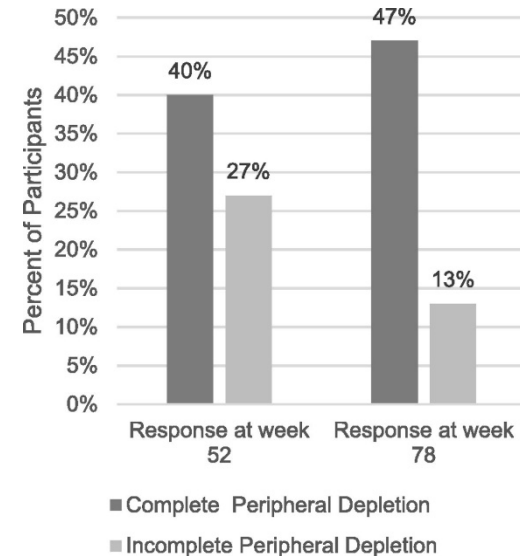
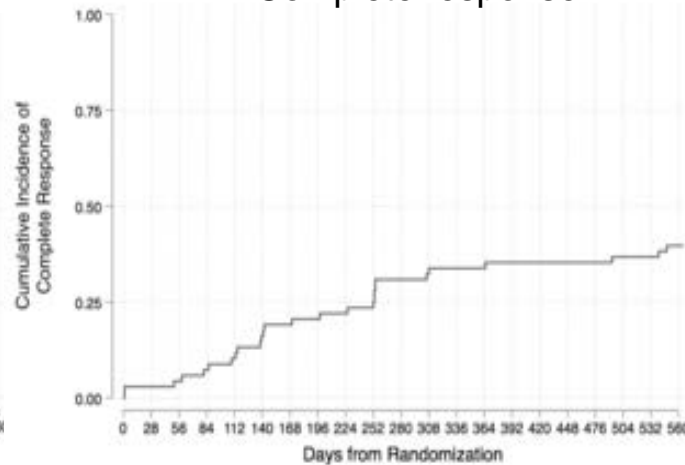
- Induction treatment
 - Class III/IV pred (\pm IV MP) + MMF or IV CYC
 - Class V pred + MMF (or AZA or CNI or IV CYC)
- Maintenance treatment
 - Class III/IV/V low dose pred + MMF (or AZA or CNI)
- Role of RTX still not clear, negative trial but positive case series
- Anti-dsDNAab and C3/4 levels can be used in monitoring

B cell depletion after rituximab and clinical response in lupus nephritis

Complete B cell depletion



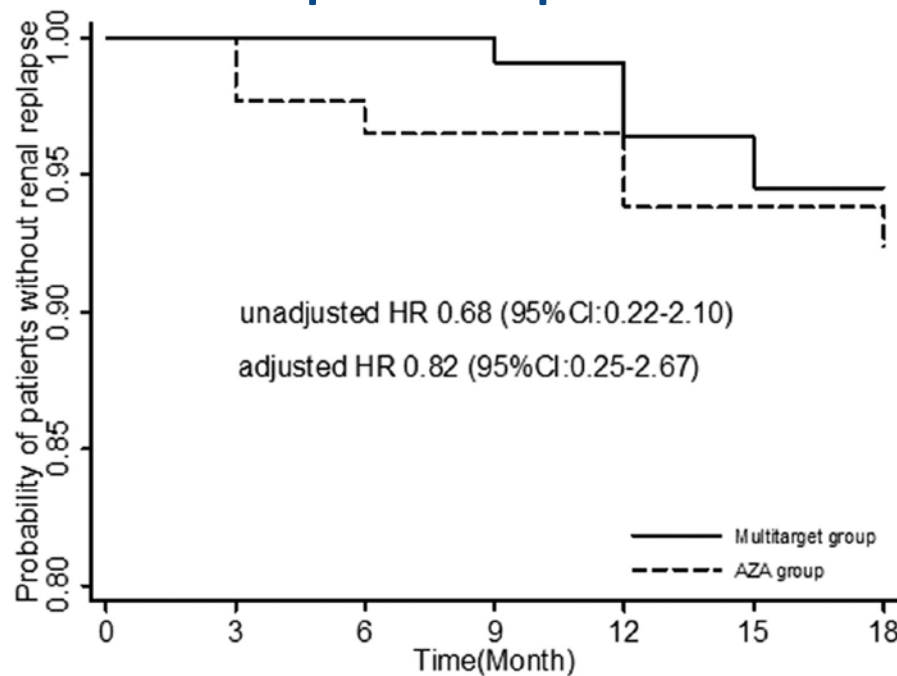
Complete response



- 68 LN patients from LUNAR trial treated with rituximab, day 1, 15, 168, 182
- Complete B cell depletion (0) in 78%, median 182 days
- Complete depletion associated with complete clinical response
- Speed and duration of depletion associated with response

Gomez Mendez et al, Clin J Am Soc Nephrol 2018 (epub ahead of print)

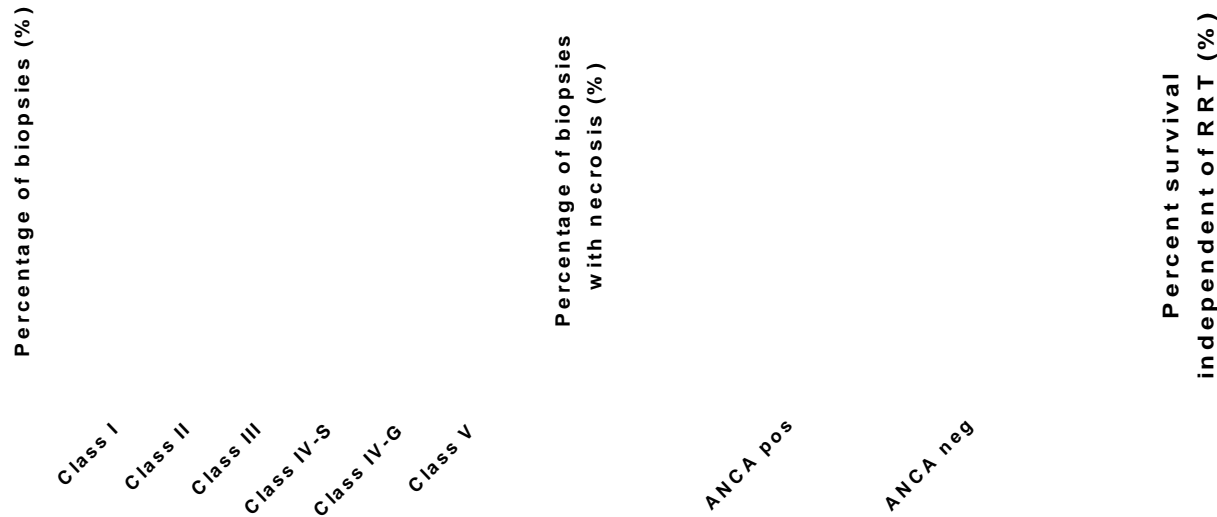
Multitarget therapy as maintenance treatment for lupus nephritis



- Extension of trial comparing multitarget therapy (TAC/MMF/Pred) with IV CYC (*Liu et al, Ann Intern Med 2015*)
- Patients continued multitarget therapy, or started AZA after IV CYC
- Similar probability of renal relapse in both groups
- More adverse events in AZA group

Zhang et al, J Am Soc Nephrol 2017; 28: 3671-3678

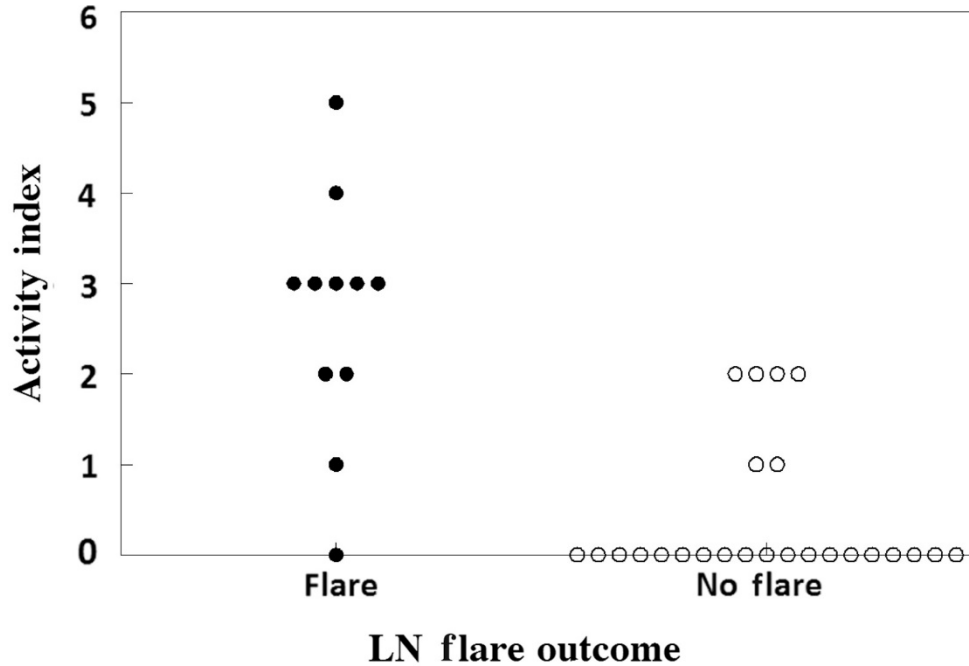
Histopathological features and outcomes in ANCA+ve patients with lupus nephritis



- Study of 32 ANCA+ve and 222 ANCA-ve LN patients in UK
- ANCA+ve patients more class IV-S, glomerular necrosis
- ANCA+ve patients higher dsDNAab, lower C3, higher creatinine
- Trend to worse renal outcome in ANCA+ve patients

Turner-Stokes et al, Kidney Int 2017; 92: 1223-1231

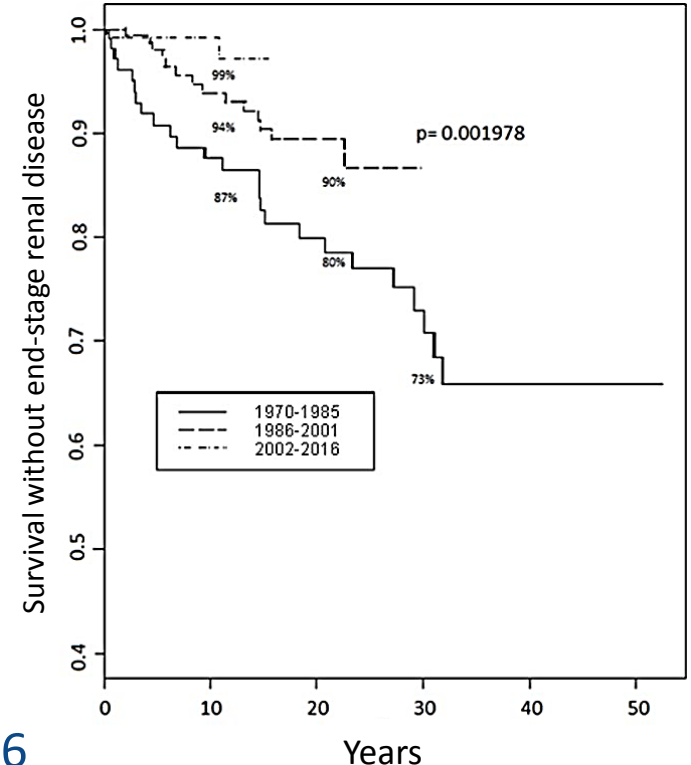
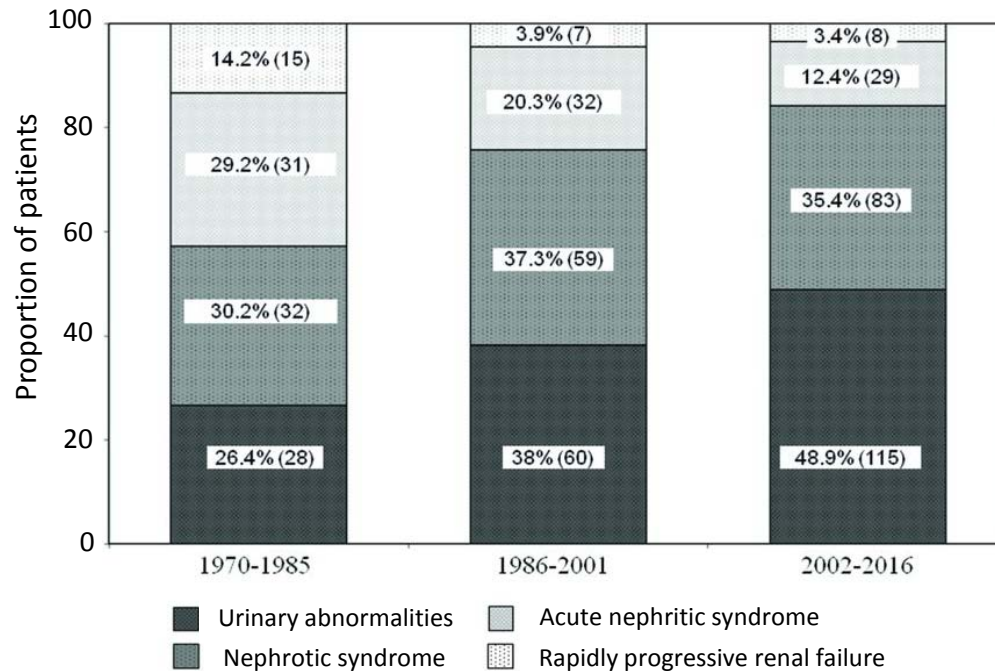
Activity index on repeat biopsy of LN patients developing flare on withdrawing treatment



- 36 LN patients in clinical remission for > 12 m
- Repeat biopsy before tapering immunosuppression
- LN flares commoner in those with higher AI
- AI and duration SLE at biopsy predicted flare

De Rosa et al, Kidney Int, 2018 (epub ahead of print)

Changes in presentation and prognosis of lupus nephritis



- Study of 499 LN patients in Italy, 1970-2016
- Increase in milder presentation over time
- No changes in histological class over time
- Renal survival at 10 y rose from 87% to 99%

Moroni et al, Ann Rheum Dis 2018; 77: 1318-1325

Take Home Message

- Complete B cell depletion with rituximab associated with clinical response in LN
- Multitarget therapy effective in maintenance of LN
- ANCA +ve LN patients have more class IV-S with glomerular necrosis, and trend to worse renal outcome
- Clinical flares of LN on withdrawing treatment are more common in those with high activity index on repeat biopsy
- Over time, there has been an increase in milder presentations of LN, with improved renal survival at 10 y

References

- Jayne et al, J Am Soc Nephrol 2017; 28: 2756-2767
- McAdoo et al, Nephrol Dial Transplant 2018 (epub ahead of print)
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- Terrier et al, Ann Rheum Dis 2018; 77: 1151-1157
- Charles et al, Ann Rheum Dis 2018; 77: 1144-1150
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- McAdoo et al, Kidney Int 2017; 92: 693-702
- Van Daalen et al, Clin J Am Soc Nephrol 2018; 13: 63-72
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Abbreviations

AAV	ANCA-associated vasculitis
ab	antibody
AI	activity index LN
ANCA	anti-neutrophil cytoplasm antibody
AZA	azathioprine
C3	complement component 3
C5aR	complement component 5a receptor
CKD	chronic kidney disease
CNI	calcineurin inhibitor
COPD	chronic obstructive pulmonary disease
CYC	cyclophosphamide
dsDNab	double stranded DNA antibody
ESRD	end stage renal disease

Abbreviations

GBM	glomerular basement membrane
GPA	granulomatosis with polyangiitis
LN	lupus nephritis
MMF	mycophenolate mofetil
MN	membranous nephropathy
MP	methyl prednisolone
MPA	microscopic polyangiitis
MPO	myeloperoxidase
MTX	methotrexate
PE	plasma exchange
pred	prednisolone
PR3	proteinase-3
RTX	Rituximab
SLE	systemic lupus erythematosus