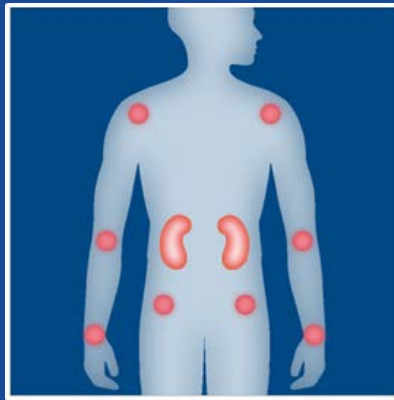


# Nephro Update Europe 2017

6-7 October, Vienna

## Systemic Autoimmune Diseases



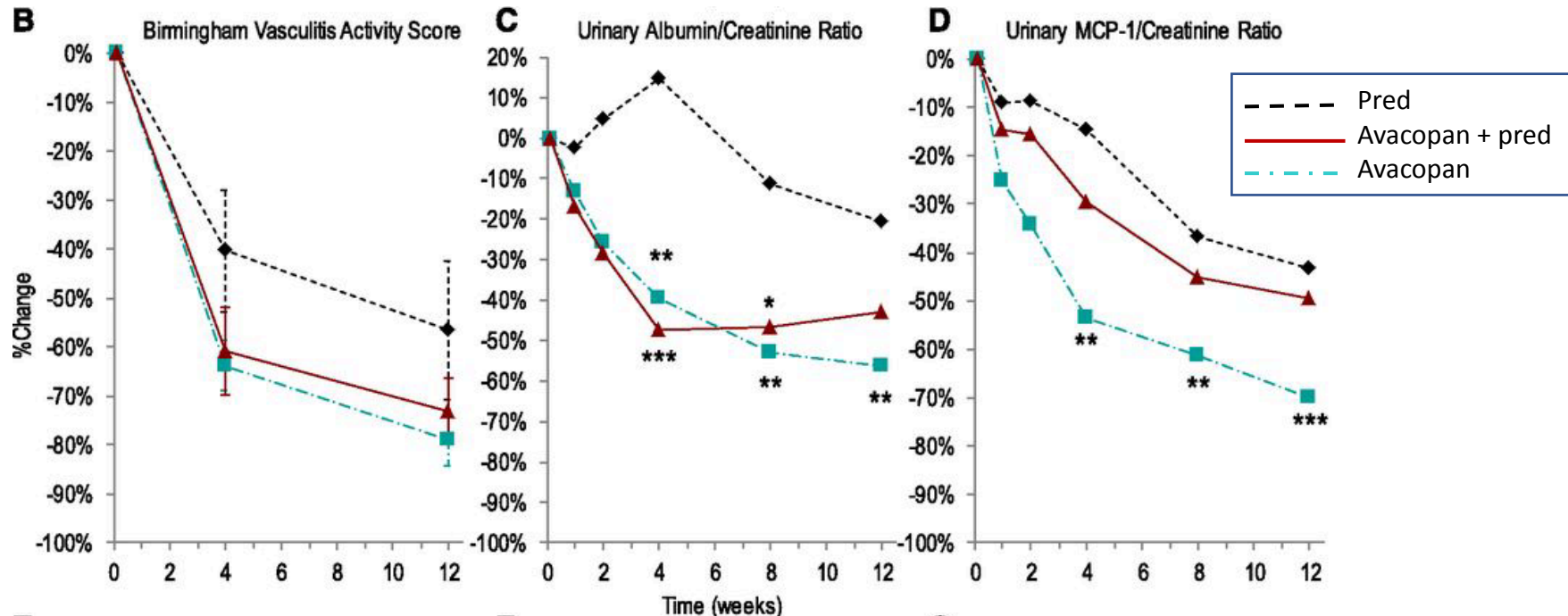
Charles Pusey, UK

# 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%

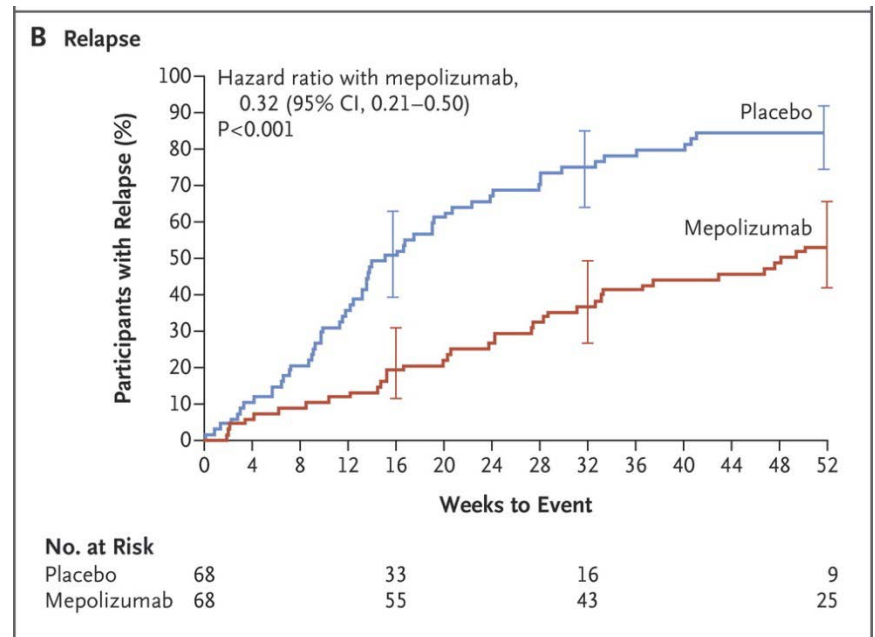
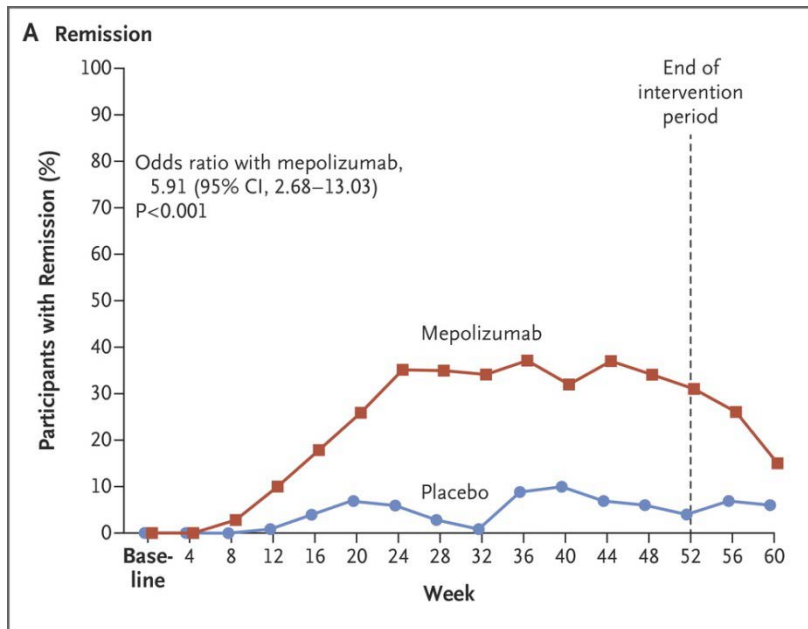
# CLEAR – Randomised trial of avacopan versus prednisolone as induction therapy for AAV



- Patients also received CYC or RTX
- Avacopan was effective in replacing corticosteroids

*Jayne et al, J Am Soc Nephrol 2017 (epub ahead of print)*

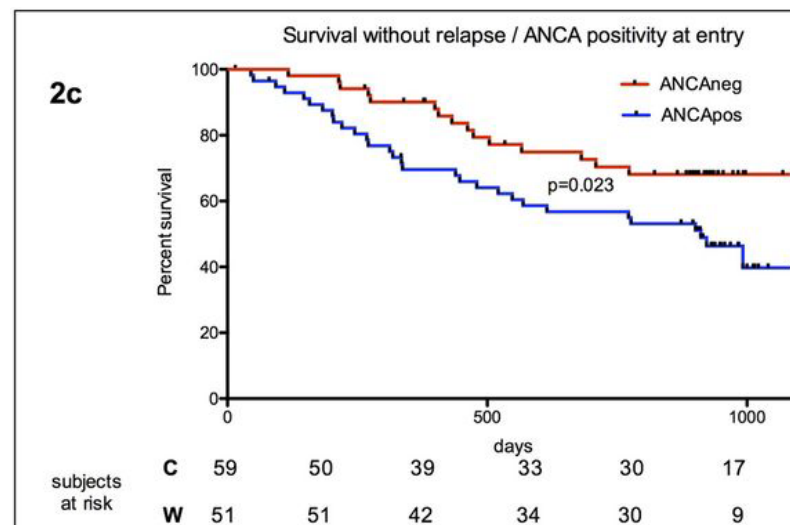
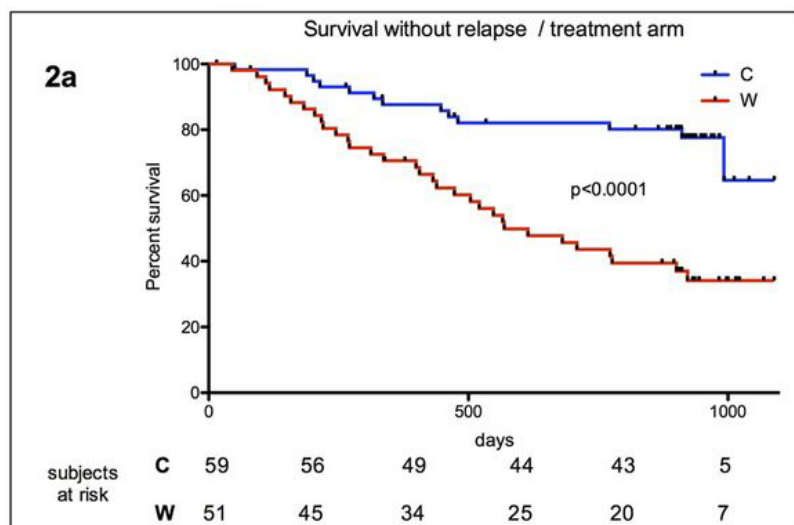
# Randomised trial of mepolizumab in EGPA



- Mepolizumab or placebo for 1 year in relapsing/refractory EGPA
- Treated patients showed more weeks of remission, fewer relapses

*Wechsler et al, N Engl J Med 2017; 376: 1921-1932*

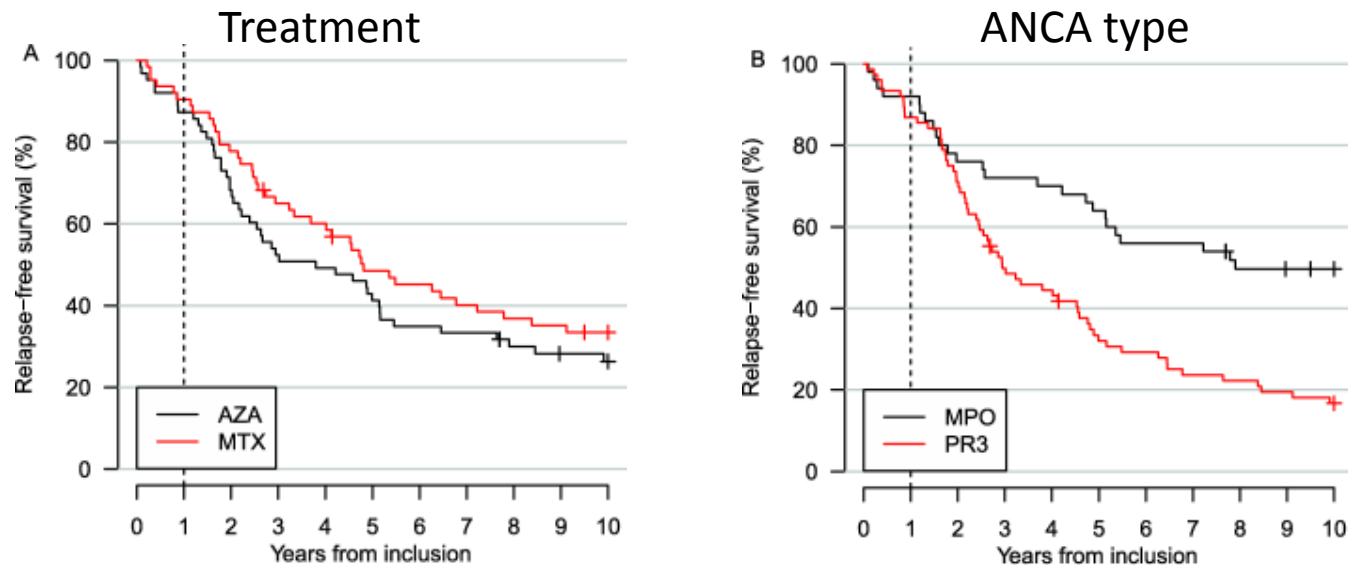
# REMAIN – Randomised trial of prolonged treatment for remission maintenance in AAV



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

*Karras et al, Ann Rheum Dis 2017 (epub ahead of print)*

# WEGENT – Follow up of randomised trial of azathioprine versus methotrexate in maintenance therapy of AAV

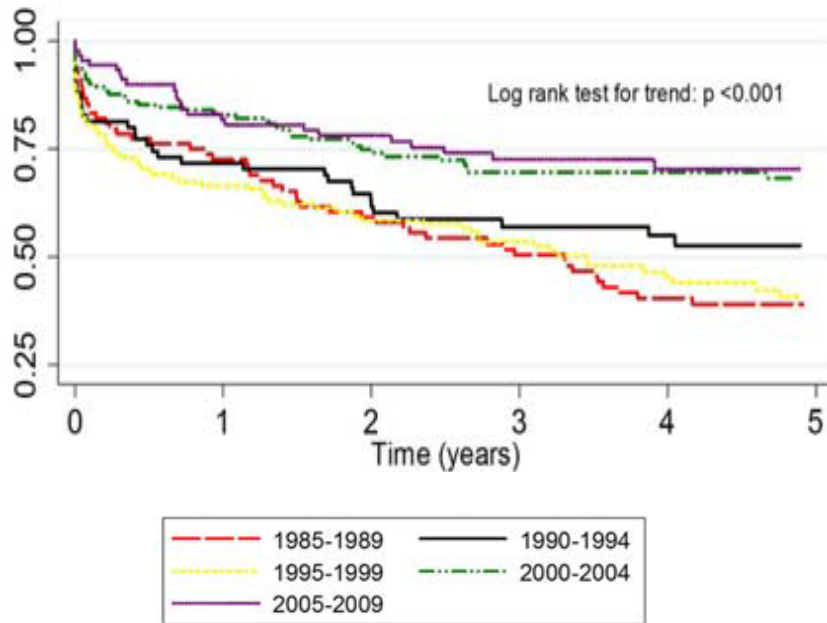


- 10 y follow up of the WEGENT trial of AZA v MTX
- Similar overall survival and relapse free survival, and adverse events
- Relapse free survival lower in PR3-ANCA v MPO-ANCA

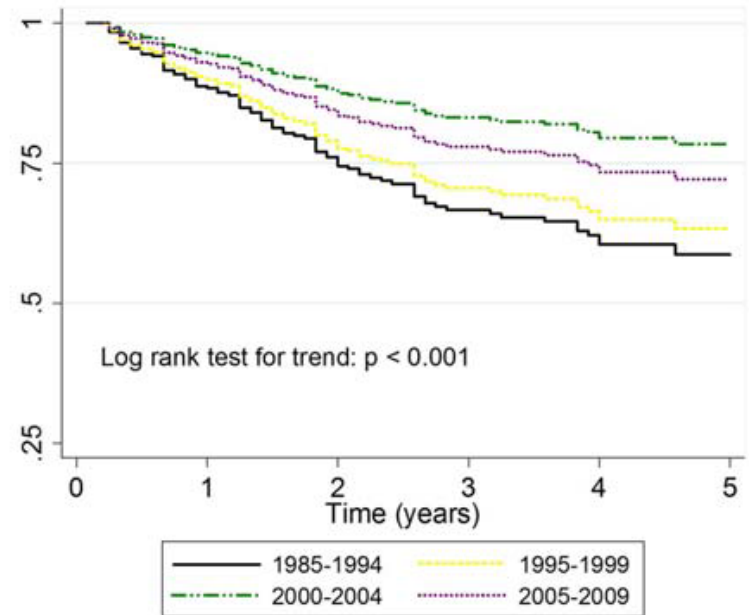
*Puechal et al, Arthritis Rheum 2016; 68: 690-701*

# Risk of death or ESRD in AAV by year of diagnosis in US

Kaplan-Meier



Cox proportional hazards



- Decreasing risk of death or ESRD over time in 554 AAV patients
- Overall 5y patient survival 72%, renal survival 65%
- Baseline serum creatinine a significant predictor of death or ESRD

*Rhee et al, Arthritis Rheum 2016; 68: 1711-1720*

# Take Home Message

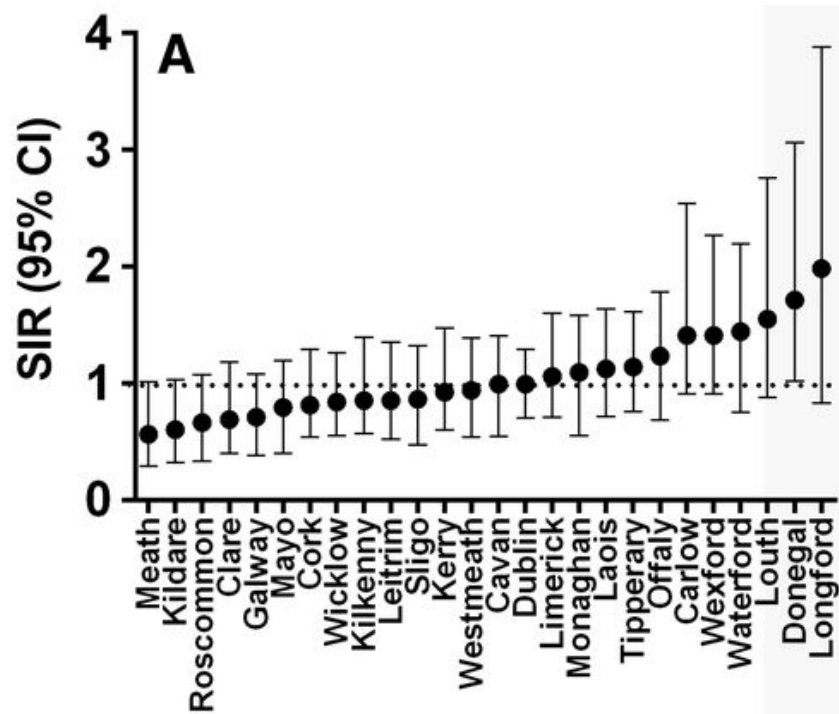
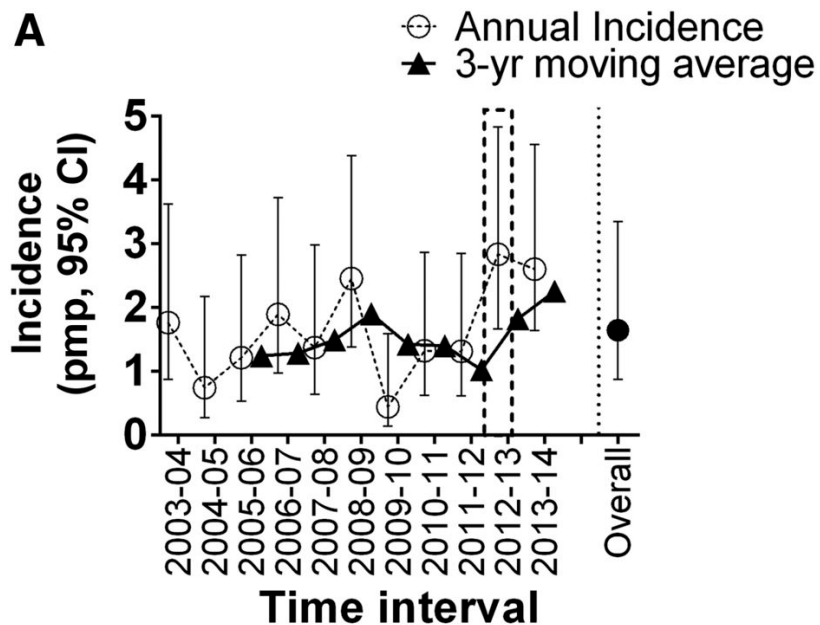
- Avacopan (C5aR inhibitor) can substitute for corticosteroids in induction of MPA/GPA – but only short-term, phase 2 study
- Mepolizumab (anti-IL5 mAb) of benefit in relapsing/refractory EGPA – but only half the patients had protocol-defined remission
- Continued AZA/low dose pred for 48m v 24m reduces relapse and improves renal outcome in AAV – but causes more adverse events
- Long-term follow up of WEGENT trial shows AZA and MTX equivalent for maintenance
- Large US series of AAV (1985-2009) shows decreasing risk of ESRD or death over time – serum creatinine at presentation was predictor of ESRD/death

# 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 very 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

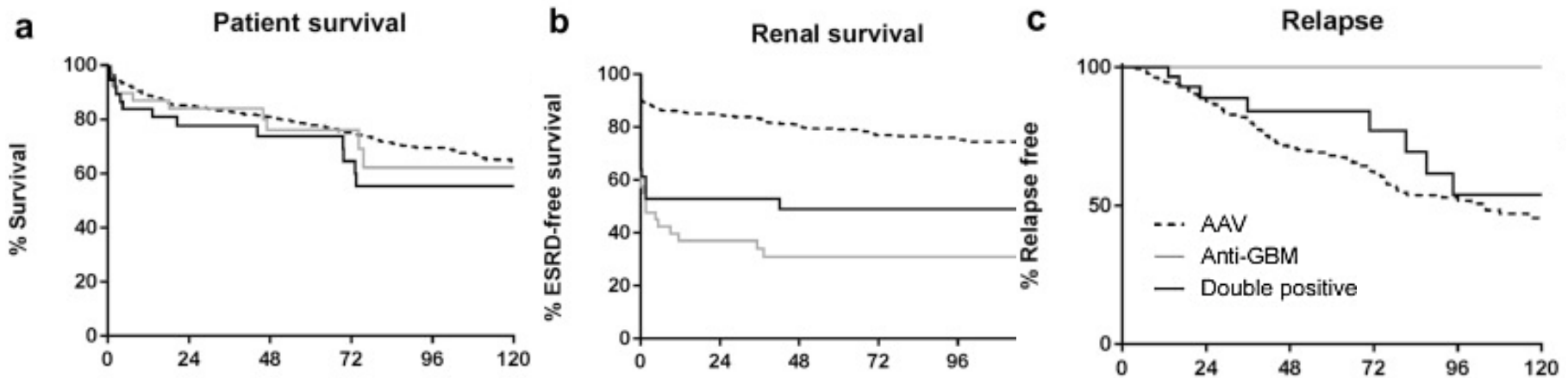
# Spatial and temporal clustering of anti-GBM disease



- Study of 79 cases in Ireland (2003-2014), national incidence 1.64pmp/y
- Temporal cluster in 2012/3, incidence 2.83 (30% double +ve)
- Spatial cluster in Donegal, incidence 1.71 (71% double +ve)
- Renal survival similar across country, regardless of clustering

*Canney et al, Clin J Am Soc Nephrol 2016; 11:1392-1399*

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

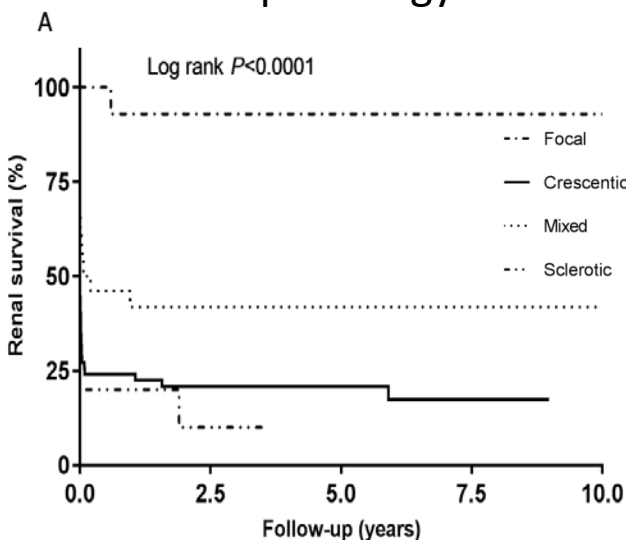


- Study of 41 anti-GBM, 37 double +ve, and 568 AAV patients
- Renal survival double +ve patients similar to anti-GBM
- Trend for more double +ve patients to come off dialysis
- Relapse in double +ve patients similar to AAV

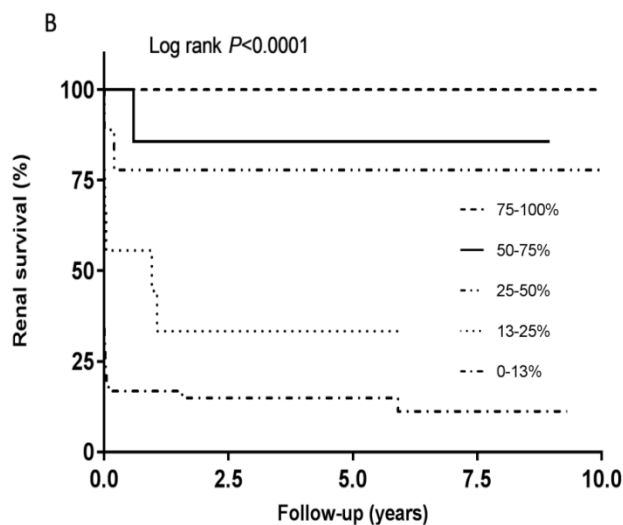
*McAdoo et al, Kidney Int 2017; epub ahead of print*

# Predicting outcome in anti-GBM disease

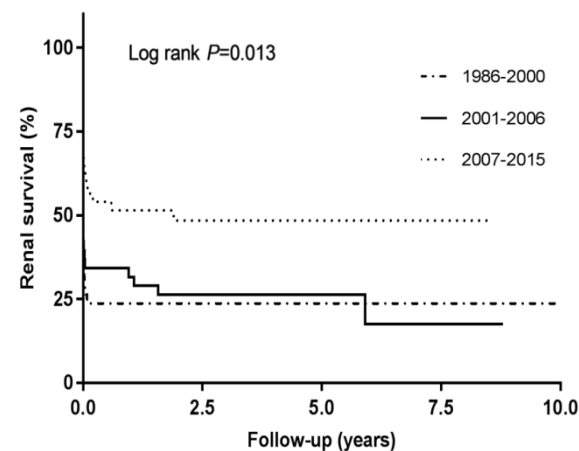
Histopathology class



% normal glomeruli



Year of diagnosis



- Study of 123 anti-GBM patients, 1986-2015
- Dialysis at presentation, % normal glomeruli, interstitial infiltrate, predict ESRD

*Van Daalen, Clin J Am Soc Nephrol (in press)*

# Take Home Message

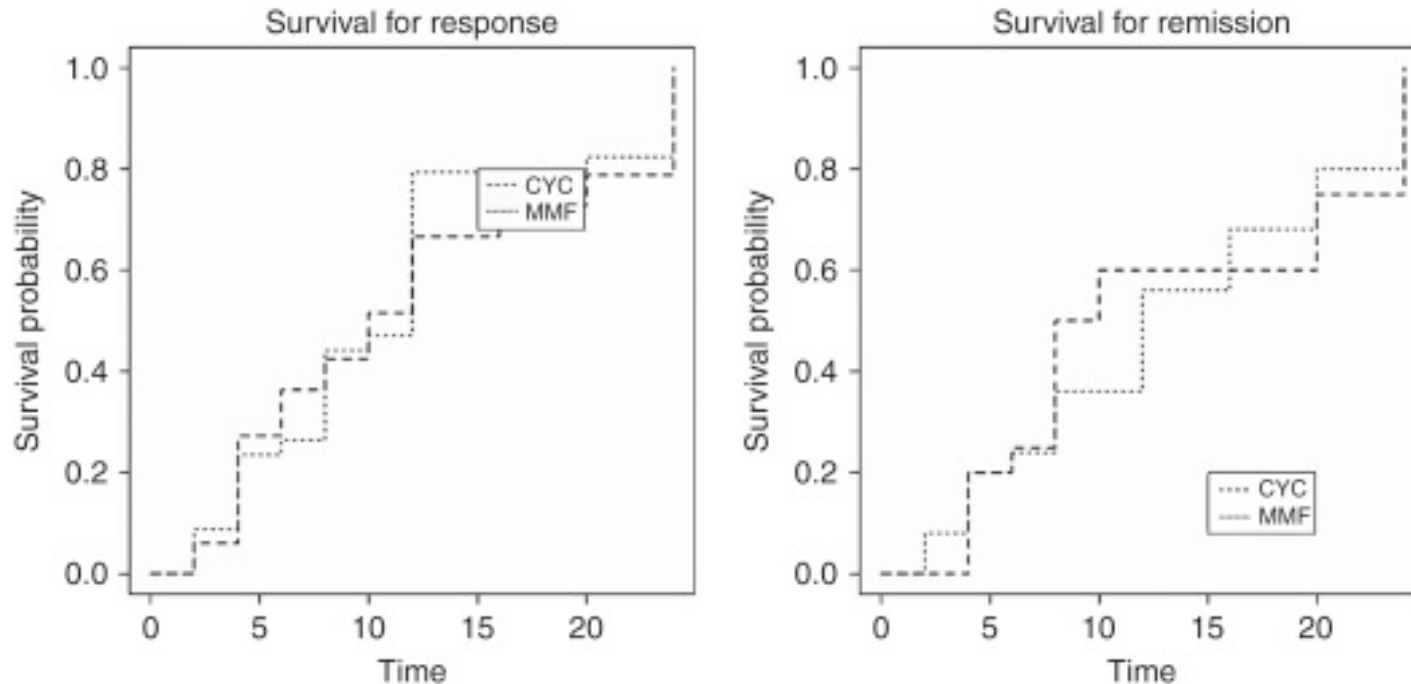
- Incidence of anti-GBM disease in Ireland 1.64pmp/y, with spatial and temporal clustering
- Renal survival in double-positive patients similar to anti-GBM disease, but worse than AAV
- Double-positive patients show trend to better renal recovery from dialysis, and relapse similar to AAV
- Histopathologic class of biopsy in anti-GBM disease (as for AAV) shows good renal recovery in focal class, but no overall correlation with ESRD
- Dialysis dependency at presentation, % normal glomeruli and interstitial infiltrate predict ESRD

# Lupus nephritis

# State of the Art

- Induction treatment
  - Class III/IV      pred (+ 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

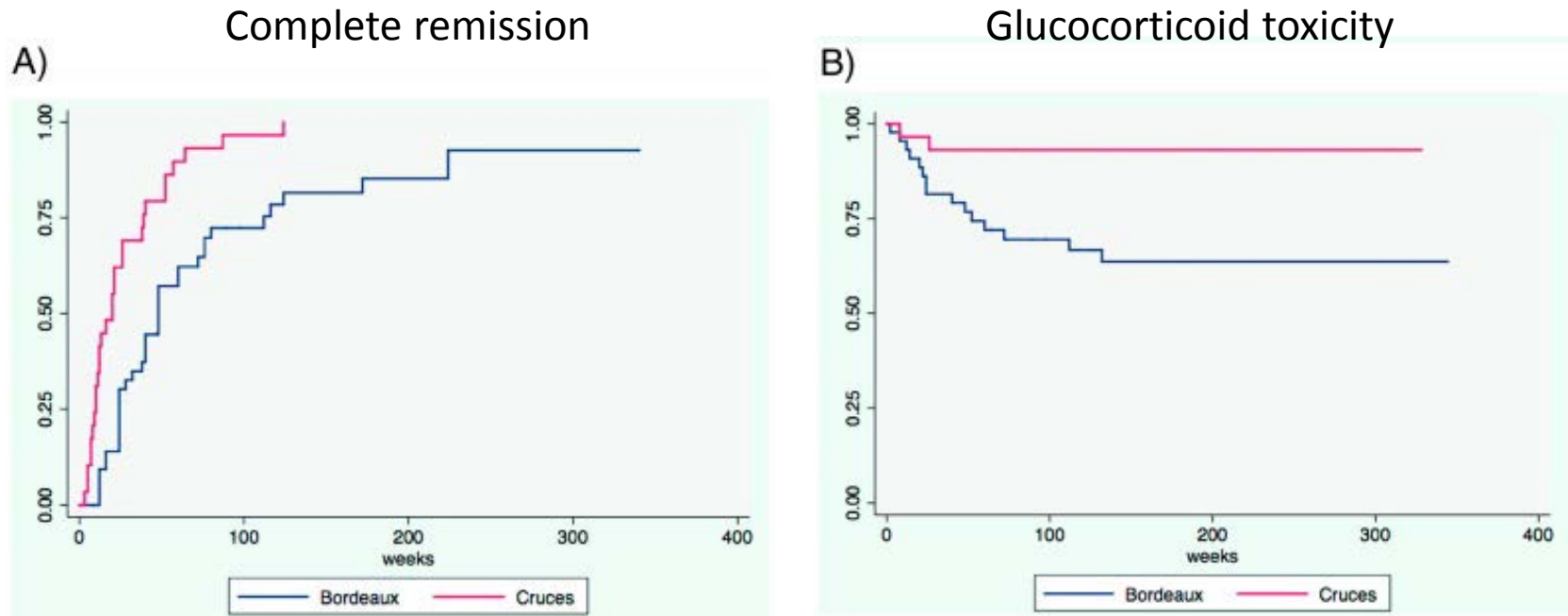
# Randomised trial of IV cyclophosphamide versus mycophenolate mofetil in lupus nephritis



- LN III/IV/V treated with IV CYC or MMF with IV MP and pred
- Excluded crescentic GN, creat >265, severe extrarenal disease
- Similar treatment response and remission rate at 6m

*Rathi et al, Kidney Int 2016; 89: 235-242*

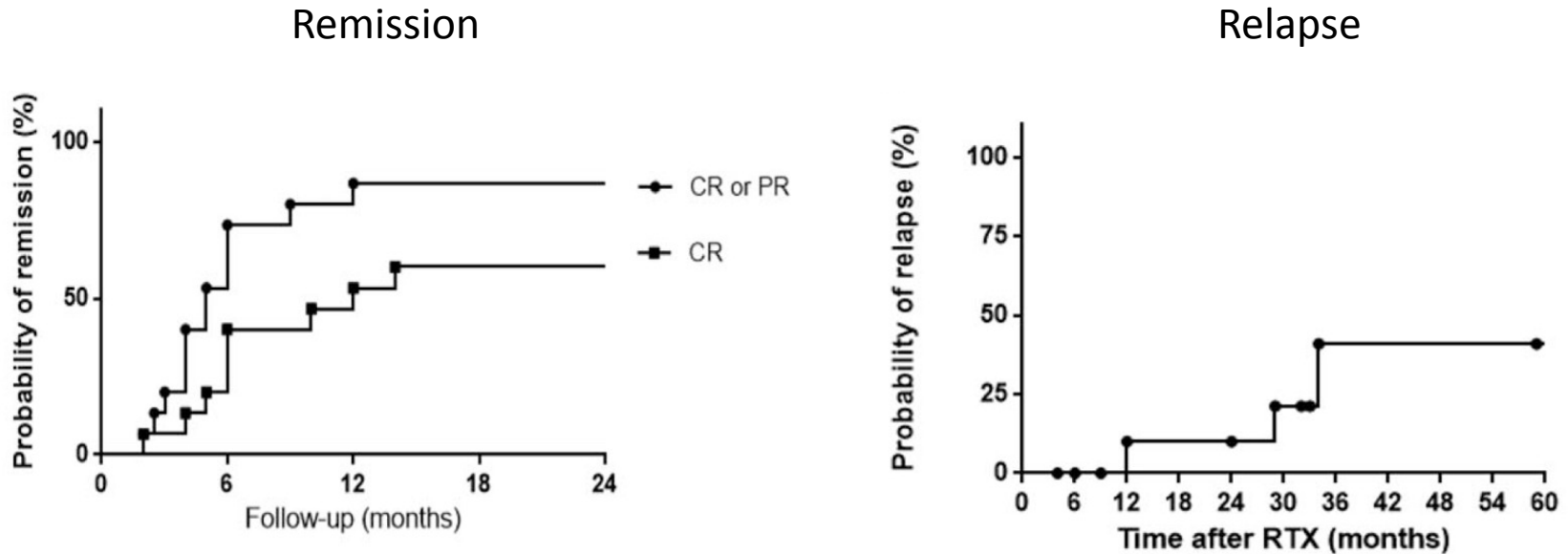
# Pulsed methyl prednisolone and reduced dose oral steroids in lupus nephritis



- Study of 73 LN patients comparing steroid protocols
- Pulse MP and pulse cyclo with low dose oral pred (Cruces)
- More remissions and less toxicity than standard treatment

*Ruiz-Irastorza et al, Autoimmun Rev 2017; 16: 826-832*

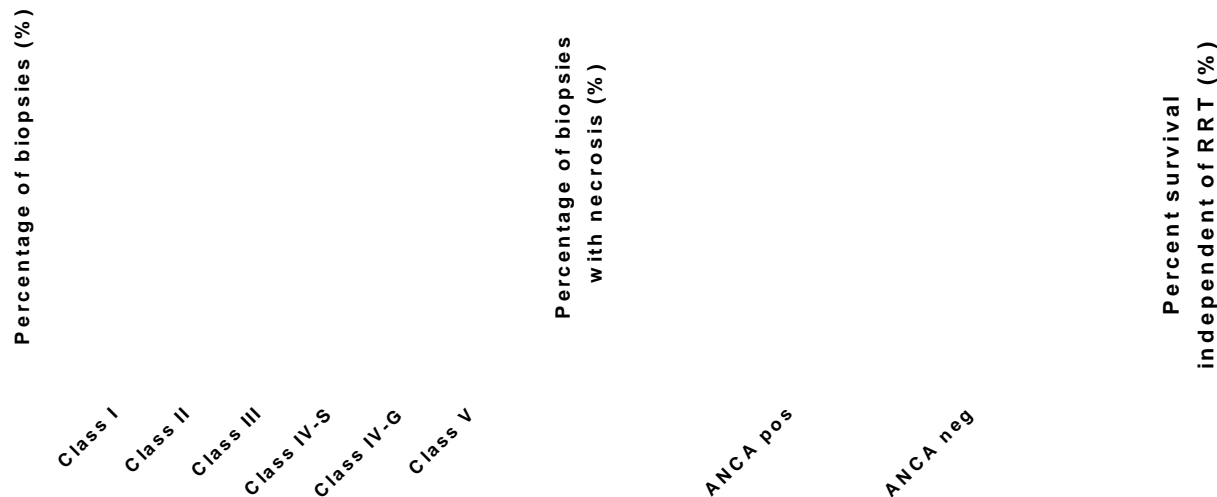
# Rituximab alone for membranous lupus nephritis



- Study of 15 class V LN patients, median PCR 4.9 g/g
- Treated with RTX and low dose oral prednisolone
- Remission in 13/15, relapse in 3/13; no adverse events

*Chavarot et al, Medicine, 2017; 96: 27(e7429)*

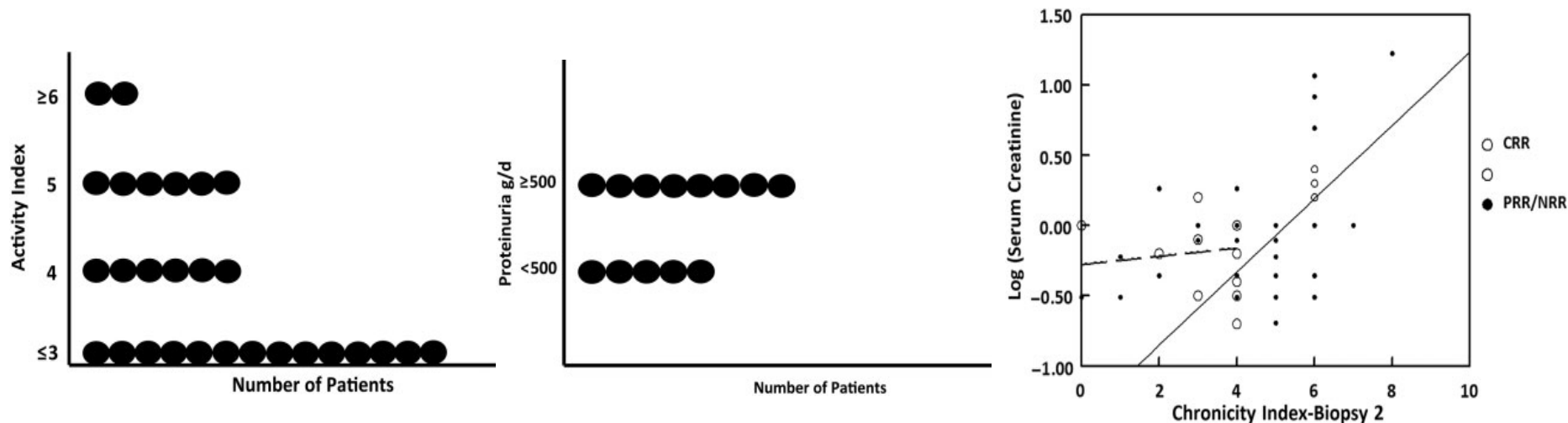
# Histopathological features and outcomes in ANCA+ve patients with lupus nephritis



- Study of 32 ANCA+ve and 222 ANCA-ve LN patients
- 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 (epub ahead of print)*

# Histological versus clinical remission in lupus nephritis



- 69 patients with LN III/IV treated with CYC or MMF with pred for 6m and rebiopsied
- 29% of those in clinical remission had activity index  $\geq 5$
- 62% of those in histologic remission had proteinuria  $> 500\text{mg/day}$
- Chronicity index associated with development of CKD

*Malvar et al, Nephrol Dial Transplant, 2017; 32: 1338-1344*

# Take Home Message

- MMF and IV CYC equivalent in treatment of less severe LN
- Steroid sparing protocol with pulse MP and IV CYC can be effective in LN with less toxicity than standard treatment
- Rituximab and low dose pred can be effective in class V LN (as reported in primary MN) – but small cohort study
- Patients with LN who are ANCA +ve have more class IV-S with glomerular necrosis, and trend to worse renal outcome
- In treated class III/IV LN patients there is considerable discordance between clinical and histological response at 6 months – suggesting that repeat biopsy is valuable.

# References

1. Jayne et al, J Am Soc Nephrol 2017 (epub ahead of print)
2. Wechsler et al, N Engl J Med 2017; 376: 1921-1932
3. Karras et al, Ann Rheum Dis 2017 (epub ahead of print)
4. Puechal et al, Arthritis Rheum 2016; 68: 690-701
5. Rhee et al, Arthritis Rheum 2016; 68: 1711-1720
6. Canney et al, Clin J Am Soc Nephrol 2016; 11:1392-1399
7. McAdoo et al, Kidney Int 2017 (epub ahead of print)
8. Van Daalen et al, Clin J Am Soc Nephrol (in press)
9. Rathi et al, Kidney Int 2016; 89: 235-242
10. Ruiz-Irastorza et al, Autoimmun Rev 2017; 16: 826-832
11. Chavarot et al, Medicine, 2017; 96: 27(e7429)
12. Turner-Stokes et al, Kidney Int 2017 (epub ahead of print)
13. Malvar et al, Nephrol Dial Transplant, 2017; 32: 1338-1344

# 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              |
| CI      | chronicity index LN                           |
| CKD     | chronic kidney disease                        |
| CNI     | calcineurin inhibitor                         |
| CYC     | cyclophosphamide                              |
| dsDNAab | double stranded DNA antibody                  |
| EGPA    | eosinophilic granulomatosis with polyangiitis |
| ESRD    | end stage renal disease                       |

# Abbreviations

|      |                                  |
|------|----------------------------------|
| GBM  | glomerular basement membrane     |
| GPA  | granulomatosis with polyangiitis |
| IL-5 | interleukin-5                    |
| 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                        |