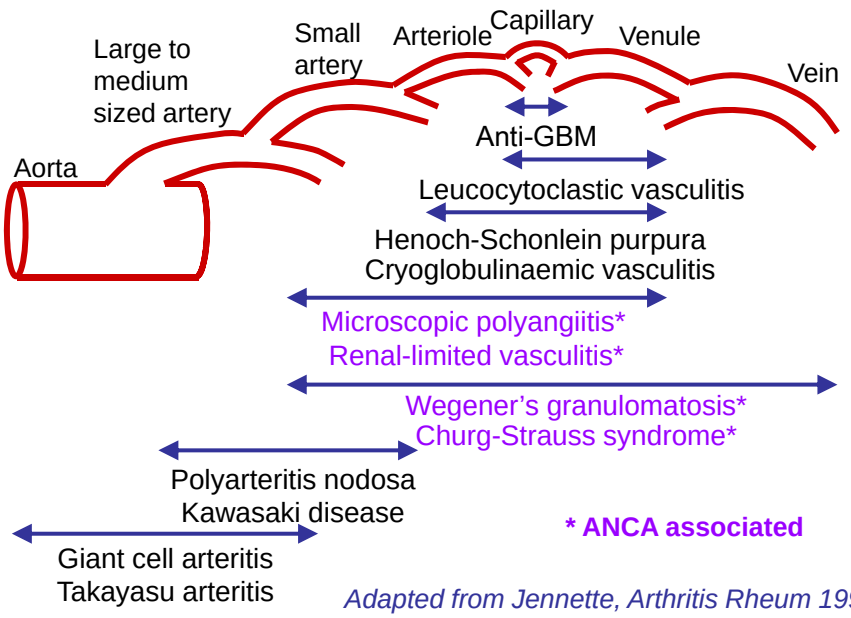
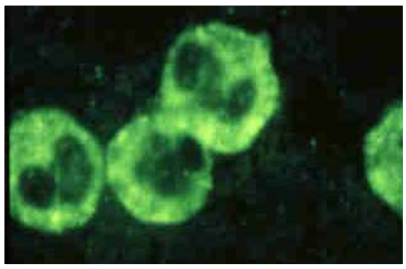
Classification of systemic vasculitis



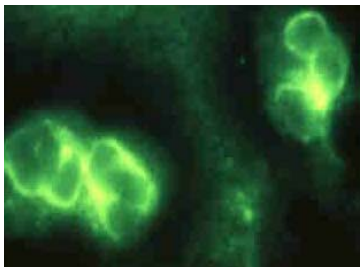
Adapted from Jennette, Arthritis Rheum 1994

Anti-neutrophil cytoplasm antibodies in systemic vasculitis

- Recognise neutrophil enzymes proteinase-3 or myeloperoxidase
- Identified by immunofluorescence and specific ELISA for PR3 or MPO



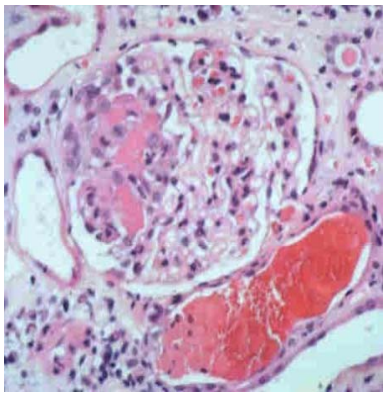
C-ANCA, Anti-PR3



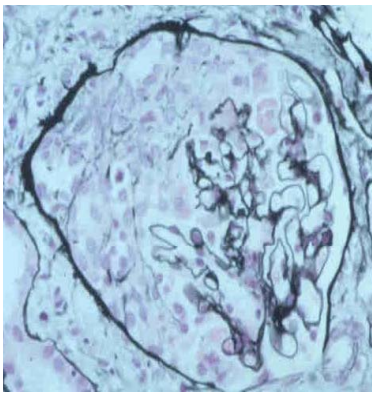
P-ANCA, Anti-MPO

Renal biopsy

Segmental fibrinoid necrosis

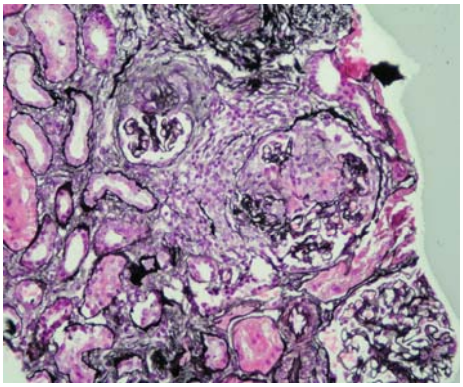


Established cellular crescent

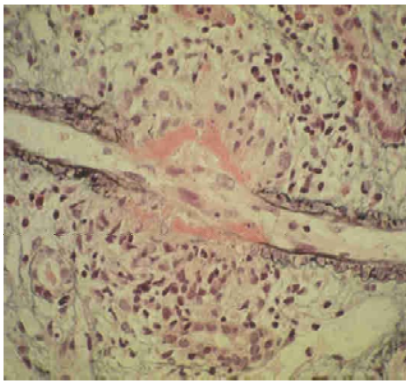


Renal biopsy

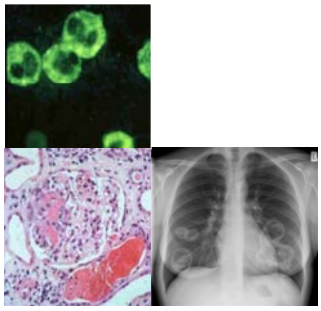
Lesions of different ages



Fibrinoid necrosis of vessel



What was the standard approach to induction therapy in ANCA-associated vasculitis?



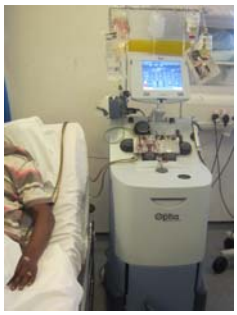
Treatment of ANCA-associated vasculitis

Induction

Prednisolone 1 mg/kg daily (max 60 mg) tapering weekly

Cyclophosphamide 2 mg/kg daily for 3 months (adjusted for age and renal function)

± Plasma exchange 4 L daily for 7-10 days or
Methyl prednisolone 10-15 mg/kg for 3 days
(for severe renal/other organ involvement)



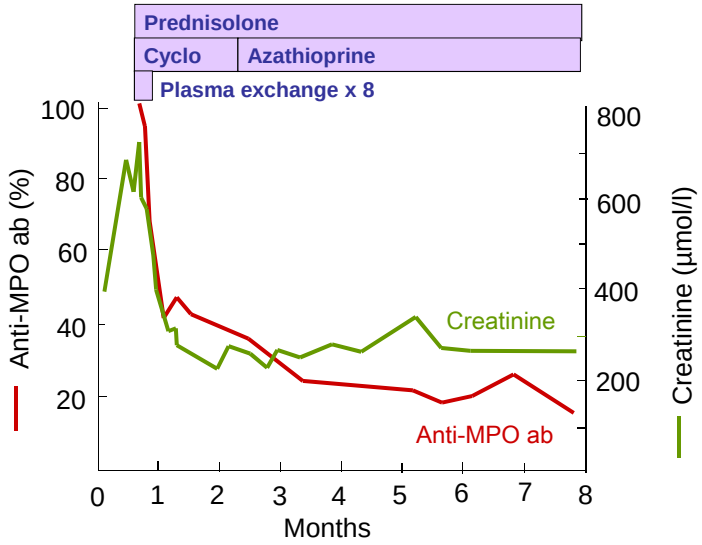
Hammersmith Hospital

Maintenance

Prednisolone 20 mg daily tapering slowly

Azathioprine 1-2 mg/kg daily

Effect of treatment on creatinine and anti-MPO antibodies

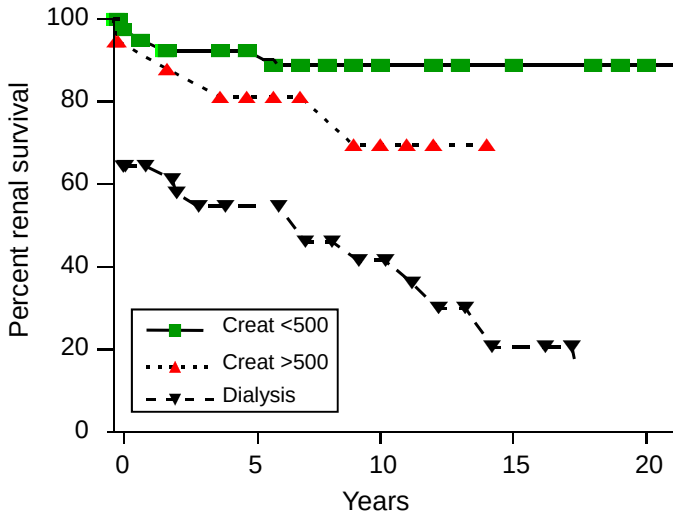


One year outcome in severe vasculitis treated with PE

	n	Patient survival (%)	Renal survival (%)
Creat <500	53	87	98
Creat >500	24	79	94
Dialysis	91	63	64
Total	168	73	81

Salama, unpublished

Long-term renal survival in severe vasculitis treated with PE

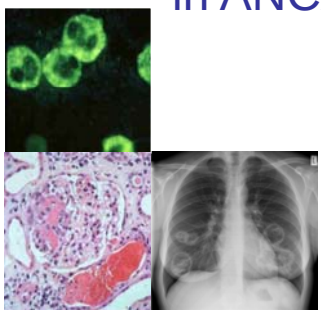


London vasculitis study

- 246 patients with ANCA-associated vasculitis
- Median age 66 yr; median creatinine 342
- Treated with pred, cyclo ± PE
- Remission 81%; relapse 34% (WG>MP)
- 1 yr survival 84%; 5 yr survival 76%
- ERF 28% by 5 yr; but 45% if creat >500

Booth, Am J Kid Dis 2003

What have we learnt from European Vasculitis Study Group (EUVAS) trials of induction therapy in ANCA-associated vasculitis?

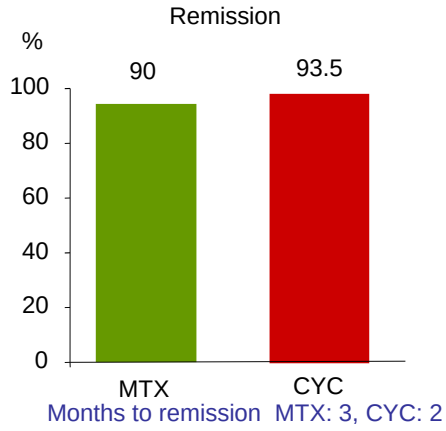


EUVAS approach to trials in AAV

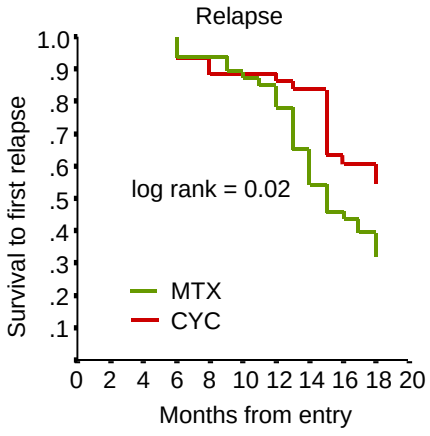
- Subgroup according to severity
- High intensity treatment to induce remission, low intensity to prevent relapse
- Agree standard regimen by consensus
- Test against best alternative by randomised controlled trial
- Use standardised scoring systems (BVAS)

NORAM

Randomised trial of methotrexate versus cyclophosphamide in treatment of early systemic Wegener's granulomatosis



Months to remission MTX: 3, CYC: 2

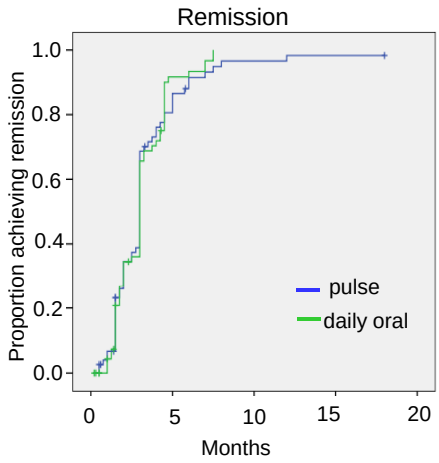


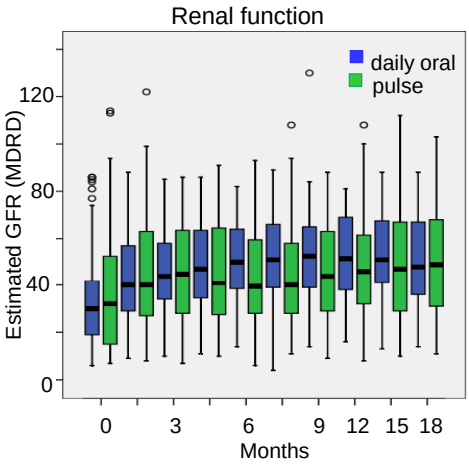
EUVAS

de Groot, Rheumatol 2005

CYCLOPS

Randomised trial of daily oral versus pulse cyclophosphamide as therapy for ANCA-associated systemic vasculitis



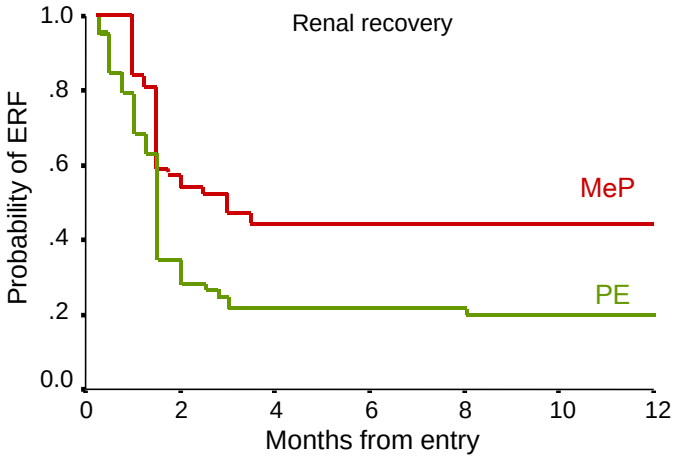


EUVAS

de Groot, Ann Intern Med 2009

MEPEX

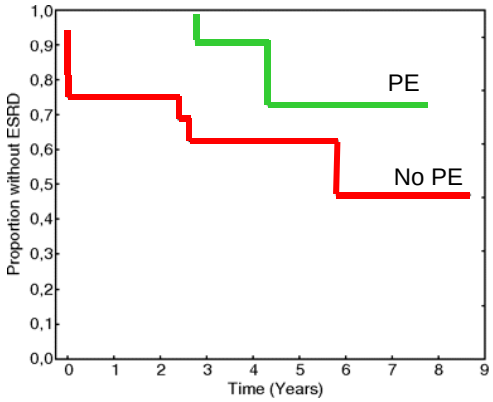
Randomised trial of plasma exchange versus methyl prednisolone as additional therapy for severe ANCA +ve glomerulonephritis



EUVAS

Jayne, J Am Soc Nephrol 2007

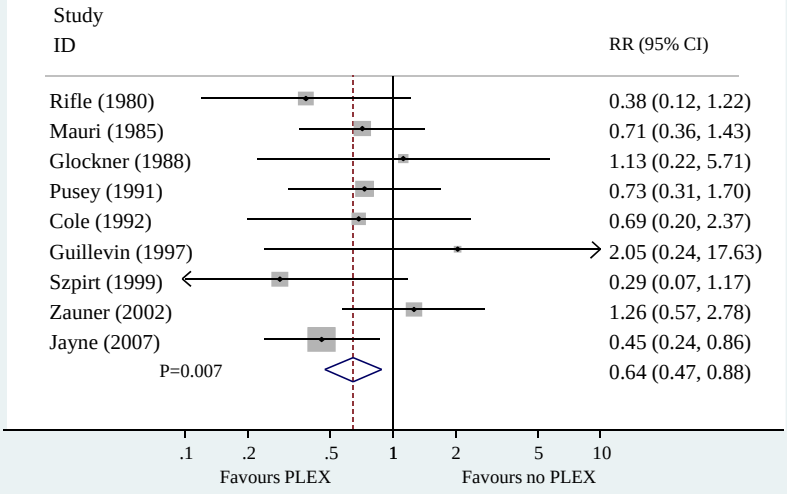
Randomised trial of PE for induction and cyclosporin for maintenance in WG



PE was of benefit in patients with creatinine >250

Szpirt, Nephrol Dial Transplant 2010

Effect of adjunctive PE on development of ESRD in AAV



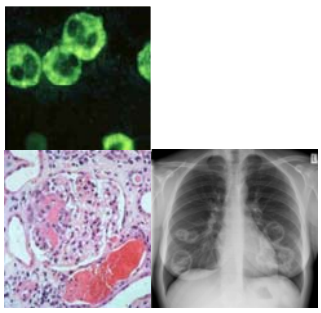
Walsh, Am J Kidney Dis (in press)

PEXIVAS

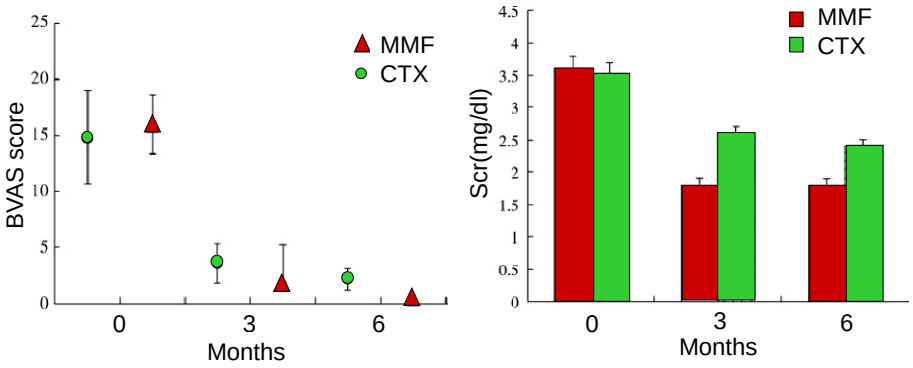
Plasma exchange and glucocorticoid dosing in the treatment of ANCA-associated vasculitis

EUVAS/VCRC

What alternative approaches to induction therapy are being investigated?



Randomised trial of mycophenolate versus cyclophosphamide for induction of remission in AAV



Remission: MMF 78%, CTX 62%

Normal RF: MMF 44%, CTX 15%

Hu, Nephrol Dial Transplant 2008

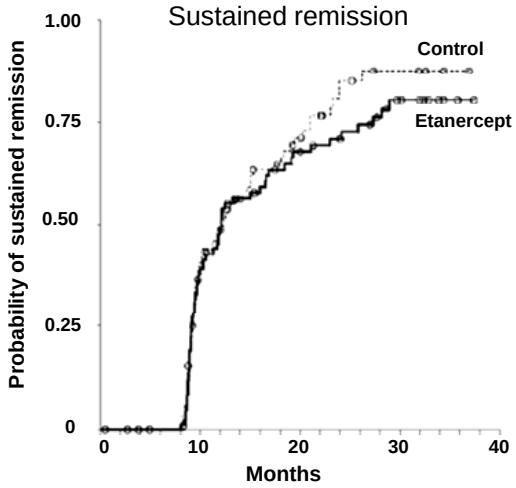
MYCYC

Randomised trial of mycophenolate mofetil versus cyclophosphamide for induction of remission in ANCA-associated vasculitis

EUVAS

WGET

Randomised trial of additional etanercept versus standard therapy for Wegener's granulomatosis

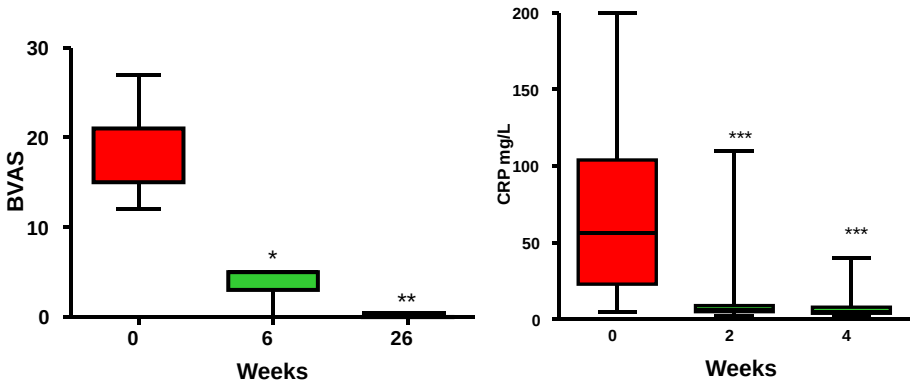


The Wegener's Granulomatosis Etanercept Trial (WGET) Research Group

WGET, N Engl J Med 2005

CycLowVas

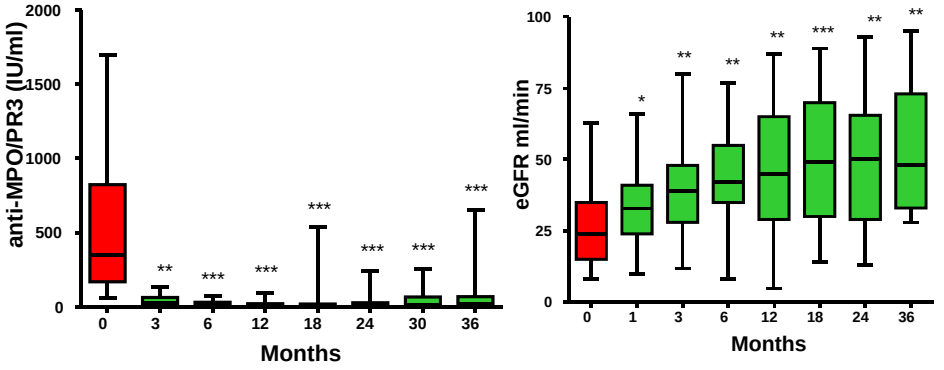
Prolonged remission following rituximab and low dose cyclophosphamide therapy for ANCA-associated renal vasculitis



Mansfield, unpublished

CycLowVas

Prolonged remission following rituximab and low dose cyclophosphamide therapy for ANCA-associated renal vasculitis

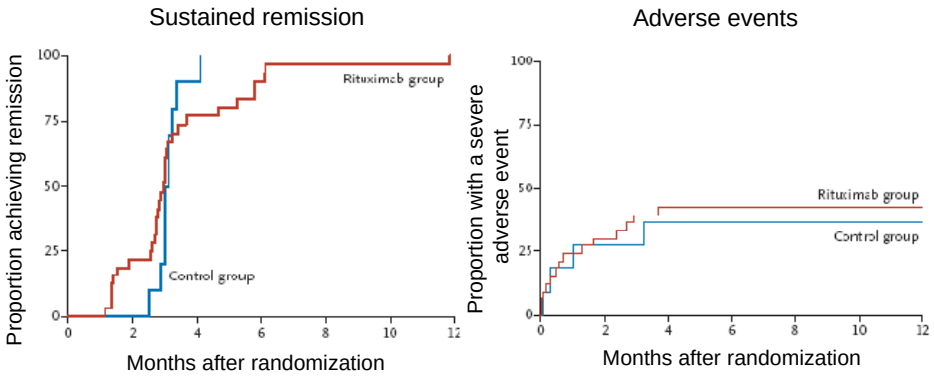


Renal relapse in 3/23 patients at 17-36 months

Mansfield, unpublished

RITUXVAS

Randomised trial of rituximab versus cyclophosphamide as induction therapy for ANCA-associated renal vasculitis

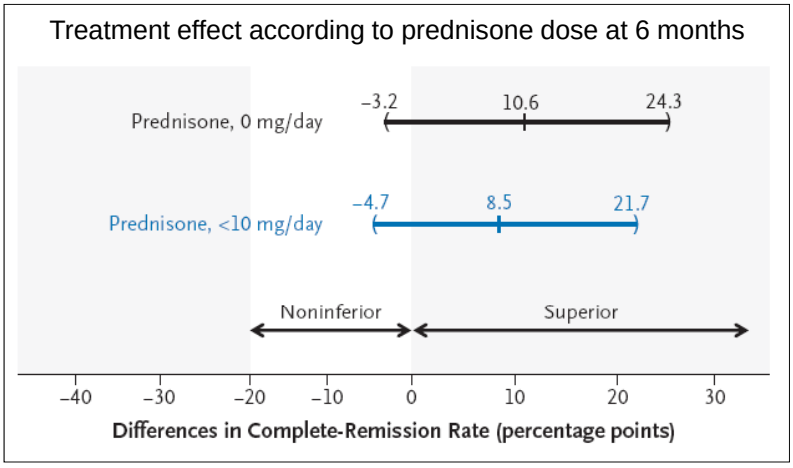


EUVAS

Jones, N Engl J Med 2010

RAVE

Randomised trial of rituximab versus cyclophosphamide for ANCA-associated vasculitis



Rituximab was more effective in patients with relapsing disease

Stone, N Engl J Med 2010

Approaches to induction therapy in relapsing/refractory AAV

Current

IV immunoglobulin

Anti-TNF Ab

Anti-B cell Ab

Anti-T cell Ab

Deoxyspergualin

Proposed

Costimulatory blockade

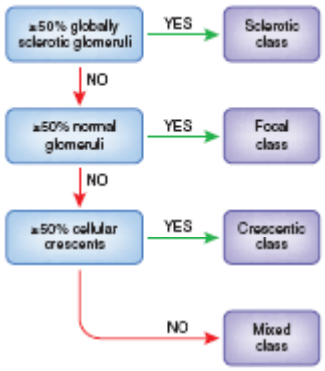
Anti-BLyS Ab

Anti-IL6, anti-IL17 Ab

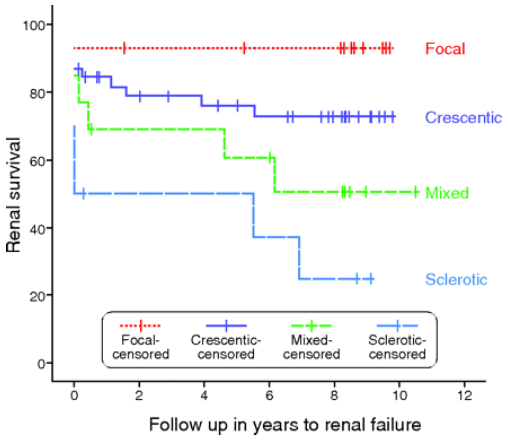
Inhibitors of signalling (Syk, p38MAPK, CDK)

Histopathologic classification of ANCA-associated glomerulonephritis

Flowchart



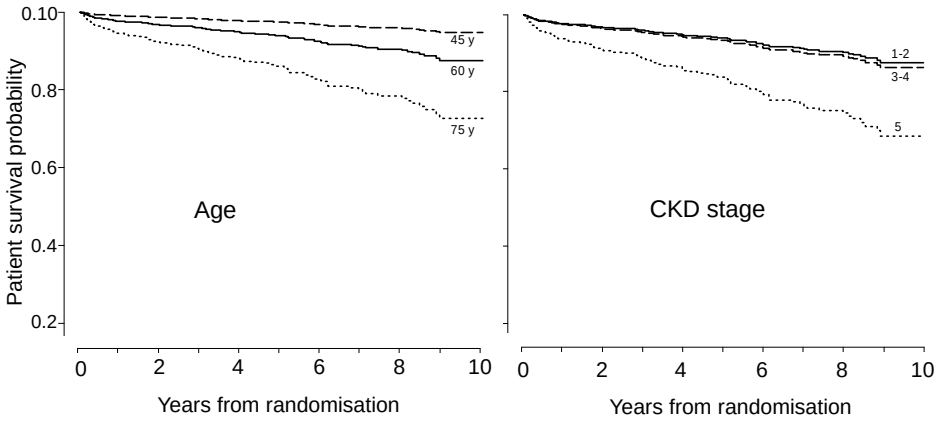
Renal survival



EUVAS

Berden, J Am Soc Nephrol 2010

Determinants of outcome in long-term follow-up of patients in EUVAS trials



EUVAS

Flossmann, Ann Rheum Dis (in press)

Conclusions (1)

- Standard therapy is effective at inducing remission in over 80% of patients with AAV, but with significant side effects
- Methotrexate is as effective as cyclophosphamide at inducing remission in patients with limited or early systemic WG
- Pulse intravenous cyclophosphamide is as effective as oral cyclophosphamide for patients with creatinine <500
- The addition of plasma exchange improves renal outcome in patients presenting with creatinine >500, and in one study creatinine >250

Conclusions (2)

- One study suggests that MMF is as effective as cyclophosphamide at inducing remission in AAV – this remains to be confirmed
- Etanercept is of no additional benefit in inducing sustained remission in WT – the role of anti-TNF antibodies remains unclear
- Rituximab (+/- low dose cyclophosphamide) is as effective at inducing remission as standard cyclophosphamide regimens
- The role of other biological agents and inhibitors of signalling pathways needs to be investigated

Thanks to many colleagues at Imperial and in EUVAS