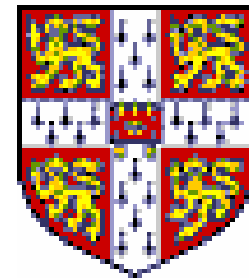


Vasculitis Foundation; Cambridge 2007

New treatments for vasculitis

David Jayne
Vasculitis and Lupus Clinic
Addenbrooke's Hospital
Cambridge UK



- Why do we need new treatments ?
- What are they ?
- When do we need them ?

- Steroids 1948
- Immunosuppression 1960s
 - Cyclophosphamide
 - Methotrexate
 - Azathioprine
- Plasma exchange 1975
- Immunoglobulin 1990

What are they ?

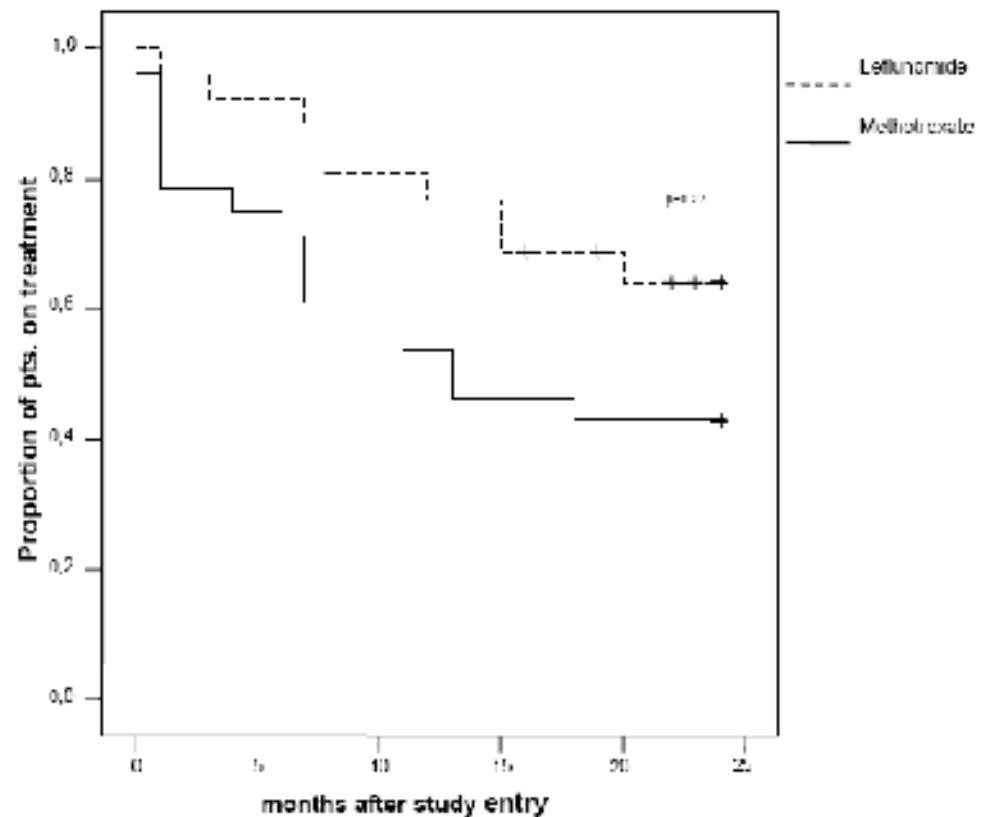
- Newer immune suppressives
- 'Biologicals'

Newer immune suppressives

- Leflunomide (Arava)
- MMF (Cellcept)
- DSG (Gusperimus)

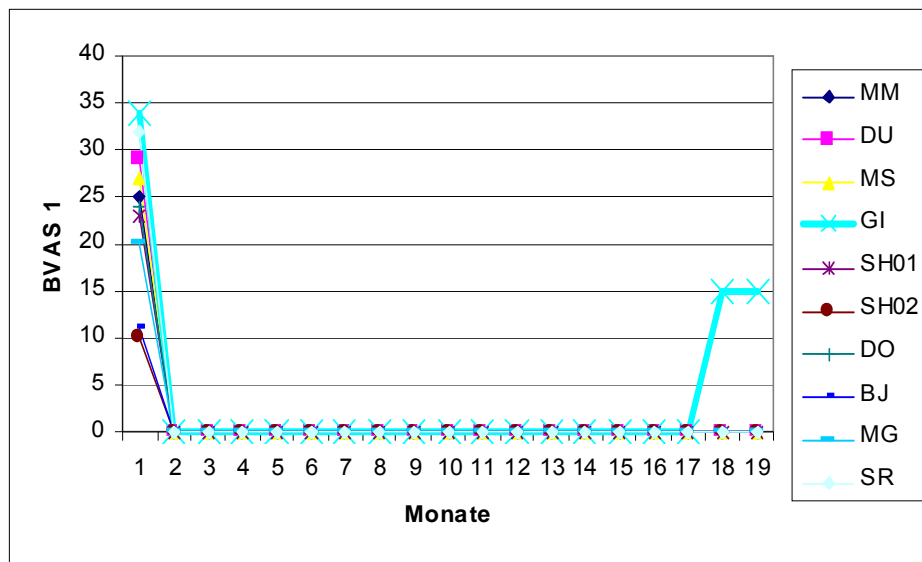
Leflunomide as remission therapy

- 54 WG
- CYC induction
- 2 years LEF vs. MTX
- More relapses with MTX
- More severe adverse events with LEF



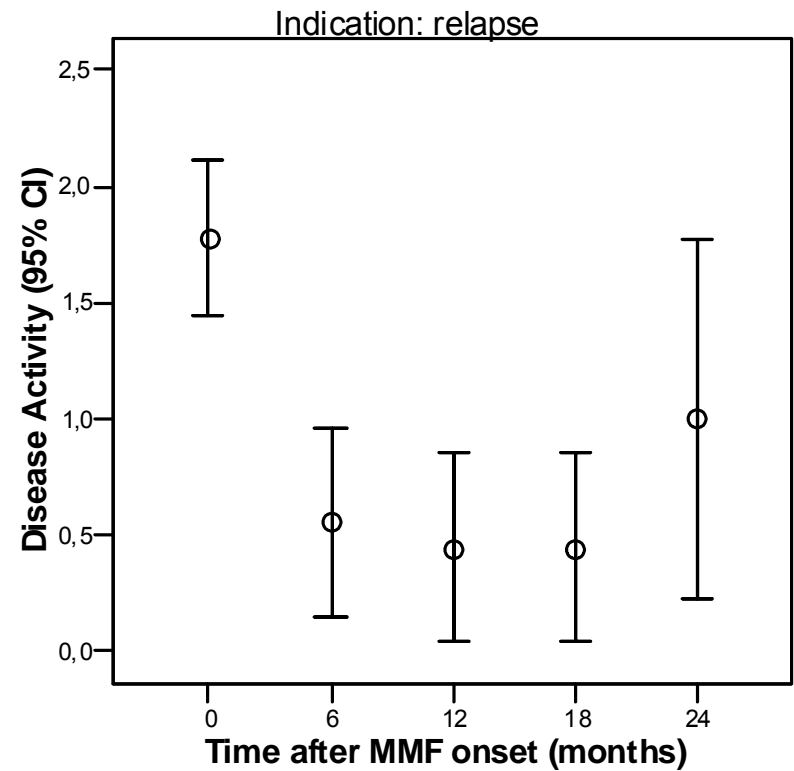
Mycophenolate mofetil for remission maintenance in vasculitis n=12

Nowack J Am Soc Nephrol 1999

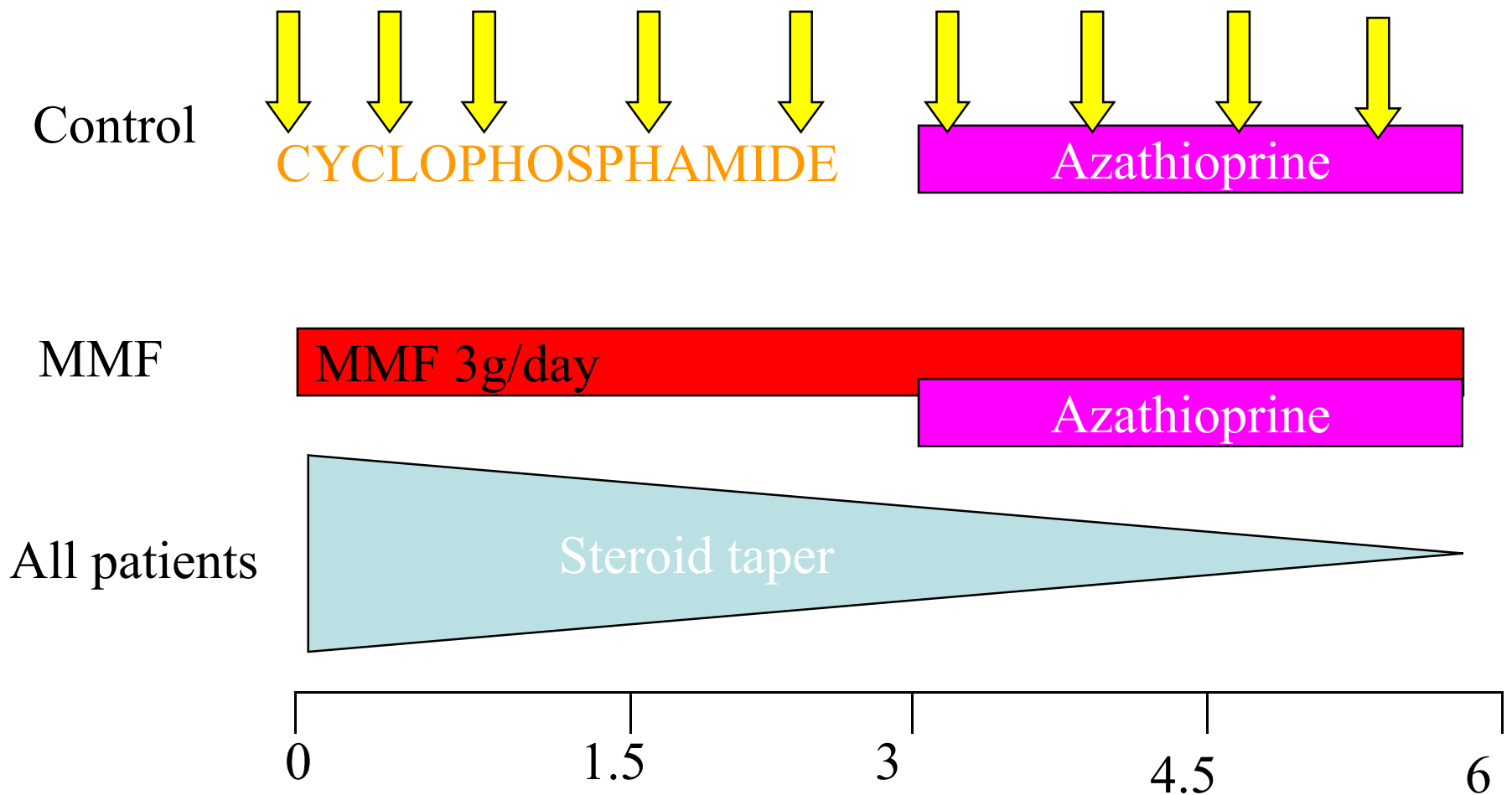


Mycophenolate mofetil as a 'second line' for relapsing vasculitis n=53

Koukoulaki et al, 2005 Nephron Clin Pract



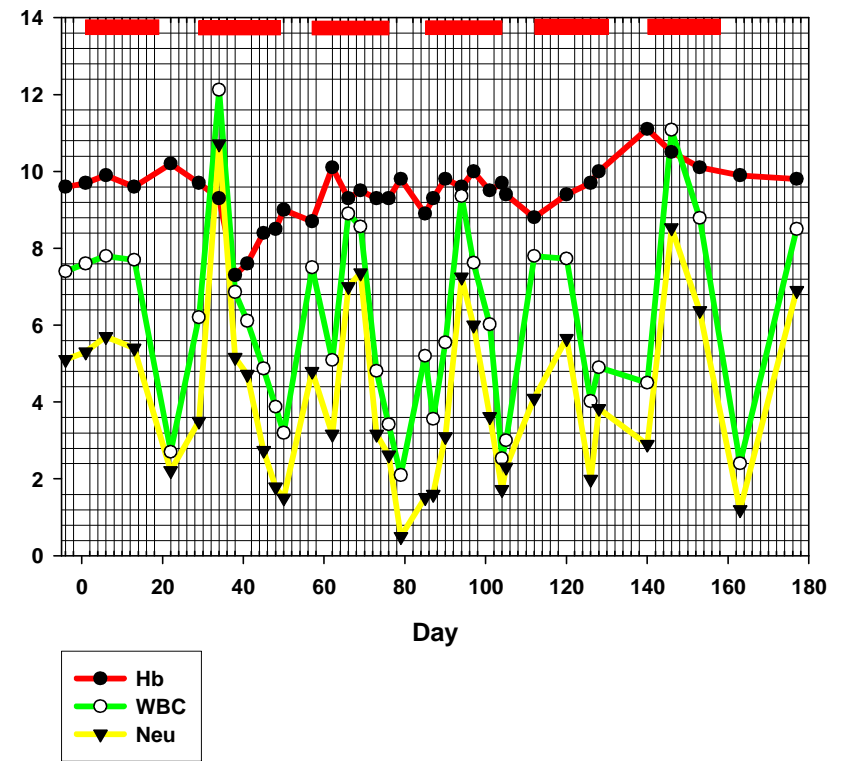
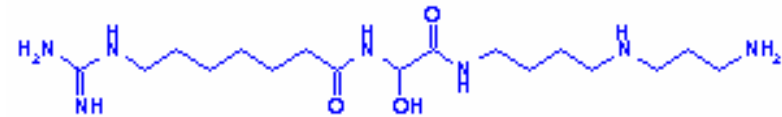
Mycophenolate for induction (MYCYC) - recruiting





Deoxyspergualin (Gusperimus)

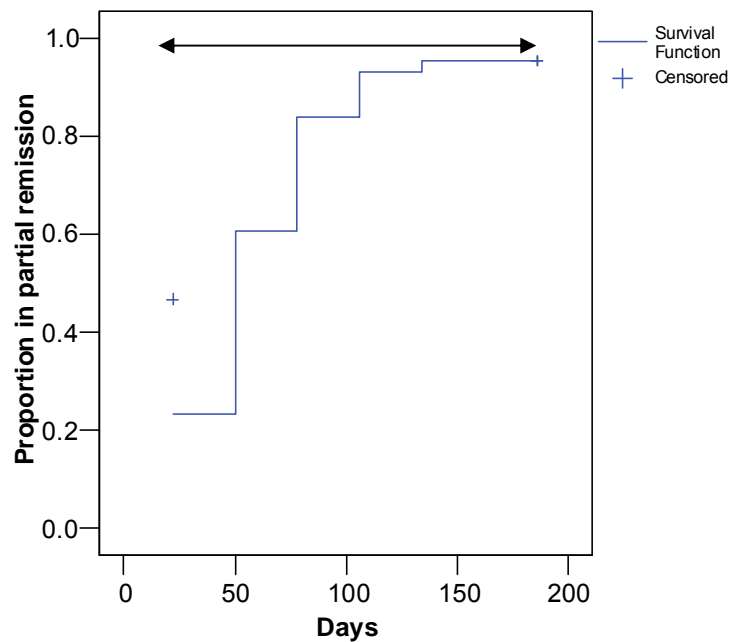
- Novel immunosuppressant
- Licensed for Rx of acute graft rejection in Japan
- Synthetic analogue of a *Bacillus laterosporus* protein



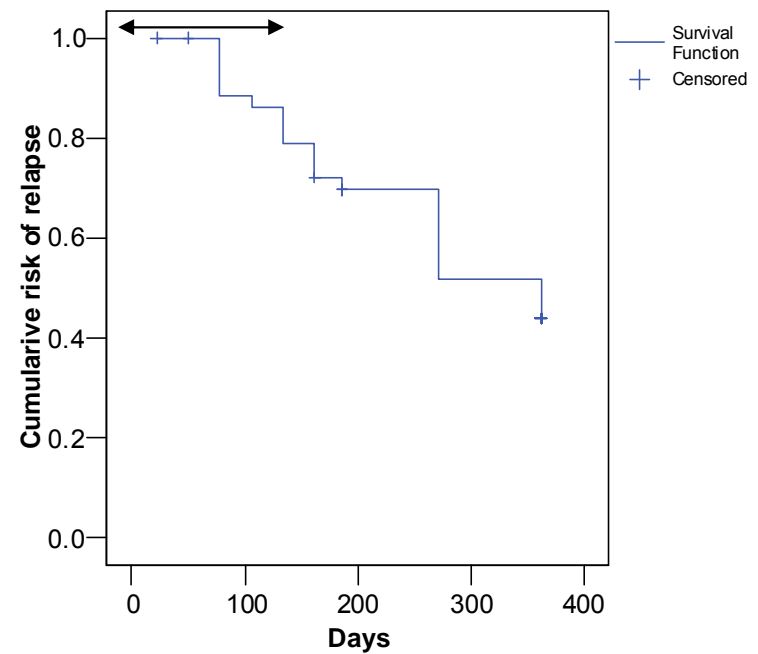
Outcome

- 42/45 (93%) responder
 - 47% complete remission
 - 47% partial remission

Time to remission

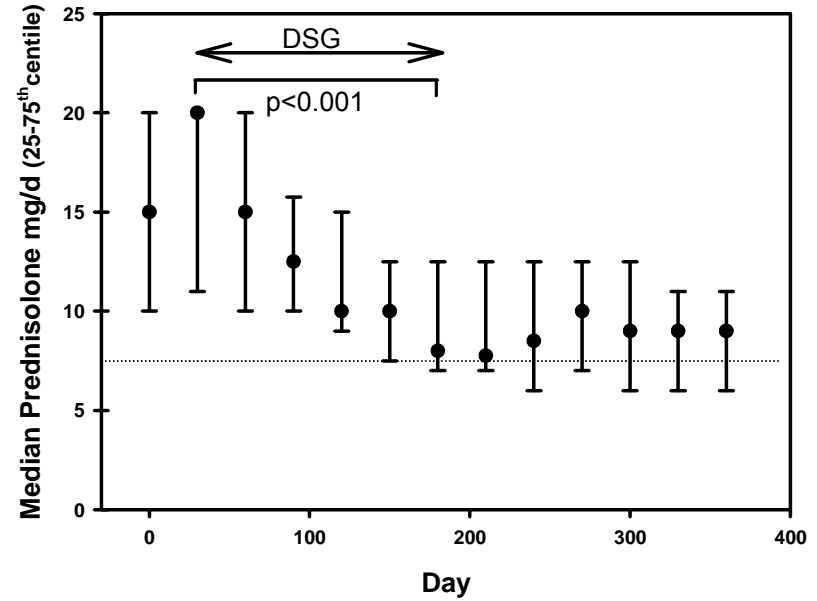
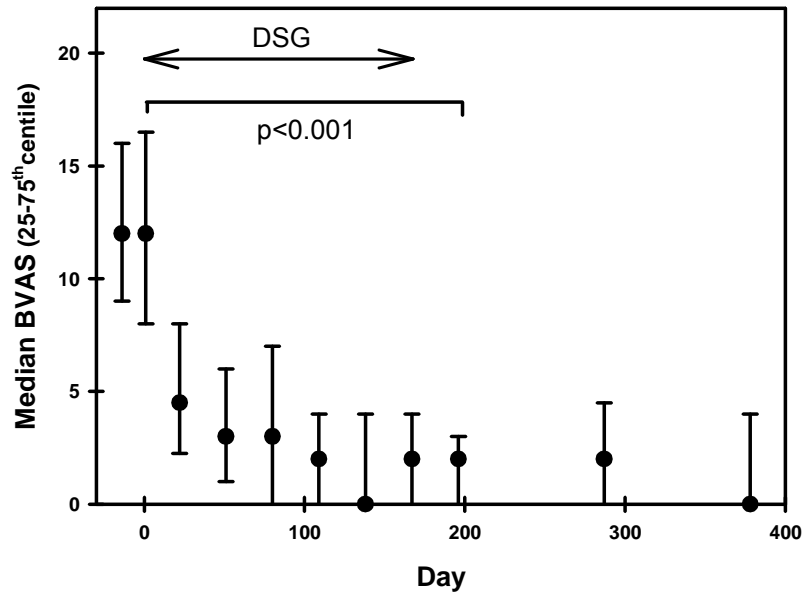


Time to flare



Disease Activity

Steroids

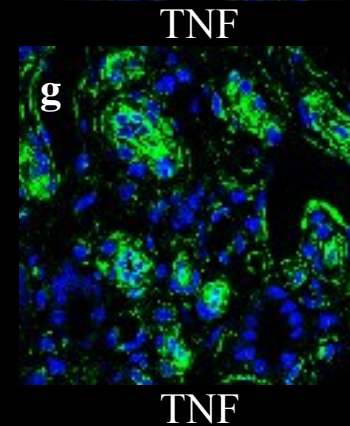
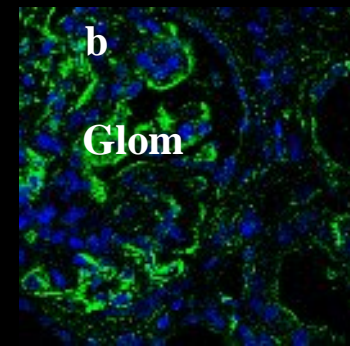
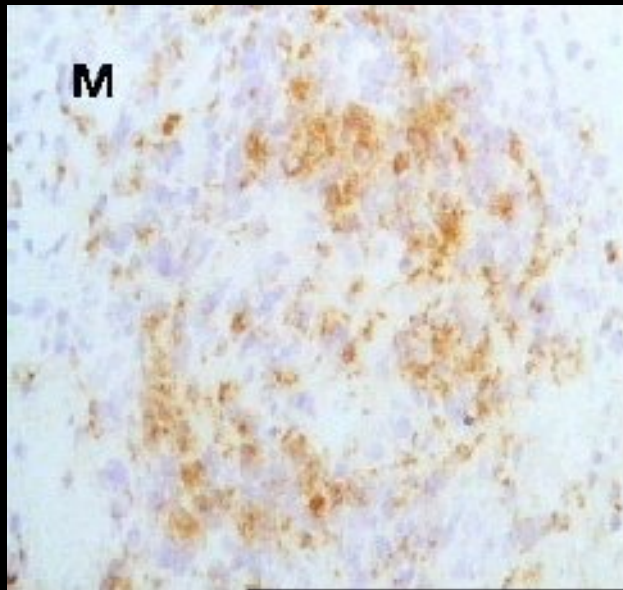


Biologicals

- Block messengers
 - TNF
- Remove immune cells
 - T cell depletion
 - B cell depletion

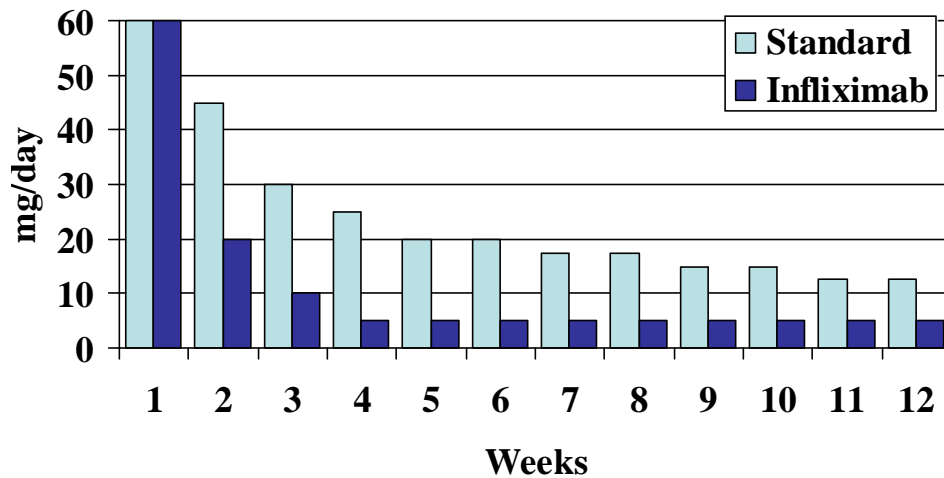
TNF α blockade for vasculitis ?

- TNF is a key messenger in the immune system
- Activates immune cells
- Works together with ANCA



Infliximab in ANCA vasculitis

Prednisolone dose



Problems

relapse (30%) persistent
↑ Infection risk

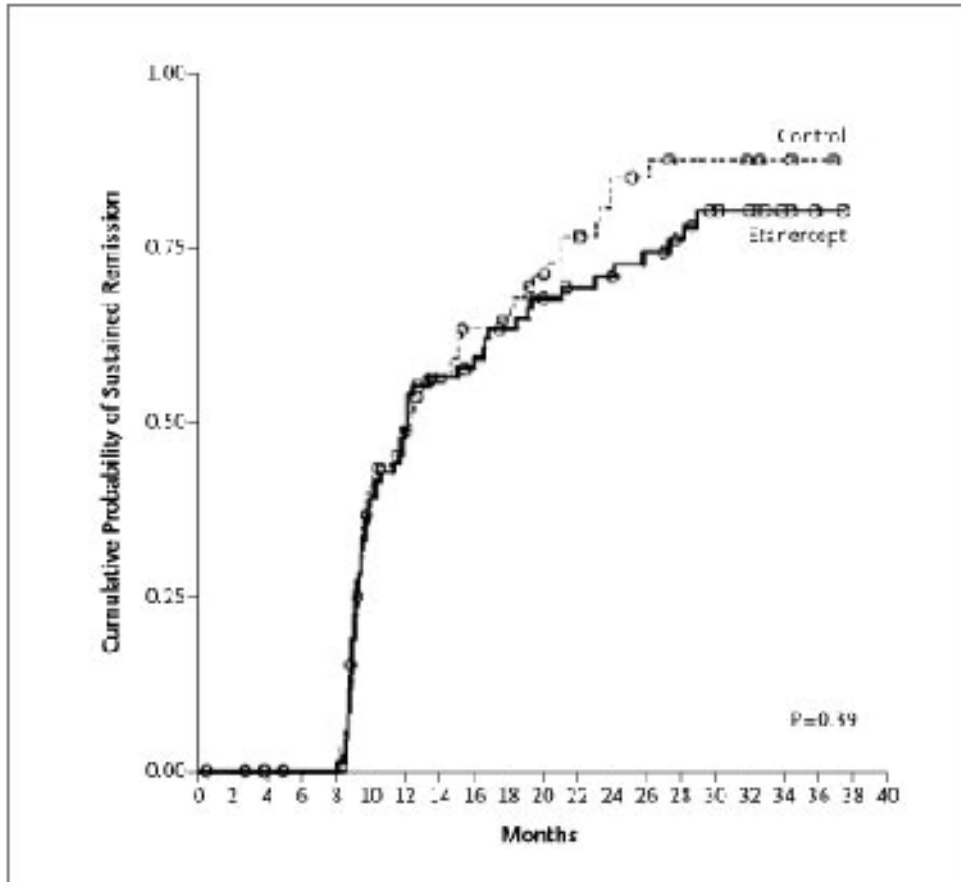
Potential indications

‘nephron rescue’
steroid sparing (↓ 40%)

Booth, JASN (abstract) 2003
Levy, JASN (abstract) 2003

TNF α blockade with Etanercept

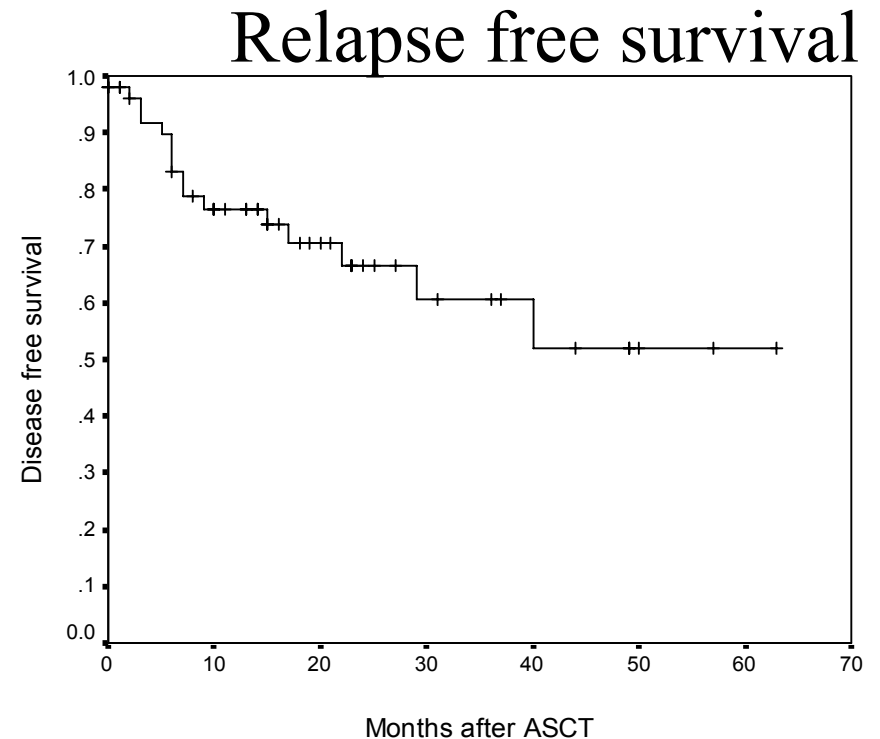
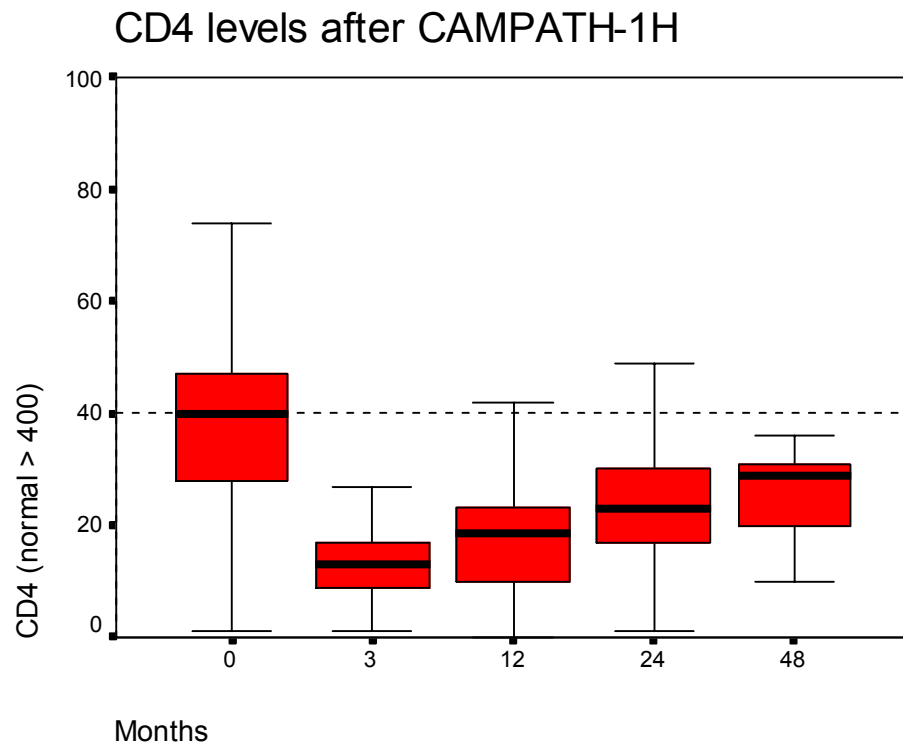
The WGET Trial Group. N Engl J Med 2005;352:351



- Examined role in remission maintenance
- Any effect on induction masked by high dose CYC/steroid
- ? Malignancy risk with etanercept

Removing T cells

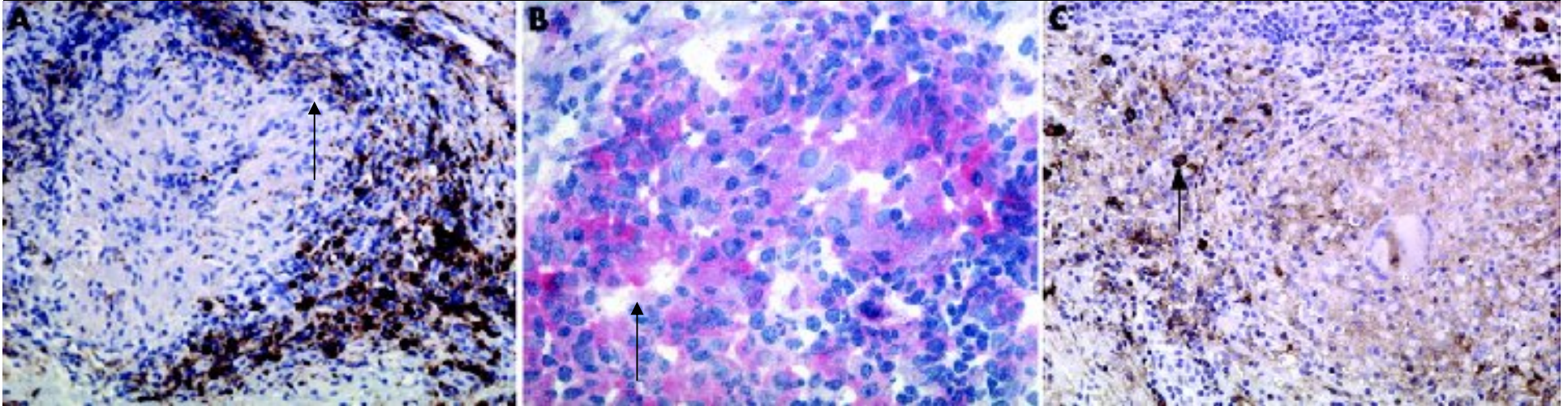
CAMPATH 1H in vasculitis (anti-CD52, Alemtuzumab) n=121



Lockwood, Lancet 1994
Jayne, Cleve Clin J Med 2002

Removing B cells

Cell phenotype in Wegener's nasal biopsy



CD20
B cell

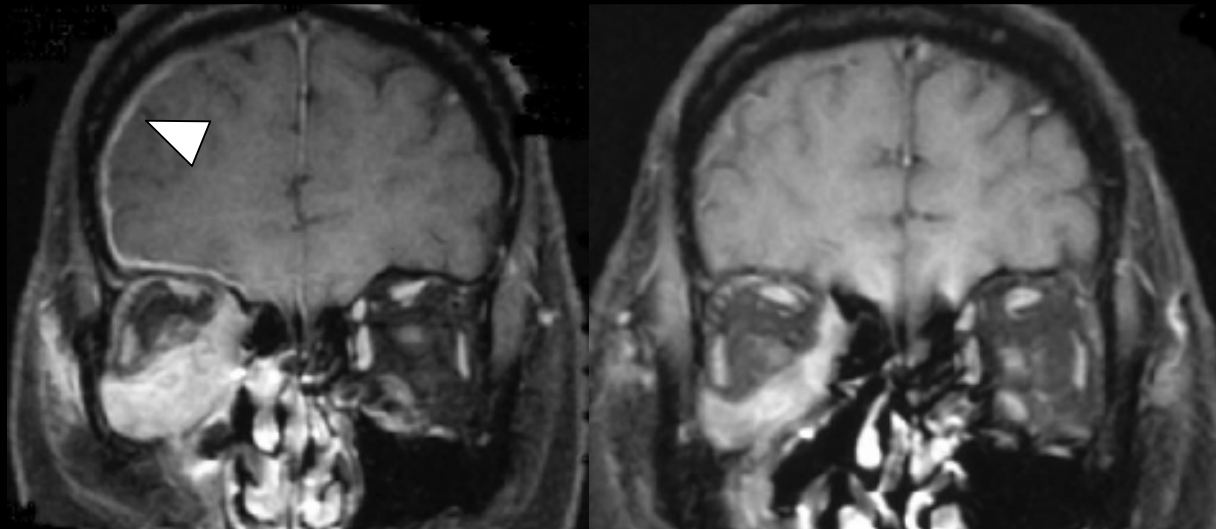
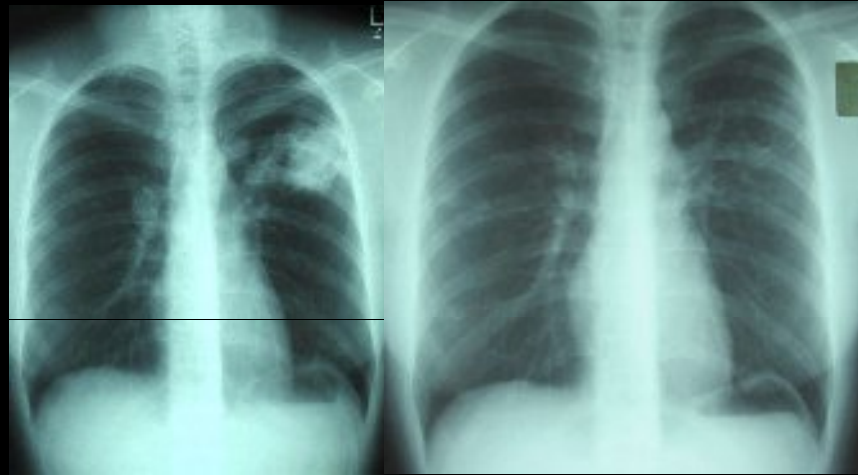
PR3-ANCA

CD38
Plasma cell

Rituximab in Wegener's

Pe-RTX

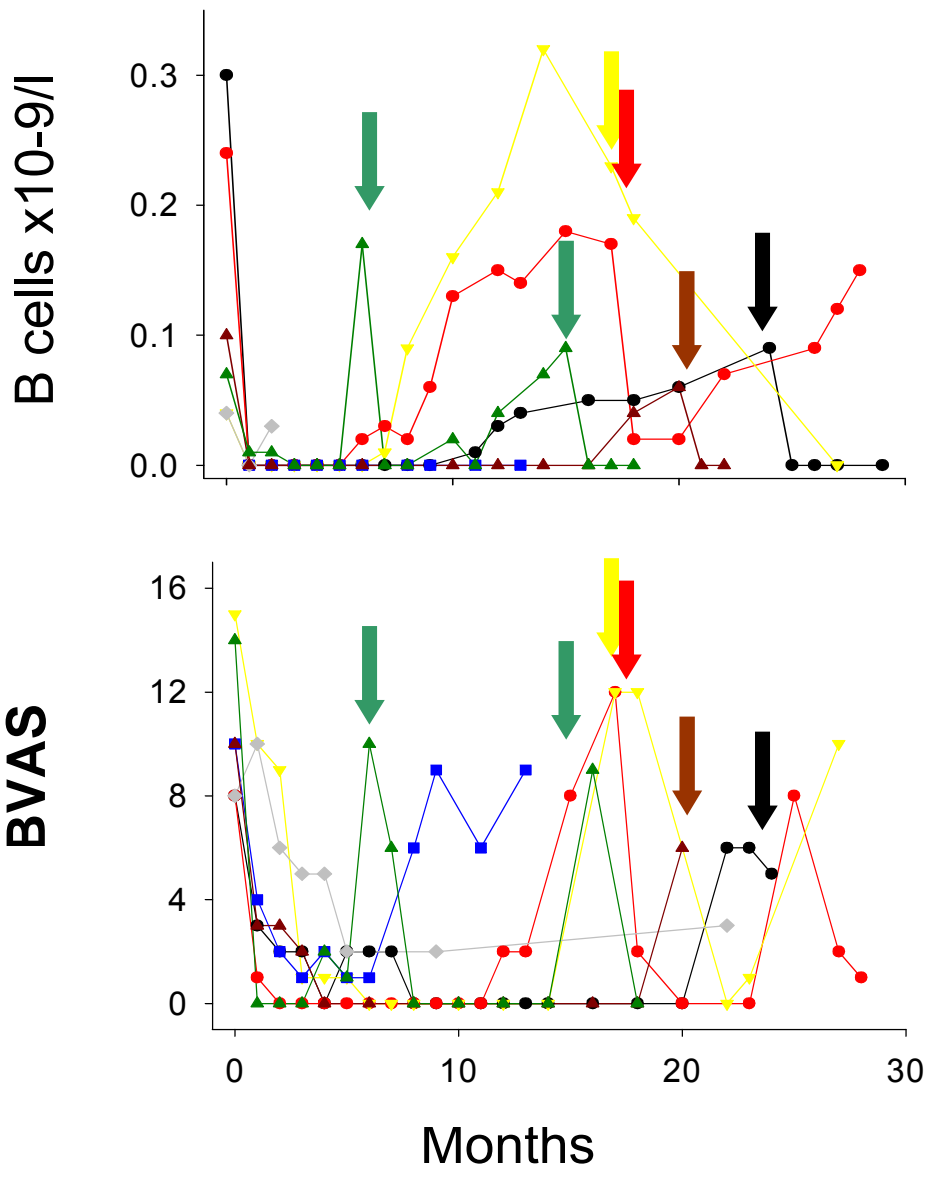
+3 months



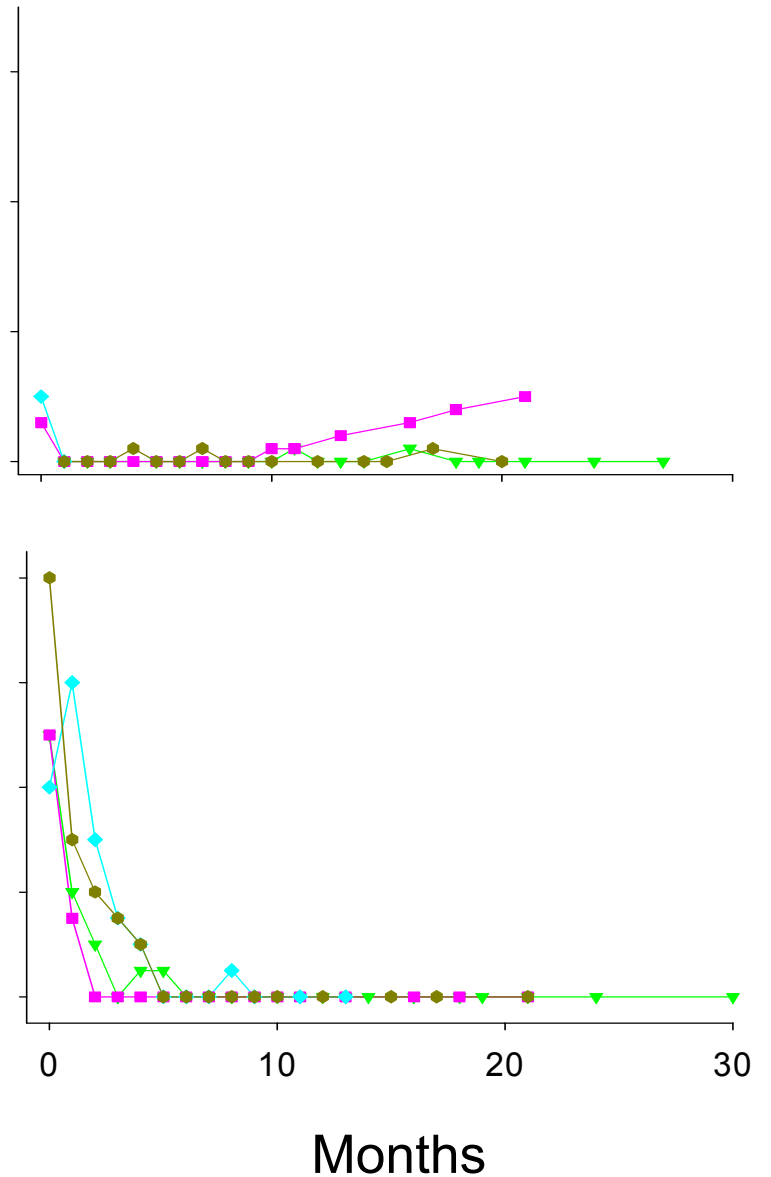
Efficacy of Rituximab –studies

Study	# Patients (# nephritis)	Remission (Nephritis)	B Cell Depletion	ANCA Serology	Relapse
Aries (2006)	8 (2)	2/8 (1/2)	8/8	0/8 became negative; no significant change in titre	NR
Eriksson (2005)	9 (7)	8/9 complete 1/9 partial (7/7)	9/9	0/7 became negative; no significant change in titre	2 (12 and 13 months)
Keogh (2005)	11 (4)	10/11 complete 1/11 partial (4/4).	11/11	8/11 became negative; all decreased titre	2 (7 and 12 months)
Keogh (2006)	10 (7)	10/10 complete (7/7)	10/10	6/10 became negative; all decreased titre	1 (9 months)
Omdal (2005)	3 (3)	3/3 complete	3/3	0/3 became negative; all decreased titre	3/3 (8, 13 and 15 months)
Smith (2006)	11 (6)	9/11 complete 1/11 partial	11/11	6/10 became negative; all decreased titre	6/10 (median 16.5 months)
Stasi (2006)	10 (6)	9/10 complete 1/10 partial	10/10	8/10 became negative; all decreased titre	3/10 (12, 16 and 24 months)

Relapse

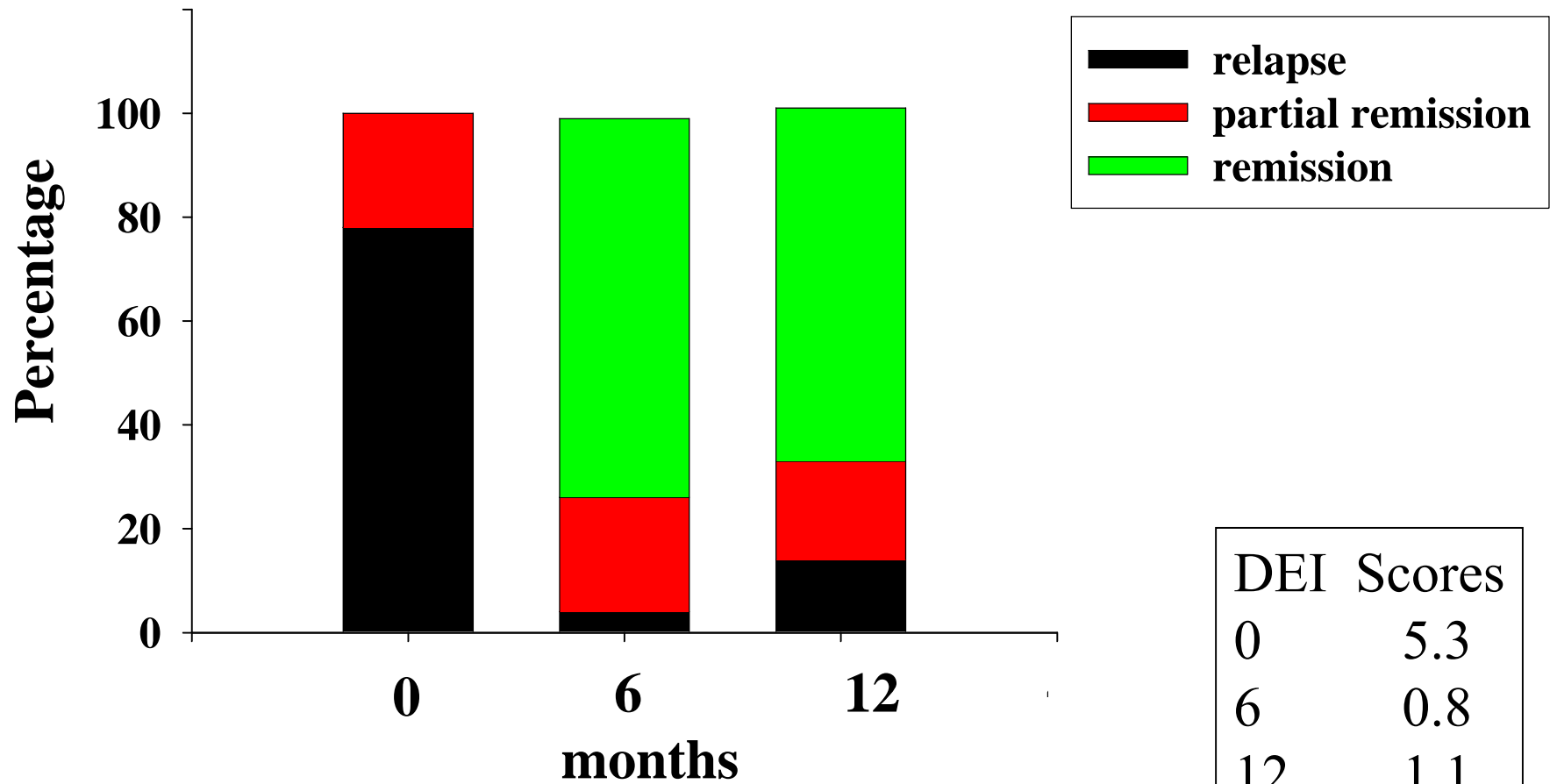


No relapse

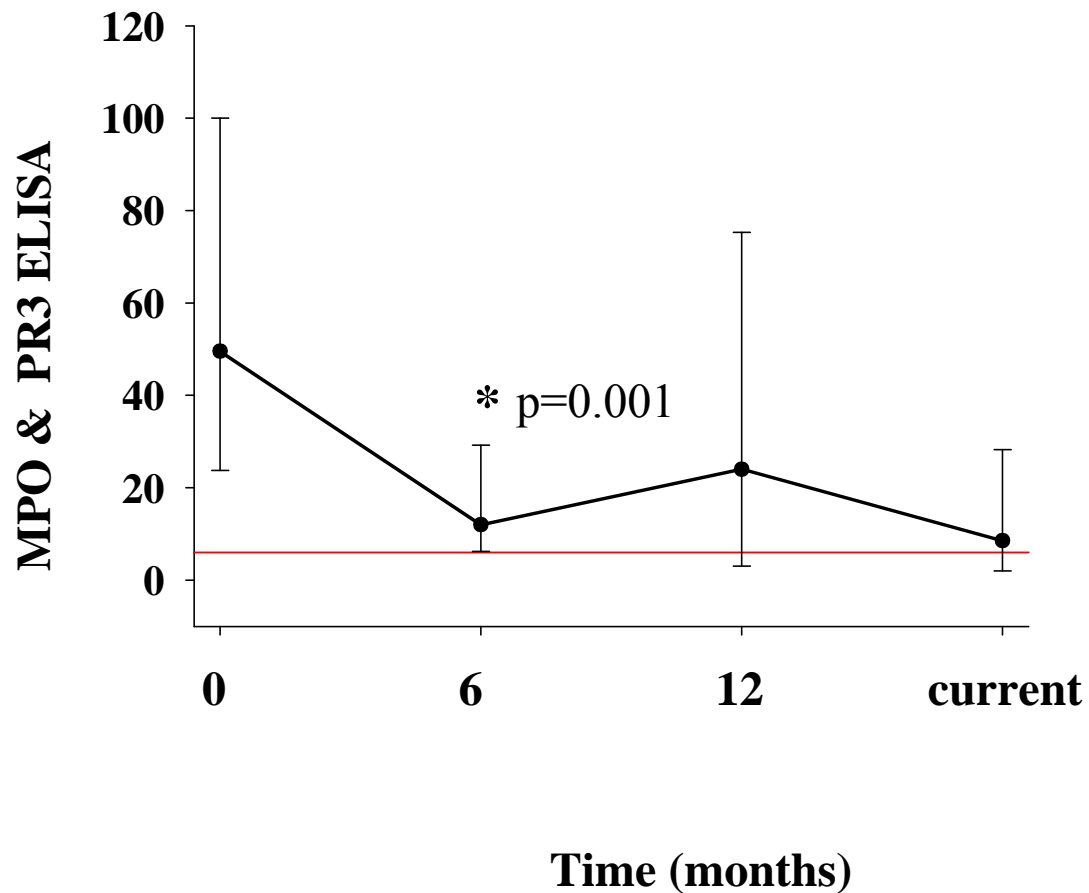


UK Retrospective, registry study, n =63

Rituximab response rates



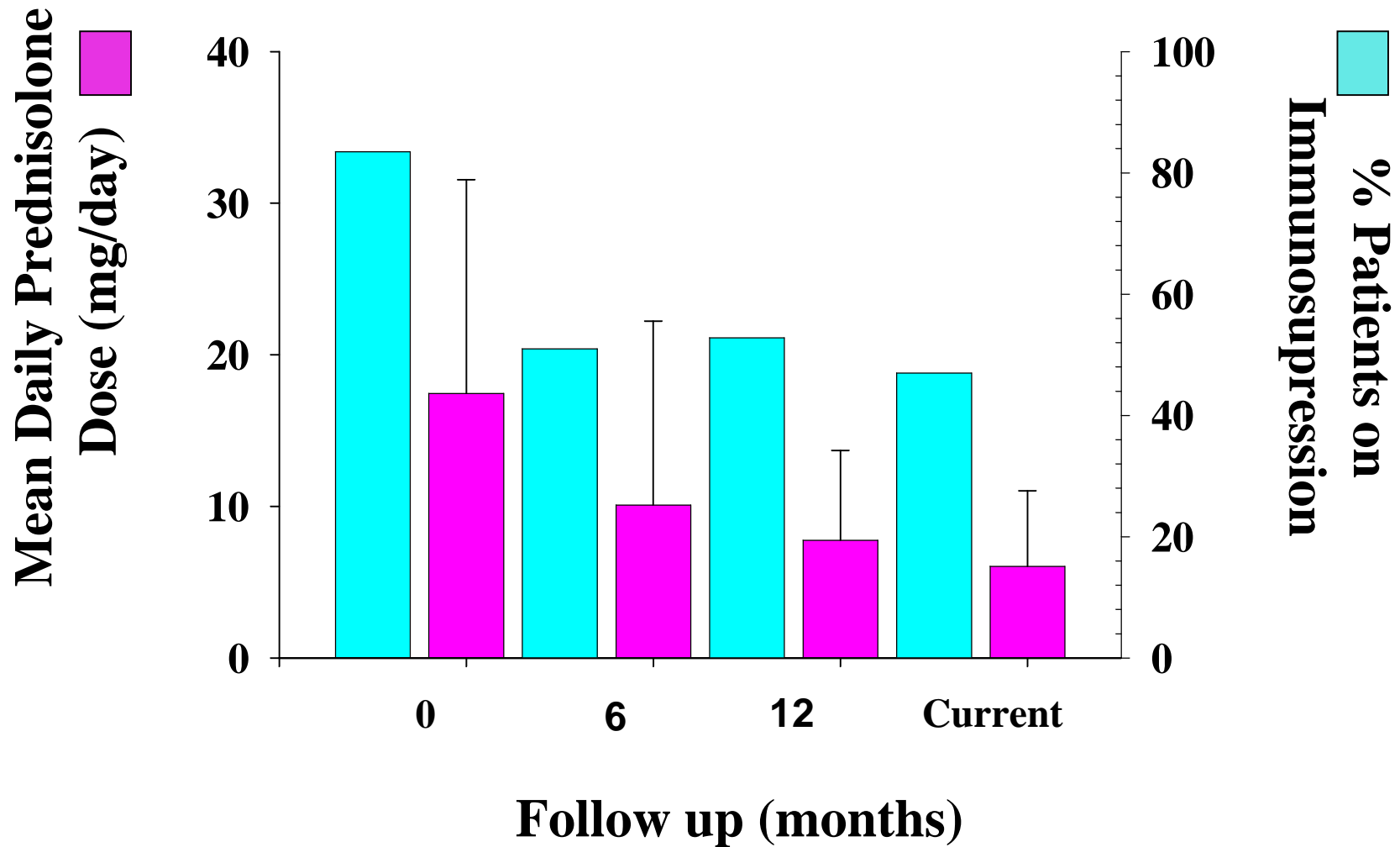
Change in ANCA levels, n=20



	ANCA Rise	No ANCA Rise
Relapse	5	14
No Relapse	1	22

P= 0.05

Prednisolone and immunosuppression




Rituximab trials

- RAVE
 - US, Genentech, Immune Tolerance Network
 - RTX vs CYC; + steroids
 - New and relapsing AASV
- RITUXVAS
 - EUVAS
 - RTX/CYC vs CYC; + steroids
 - RPGN

Summary

- Newer immune suppressives
 - MMF, leflunomide, DSG
 - Alternatives to current immune suppressives
- Biologicals
 - TNF α blockade
 - Promising but role not determined yet
 - Campath
 - Powerful drug, 'use with care', good potential
 - Rituximab
 - Preferred choice now in refractory disease
 - Promising for all patients in the future



Steroid sparing



Acknowledgements

European Vasculitis Study Group

Cambridge University

Rituximab registry

Japan/EUVAS study group