



Critical Review of Maintenance Therapy: Who to Treat and How?

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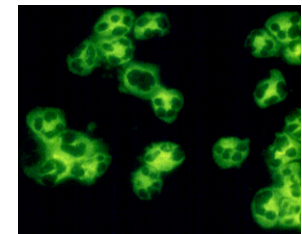
Topics

- What is remission – can it be treated?
 - What is the risk of relapse
 - What is the consequence of relapse
 - How effective are different drugs to prevent relapse
- *A case*



Case presentation – man born in 1935

- March 1986, respiratory infection, followed by arthralgia, malaise, exanthema, nasal congestion
- May -86, s-creatinine 1055 $\mu\text{mol/l}$ (12 mg/dl)
- Renal biopsy: extracapillary GN
- Oral cyclophosphamide, steroids, plasma exchange
- June -87, s-crea 146, switch to Azathioprine
- Feb -88 a positive c-ANCA test





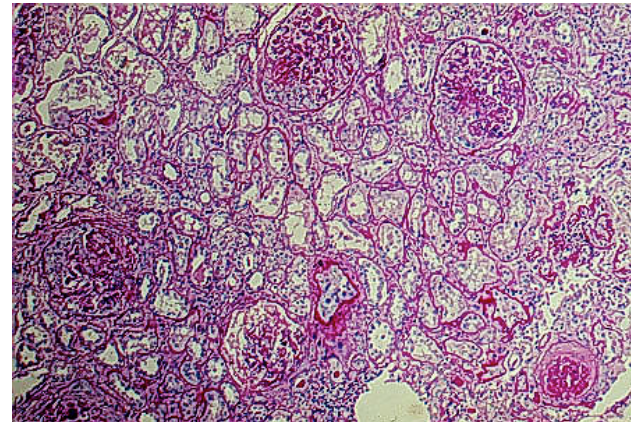
Case presentation continued

- 1992: 75 mg Aza, 5 mg prednisolone, s-crea 120 $\mu\text{mol/l}$ (1.37 mg/dl) and GFR 78 ml/min/1.73m² (iohexol clearance)
- Mild asthma and osteoarthritis
- Worked full time as farmer
- Aza was tapered to 50 mg in 1998 and stopped in 2000
- April -01 prednisolone was tapered to 2.5 mg per day
- Nov -01: Prednisolone stopped, s-crea 116 $\mu\text{mol/l}$, U-alb +1, U-Hb +1, CRP <5 mg/l, PR3-ANCA 93U



Case presentation continued

- In January 2002 arthralgia, weight loss, worse asthma.
- Feb 20, s-crea 187, PR3-ANCA 307 U, active sediment, U-alb 2+, U-Hb 3+
- Renal biopsy showed crescentic GN
- Oral Cyclophosphamide and prednisolone restarted



- May -02, switch to Aza
- Aug -02, s-crea 120, PR3-ANCA neg



Case presentation continued

- 2004, MRI show spinal stenosis, op in 2005
- 2006, Herpes Zoster
- Cataract bilat, op left side -07, right side -08
- Oct 2010: Aza 50 mg/day, Pred 5 mg/day, crea 119, PR3-ANCA 6 IU



Reflections from the case

- Relapses can occur after more than 15 years of stable remission
- A small dose of immunosuppression may prevent or postpone relapses
- Surveillance may reduce the impact of relapse
- Long time immunosuppression have side effects



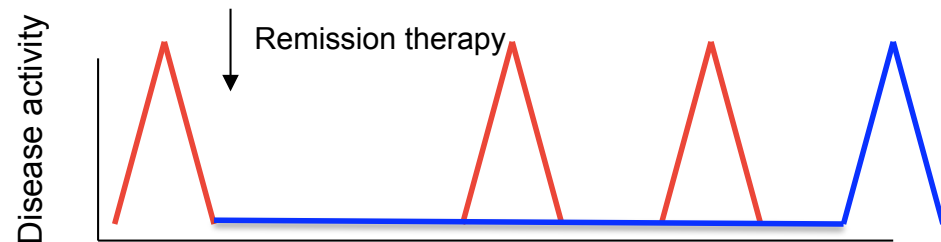
Topics

- **What is remission – can it be treated?**
- What is the risk of relapse
- What is the consequence of relapse
- How effective are different drugs to prevent relapse



What is remission?

- EULAR definition: Absence of disease activity attributable to active disease qualified by the need for ongoing stable maintenance immunosuppressive therapy¹.
- Not cure
- Not low grade disease activity
- BVAS = 0



¹Hellmich et al. Ann Rheum Dis 2007;66:605–617

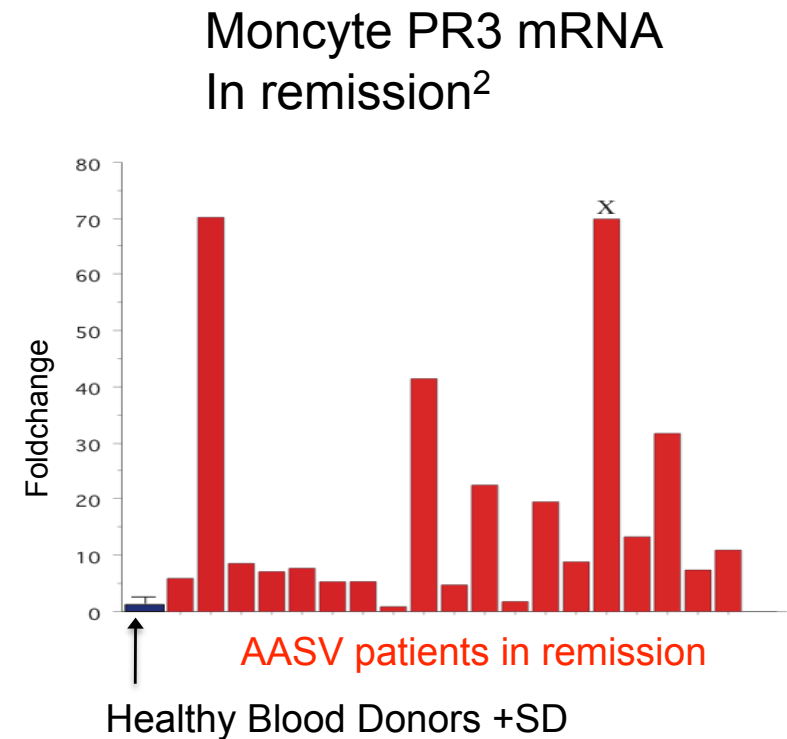
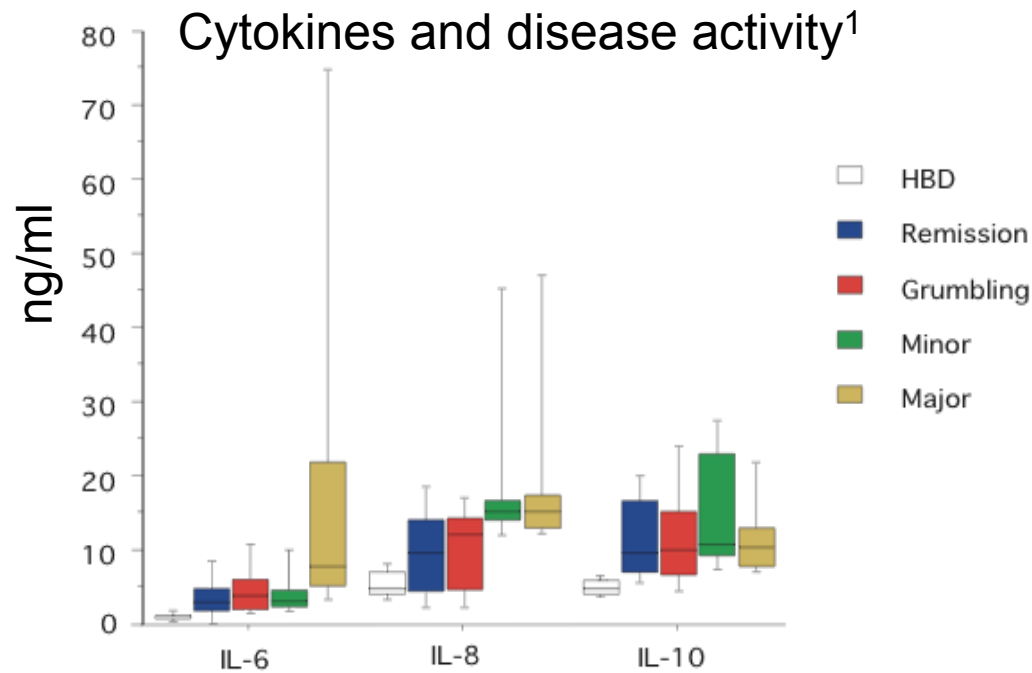


Abnormalities in remission

Category	Feature	Activity	Reference
Autoantibodies	ANCA	+/0	
Leukocytes	Activated T-cells (CD25+, HLA-DR+)	0	Arthritis Research & Therapy 2010; 12:204
	Effector memory T-cells (CD4+CD28-)	0	
	Plasmacytoid dendritic cells	?	ASN abstract 2010
	B –cell subsets		J Rheumatol 2010
	PR3+/CD177+ neutrophils	0	Clin Exp immunol
Cytokines	Il-6, Il-10, Il-8	+	<i>Mediators of Inflammation</i> . 2004;13:275-83
	U-MCP-1, s-MCP-1	+	
Autoantigens	Plasma PR3	0	
	Neutrophil PR3 mRNA	+	
	Monocyte PR3 mRNA	0	<i>Clin Exp Immunol</i> 2005;141:174-82
Others	Adhesion molecules		NDT 2001; 16:276-85
	S-FAS	0	
	Soluble Il-2 receptor	+	Ann Rheum Dis. 2006 Nov; 65(11):1484-9
	Soluble CD14	0	NDT 2001; 16:1631-7



Examples of deviations in remission



¹Ohlsson et al *Mediators of Inflammation*. 2004;13:275-83
²Ohlsson et al, *Clin Exp Immunol* 2005;141:174-82



Topics

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Risk of relapse in AASV

Table III. Relapse rates in AASV.

Citation	Disease – No. of patients	Relapse rate, %
Booth 2003 (54)	WG – 82 MPA – 120 CSS – 11 RLV – 33	34 at 13 mo
Koldingsnes 2003 (16)	WG – 56	60 at 18 mo
Gordon 1993 (55)	WG – 15	52 at 18 mo
Jayne 2003 (7)	WG – 95 MPA – 60	16 on AZA at 18 mo 14 on CYC at 18 mo
De Groot 2005 (8)	WG – 89 MPA – 6	70 on MTX at 18 mo 47 on CYC at 18 mo
Reinhold-Keller 2002 (56)	WG – 71	37 at 19 mo
Aasarod 2000 (15)	WG – 108	55 at 22 mo
Gordon 1993 (55)	MPA – 95	25 at 24 mo
WGET 2005 (23)	WG – 179	57 at 27 mo
Gordon 1993 (55)	WG – 28	44 at 42 mo
Hoffman 1992 (9)	WG – 99	56 at 60 mo
Guillevin 1999 (17)	CSS – 96	25 at 69 mo

AZA: azathioprine; CSS: Churg-Strauss Syndrome; CYC: cyclophosphamide; MPA: microscopic polyangiitis; MTX: methotrexate; RLV: renal limited vasculitis; WG: Wegener's granulomatosis.

*Mukhtyar et al,
Clin Exp Rheumatol
2006; 24 (Suppl. 43):
S93-S99.*



Factors associated with relapse

- WG vs. MPA^{1,2,3}
- PR3-ANCA vs. MPO-ANCA^{1,2,3}
- Lung involvement vs. not^{1,2}
- ENT involvement vs. not^{2,3}
- c-ANCA-positivity after treatment³
- Nasal Staph Aureus⁴

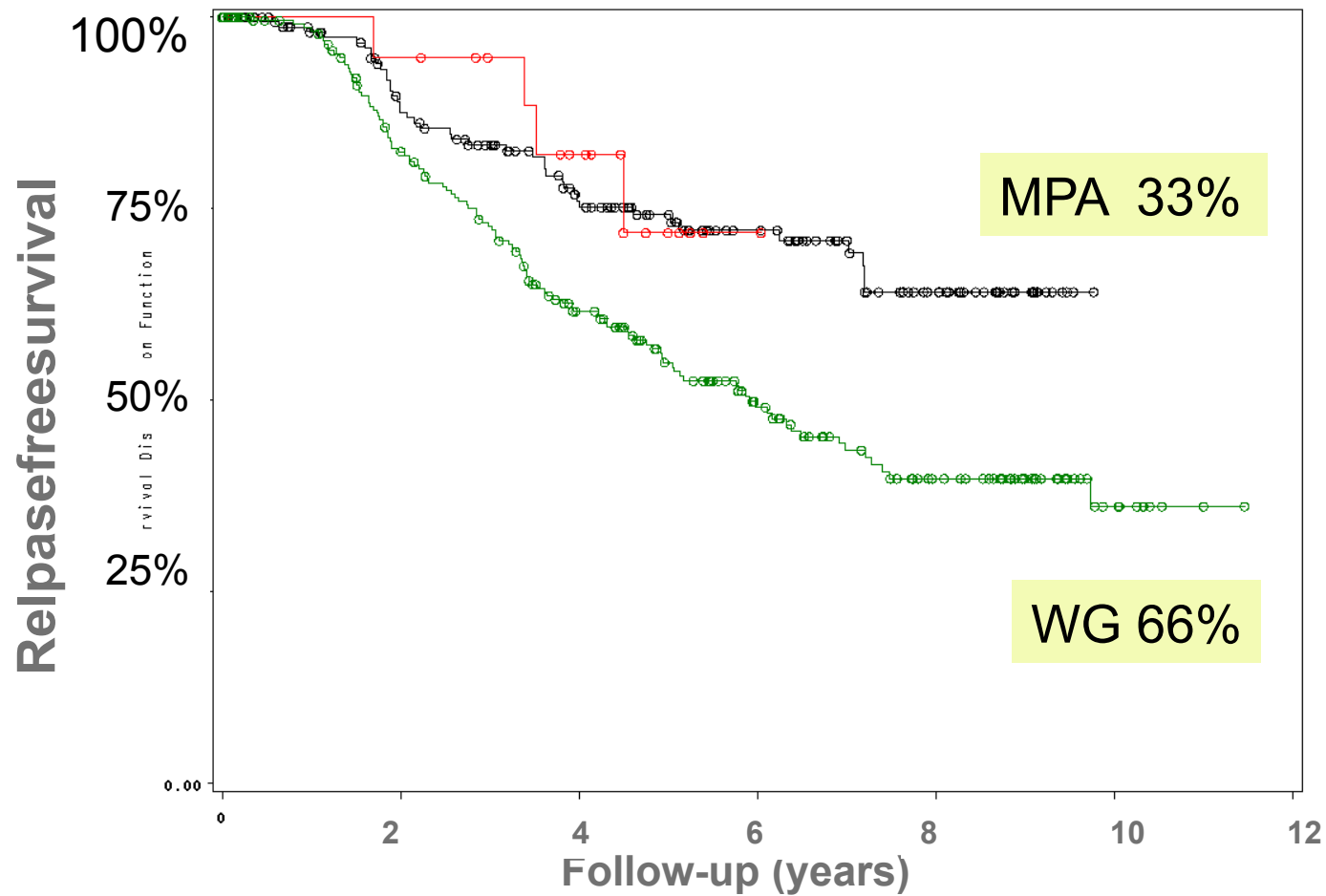
¹Pagnoux et al, Arthritis Rheum. 2008; 58:2908-18. ²Hogan et al, Ann Intern Med. 2005;143:621-31

³EUVAS long term follow up, Walsh et al. manuscript

⁴Sanders et al, Rheumatology (Oxford). 2006; 45:724-9. ⁵Ann Intern Med. 1994 Jan 1;120(1):12-7.



EUVAS long time follow-up (720 patients)

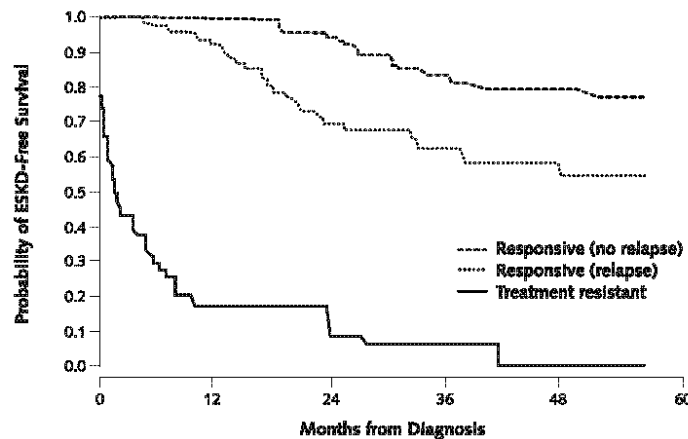


EUVAS longtime follow-up study, Walsh, et al (manuscript)



Consequence of relapse

- No significant increased risk of death¹
- Increased risk of End-stage renal disease
 - 30/109 with relapse vs 28/149 without. RR 4.7¹



- 10/31 with renal relapse vs. 2/37 without renal relapse, RR 16.8²
- RR 0.98 for non-renal relapse²

¹Hogan et al, Ann Intern Med. 2005 Nov 1;143(9):621-31

²Slot et al, Kidney International 2003; 63:670–677



Consequence of relapse

- Must be compared with the side effects of long time immunosuppression:
 - Diabetes
 - Infections
 - Malignancies
 - Osteoporosis
- Must be dependent on when relapse is diagnosed
- The rule of active surveillance have never been addressed in clinical studies



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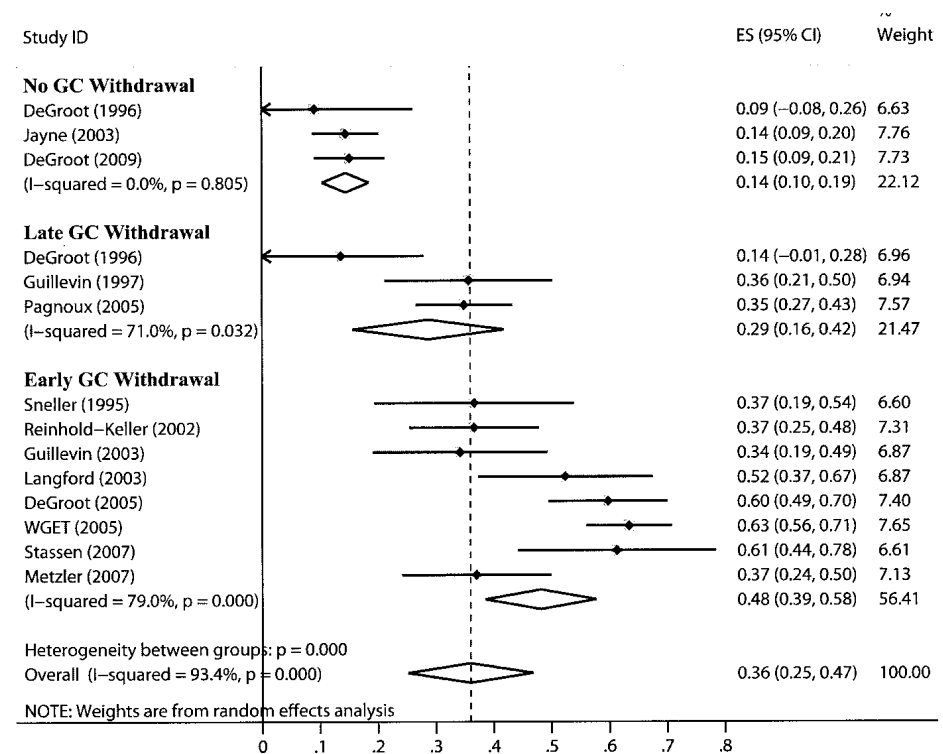
Alternative therapies for therapies for AASV

- Steroids
 - Oral prednisolone
 - Methyl-prednisolone iv
- Cytostatics
 - Cyclophosphamide
- Antimetabolites
 - Azathioprine
 - Methotrexate
 - MMF
 - Leflunomide
- Immunmodulation
 - Plasmapheresis
 - IvIgG
- Anti-cytokine therapy
 - Infliximab
- T-cell depletion therapy
 - ATG
 - Campath-1H
- B-cell depletion therapy
 - Rituximab
- Miscellaneous
 - Cyclosporin
 - DSG
 - Stemcell transplantation
 - CTLA4-Ig



Steroids

- Recent meta-analysis
- 13 prospective studies with 983 patients published after 1995
- Non-zero target 14% relapse
- Zero-target 42 % relapse
- RITUXVAS: 2010-



Walsh et al, Arthritis Care Res. 2010; 62(8):1166-73.

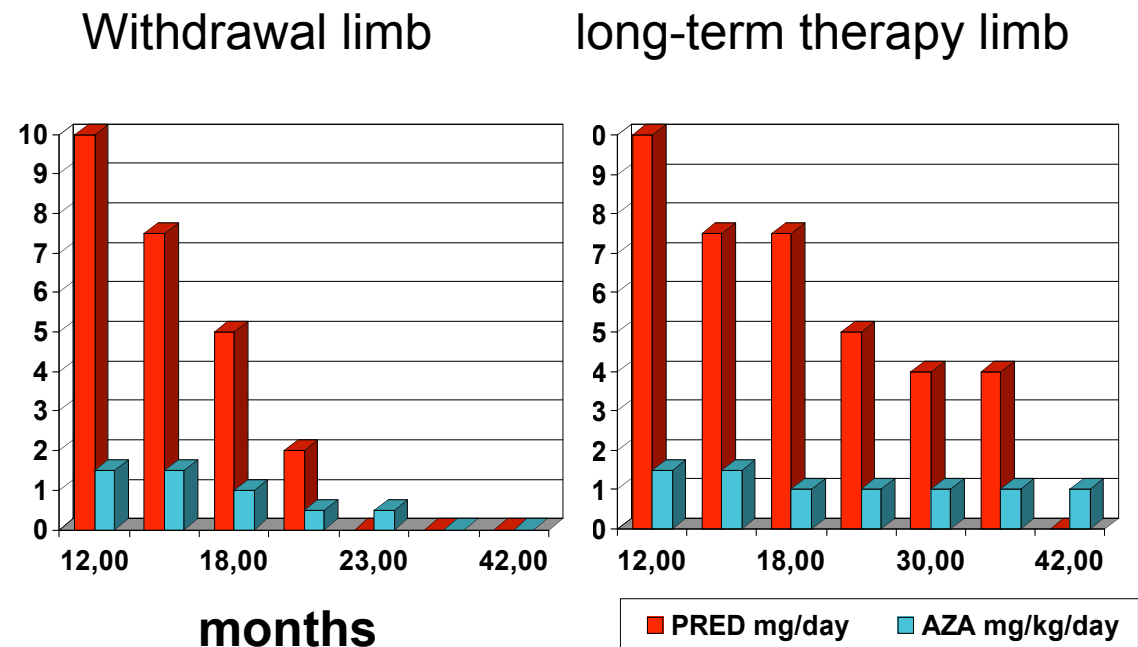


Azathioprine

- First line therapy to sustain remission
- Proven alternative to cyclophosphamide to sustain remission (CYCAZERAM)¹
Relapses at 18 months:
 - Cyc: 13.7%
 - Aza: 15.5%
- The efficacy of long term treatment to prevent relapses still unknown.

REMAIN: 2 or 4 years of Aza
Recruitment completed in
June 2010. Results 2012

REMAIN



¹Jayne et al *NEJM* 2003; 349:36-44.



Methotrexate

- Proven alternative to cyclophosphamide to induce remission in mild to moderate cases^{2,3,4}
- Similar efficacy as cyclophosphamide to sustain remission^{1,2,4}
- Ability to sustain remission is indirectly shown by high relapse rate after withdrawal^{3,4}
- Similar efficacy as Azathioprine to sustain remission-
WEGENT⁵

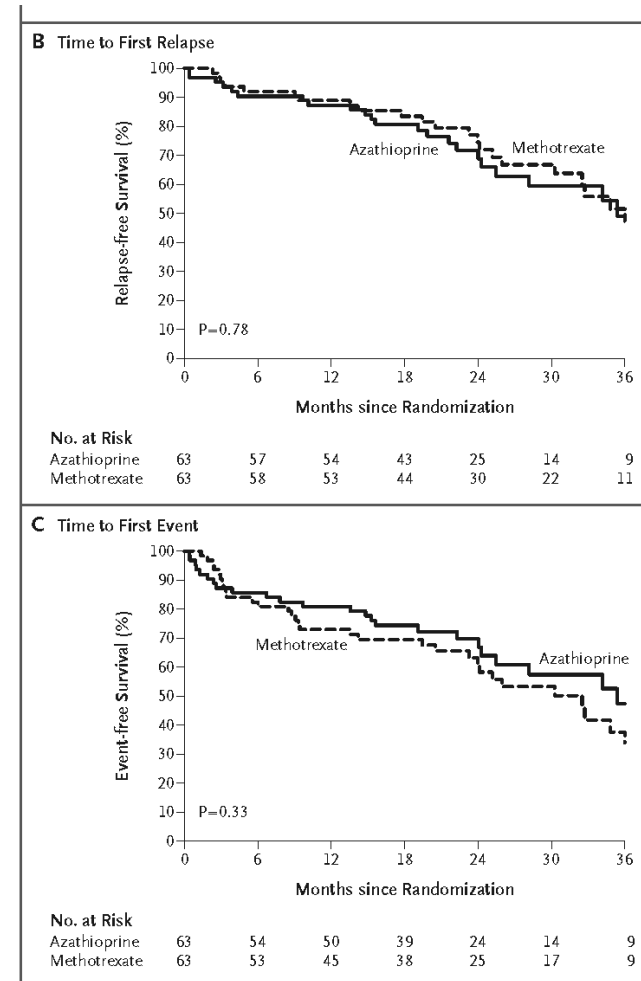
¹Reinhold-Keller et al *Arthritis Rheum* 2002; 47:326-32. ²Langford et al *Am J Med* 2003; 114:463-9.

³De Groot et al *Arthritis Rheum* 2005; 52:2461-9. ⁴Villa-Forte et al *Medicine* 2007;86:269-277.

⁵Pagnuax et al, *N Engl J Med*. 2008 Dec 25;359(26):2790-803

WEGENT

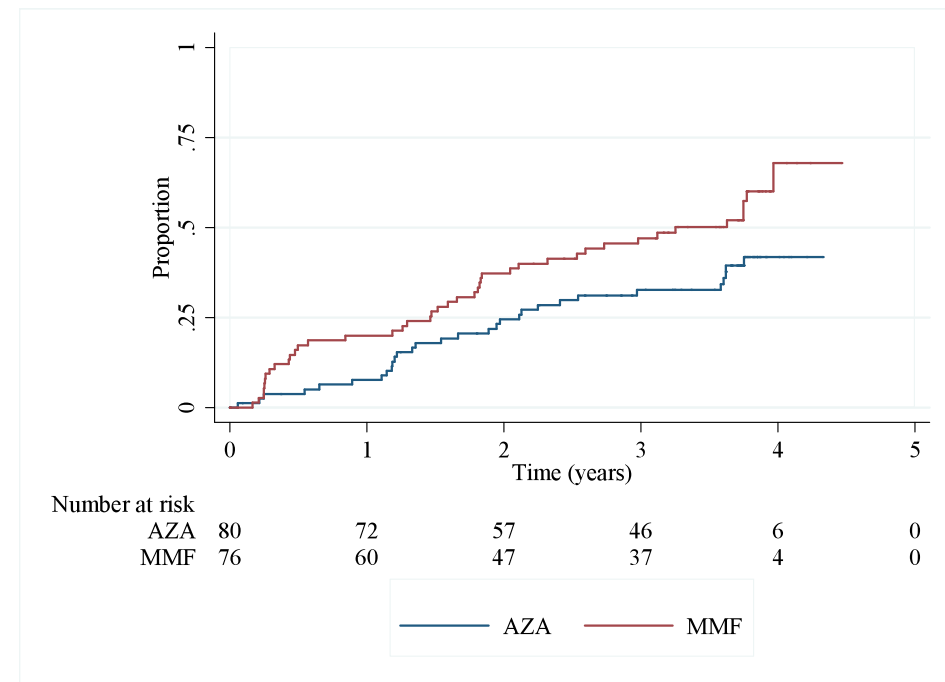
- 180 patients induced with Cyc +Pred
 - 63 Methotrexate 25/mg day,
 - 63 Azathioprine 2mg/kg
- WG/MPA 96/30
- No difference in relapse rate
- Severe adverse event:
 - Aza 7
 - Meth 12





Mycophenolate mofetil

- Positive results to sustain remission in open label studies^{1,2}
- Significantly worse than Aza in IMPROVE³ with 156 patients
 - Aza 30 relapses
 - MMF 43 relapses



Hazard ratio 1,7 CI 1,06-2,73, p=0.03

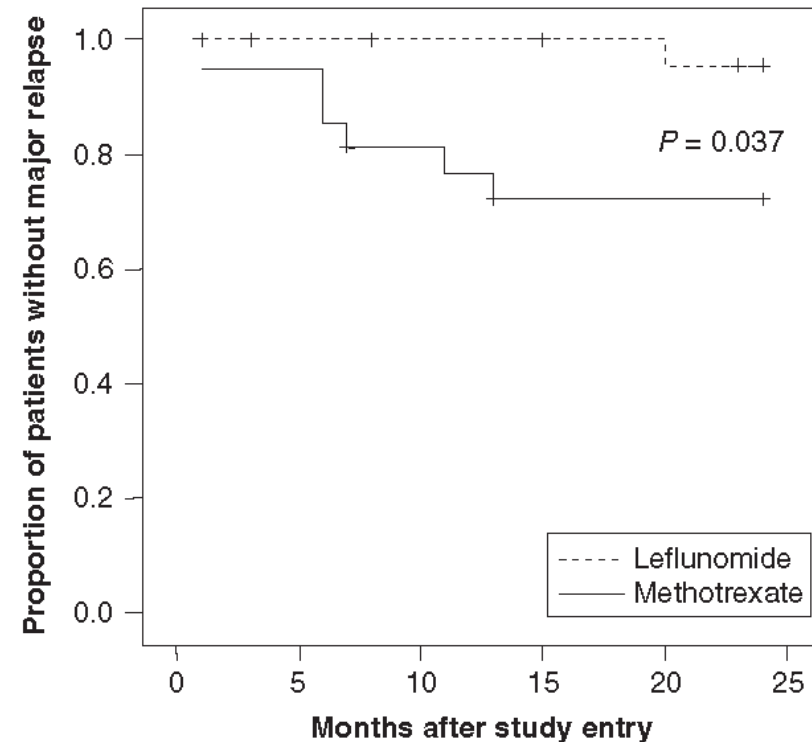
¹Nowack et al JASN 1999; 10:1965-71. ²Koukoulaki Nephron 2006;102:c100-7

³Hiemstra et al, JAMA, epub nov 8, 2010



Leflunomide

- An alternative drug to maintain remission in patients with relapses^{1,2,3} and to induce complete remission in patients with partial¹.
- Better than Methotrexate to prevent renal relapses in WG in a prospective randomized trial²
- More side effects

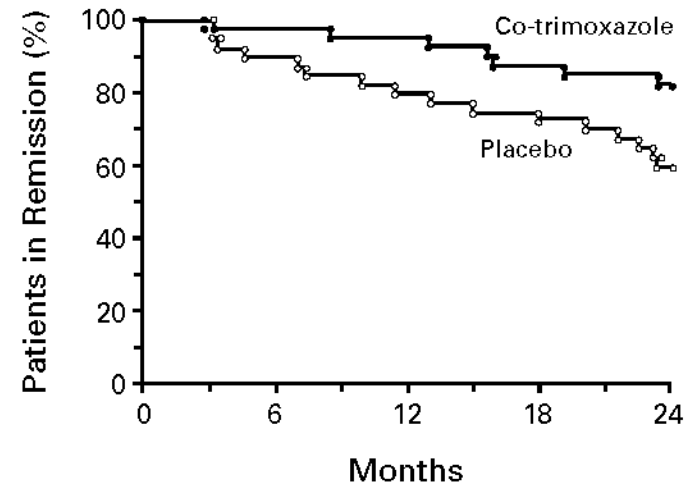


¹Metzler et al Rheumatology 2004; 43:315-20. ²Metzler et al Rheumatology 2007; 46:1087-91.
³Henes et al Clin Rheum 2007; 26:1711-5.



Trimethoprim–Sulfamethoxazole

- Effective as sole therapy in limited WG¹
- Reduce relapses in WG²
 - At least ENT relapses (1 vs 11)
 - Renal relapses non-significant (4 vs 7)



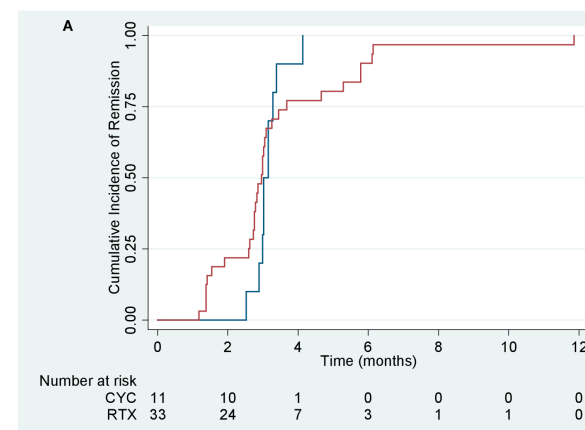
¹DeRemee et al. *Mayo Clin Proc* 1985, 60:27-32.

²Stegeman et al, *N Engl J Med*. 1996 Jul 4;335(1):16-20



Rituximab- induction of remission

- Induced remission in 11/11¹, 8-9/9², 3/3³, 2-3/8⁴, 10/10⁵, 9-10/10⁶ in case series
- Equally efficient to induce remission as standard Cyc therapy in two randomized trails
 - RAVE⁷
 - RITUXVAS⁸



¹Keogh et al *Arthritis Rheum* 2005;52:262-8. ²Eriksson *J Int Med* 2005;257:540-8.

³Omdal et al *Scand J Rheumatol* 2005; 34:229-32. ⁴Aries et al *Ann Reum Dis* 2006; 65:853-8.

⁵Keogh et al *Am J Respir Crit Care* 2006;173:180-7. ⁶Stasi et al *Rheumatology* 2006; 45:1432-6.

⁷Specks et al, *N Engl J Med*. 2010; 363(3):221-32. ⁸Jones et al, *N Engl J Med*. 2010; 363(3):211-20



Rituximab- maintenance of remission

- RITUXVAS 24 month data indicate similar relapse rate as Aza without re-treatment, and similar rate of infections
- Re-treatment prevents most relapses in uncontrolled studies
 - No relapses among 15 patients given 1 g every 6 month, followed for 3-23 months (median 11)¹.
 - 35 patients with incomplete remission or frequent relapses were given 1g every 4 months². During 12-24 months 3 relapsed.
- Randomized studies are underway
 - MAINr
 - EUVAS

¹Jones et al. Arthritis Rheumatism 2009; 60:2156-68

²Rhee et al, CJASN 2010; 5: 1394-1400



Miscellaneous

- DSG (15-deoxyspergualin) 20 patients, 6 complete remissions and 8 partial (9 Cyc resistant, 1 complete remission)¹
- Cyclosporine- To maintain remission², probably used a lot clinically, relatively little in the literature
- Anti-TNF- α
 - Etanercept showed no effect in WGET³
- Intravenous immunoglobulin (IvIgG)
 - Achieved remission in 21/22 patients with frequent relapses, but only 7 remissions lasted up to 24 months⁵
- Abatacept- CTLA4-Ig. Phase II study aborted

¹Schmitt et al JASN 2003 14:440-7. ²Haubitz et al NDT 1998; 13:2074-6.

³Stone N Eng J Med 2005; 352:351-61. ⁵Martinez et al *Arthritis & Rheum* 2008; 58:308-17.



Take home message

- Remission is not equal to cure
- Remission is a active process with several potential pharmacological targets
- Steroid dosing is important
- Cyc = Aza = Mtx
- Aza > MMF
- Lef > Mtx ?
- Rtx??



Summary: Suggested approach

- Assess the individual risk of relapse
 - Complete remission? smoldering activity?
 - WG/MPA
 - Current ANCA status
- Assess the individual consequence of a relapse
 - S-creatinine
 - Lung function
- Assess the individual ability to tolerate maintenance therapy
 - Diabetes
 - Malignancy
 - Infections
 - Pregnancy wish