



# 2011 ACR selected abstracts on vasculitis

Dr. Christian Pagnoux



# GCA, TAKAYASU and LVV



# Human Ferritin heavy chain antibodies as a marker of GCA/PMR?

- Protein array technology on 6 GCA sera
  - 37,830 proteins (cDNA fetal brain tissue expressed in E. coli)
  - Candidate Abs → confirmation by ELISA (3 ELISAs: N human heavy chain, internal; N27-Staph.)
- 64 GCA, 47 PMR, 31 GC/PMR, 40 SLE, 36 RA, 70 fever >38.5, 180 blood donors, B-NHL 48
- Protein array for ferritine heavy chain Abs
  - 14% GCA, 19% PMR, 17% both (22% before CS)
  - 3% SLE, 0% RA, 12% fever, 0% BD
- ELISA (N-term 27 AAs of ferritin heavy chain)
  - 55% all with GCA and/or PMR (92% before CS)
  - GCA/PMR 13% in remission vs. 69% during flares
  - 29% SLE, 3% RA, 1% BD

# Annexin-A1: A Potential Novel Biomarker in GCA

- Annexin-1= 37-kDa glucocorticoid-regulated protein, abundant in neutrophils, rapidly mobilized to the surface upon cell activation, exert inhibition of leukocyte adhesion to vessel wall
  - Microparticles (MP)= released into the plasma following activation of neutrophils (as well as other cells), inducing cellular cross-talk
  - 8 biopsy-proven GCA (6 women) → Blood at W1 (60 mg), 5, 9, 13, 17, 21, 25 (10 mg)
  - FACs for AnxA1 and MPs + RT-PCR for AnxA1
  - 50% of GCA neutrophils expressed AnxA1 at W1 (not monocytes or lymphocytes)
  - Levels of expression steadily declined → W24 only 20% of neutrophils expressing AnxA1
  - Not observed on neutrophils from patients with PMR or RA (only 20% of neutrophils)
  - AnxA1 also detected on plasma MP in GCA patients.
  - RT-PCR analysis: 3-fold decrease in AnxA1 gene expression at W24 as compared to W1
- High AnxA1 expression on neutrophils as a potential disease-specific biomarker for GCA?

# Doppler and SVV-VVV versus GCA

- N=30 with periadventitial small vessel vasculitis (SVV) surrounding uninflamed TA and/or isolated vasculitis of the TA vasa vasorum (VVV) = 46% satisfying ACR
  - N=30 with GCA
  - Abnormal clinical TA findings 60% versus 33.3% (NS)
  - Halo in 76.6% GCA versus 20% in SVV-VVV (P<0.01)
  - Bilateral halo 65.2% versus 16.7% (NS)
- US not appropriate for SVV/VVV GCA

# US guidance of TAB does not increase +TAB frequency (single-blinded randomized study)

- 74 consecutive patients with suspected GCA (2009-May 2011)
  - 42 women, mean age 71-75
  - 37 with clinical findings on examination; mean CRP 60-70 mg/l; mean ESR 56-58
- CDS-guided TAB (n=35; largest halo, if present, or doubtful halo, stenosis, occlusion, or wall thickening) **or** TAB performed according to conventional technique (n=39, blinded to halo)
- 43 patients were on PDN, mean dose 17.3 mg/d; 7 of them for <2 wk
- Halo detected in 20 patients from CDS-guided TAB arm vs 12 in controls
- TAB positive in 13 patients in CDS-guided TAB vs 12 in controls (NS)

→ 12 TAB + /20 patients with halo/35 group CDS-guided vs. 12/39 not guided = OR 3.4 (95% CI 1.1–10.4) = TAB associated with a greater probability of +

→ However, similar % of TAB-positive patients

## Age at onset and gender are associated with differences in GCA

- 170 biopsy-proven GCA diagnosed 1995/2005
- 94 with follow-up >4 years
  - Mean age  $74 \pm 7$  years
- Age <67 at diagnosis had more fever and higher ESR
- Age >81 at diagnosis had more frequent amaurosis fugax (29% vs. <9%) and blindness (33% vs. <7%) but lower relapse rate
- No difference according to gender but men had more frequent aortic aneurysm during follow-up

# Ischemic complications in GCA with background prior PMR

- 159 patients with GCA (Barcelona, Spain, 1986-2010), ACR 1990 → 16 (10%) with a background history of PMR
  - Median time from PMR/PDN onset to GCA =  $214 \pm 173$  days; prednisone received  $1707 \pm 1268$  mg
  - GCA usually during tapering of PDN or after unauthorized discontinuation (1 case)
  - TAB+ in 12 (75%)
  - Severe GCA-related ischemic complications between GCA onset and 4 weeks after PDN onset) = 6 patients (37.5%)
    - 4 had more than 2 events
    - visual ischemic manifestations = 6 (35%)
    - stroke and/or transient ischemic attacks = 2 (12%)
    - jaw claudication = 2 (12%)
    - large-artery stenosis of the extremities (limb claudication) = 1 (6%) of the axillary artery.
- Patients with GCA on the background of an apparently isolated PMR are at risk of developing severe ischemic complications

# Relapses in GCA

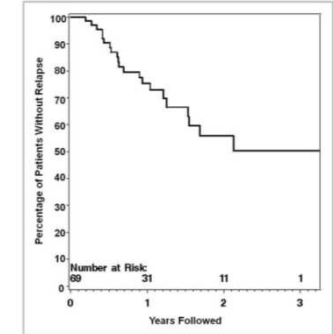


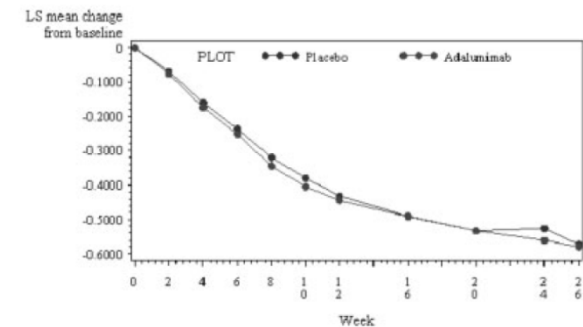
Figure. Time from diagnosis to first relapse in 69 patients with newly-diagnosed GCA

- Multicenter **VCRC cohort**
- 128 GCA (80% women, 69.9 years, follow-up 21.4 months, mean duration of disease 4.6 months), included 69 newly diagnosed
- At baseline, 39% already experienced a relapse
- **During follow-up, 59 relapses in 44 patients (34%)**
  - 10 patients (8%) had  $\geq 2$  relapses
  - MSK 64%, Headaches 54%, visual 5%
  - 34 patients were still on PDN; 13 on MTX
  - ESR 32 (increased in 60% of flares), CRP 13.5 (increased in 52% of flares); ***both tests normal in 33% at relapses***
- In the 69 newly diagnosed at enrolment
  - **24% experienced a relapse within 1 year post-diagnosis**

# RCT of adalimumab for GCA

- CS starting at 0.7 mg/kg/d + ADA (SQ, W0, 2, 4, 6, 8, 10) or placebo (double blinded)
- Primary EP= % of patients with PDN<0.1 mg/kg/d at W26 – aimed to enrol 100 (started in 2006)
- 34 ADA, 36 Placebo (73.9 years, CRP 61-66, ESR 69, Hb 11.5) PEP achieved in 47.1% ADA vs. 47.2% Placebo (NS)
  - Idem si PP rather than ITT (27 ADA vs. 36 Placebo received the full 10 weeks of Rx): 60% ADA vs. 47.2% Placebo
- SAEs 21% ADA vs. 48.6% Placebo (NS!)
  - 3 deaths (1 ADA, 2 Placebo – 2 of septic shock)
- Dose of PDN similar in both arms

→ No benefit, like with other antiTNFa...



Mariette et al. (France) #1508

# PET, interleukins and MMPs in Takayasu arteritis

- 36 TA (3 ACR criteria), 36 age- sex-matched HC
- IL-2, 6, 8, 12, 18, TNFa, MMP-3, 9 + FDG-PET
- 36 ans, 92% women
- IL6 and MMP3 higher in TA patients vs HC
- IL6 higher in active disease vs inactive
- SUV FDG-uptake higher in active vs inactive (threshold 1.3 for SUVmax), correlating with IL6 and MMP3

# PET in LVV

- 24 LVV patients 2007-2010
- FDG-PET, CRP and ESR
- Positive PET in patients with
  - Higher ESR (72 vs. 30 mm)
  - CRP NS (43 vs 6 mg/l; p=0.05)
  - 90% if both ESR & CRP abnormal; 50% if one abnormal; 20% if none
- Use of corticosteroids (vs. no use) was NOT correlated with FDG-uptake (no direct effect on FDG-uptake)

# Immunological signature of Takayasu arteritis

- 30 TA: 11 active treated + 19 inactive treated; 20 healthy donors
- 26 cytokines from culture supernatant by Luminex and ELISA; FACs of PBMCs; immunohistochemistry on carotid tissue samples from 3 patients for IFN $\gamma$ , IL17 and IL21
- PPV=100, NPV=95%
- **Expansion of TH17** in active TA by FACs (3% vs. 1.3% vs. 0.6% HD)
- **Expansion of TH1** in active TA by FACs (24.2% vs. 10.7% vs. 18.3% HD)
- **Expansion of IFN $\gamma$**  producing CD8+ in active TA by FACs (3% vs. 1.3% vs. 0.6% HD)
- **Expansion of IL21** producing CD4+ in active TA by FACs (7.9% vs. 4.1% vs. 1.7% HD)
  - Correlated with TH17 and TH1 expansions
- Tissue expression of IL17A, IFN $\gamma$ , IL6, CCL20, TLR5
- In vitro stimulation of CD4+ with IL21 increased TH17 and decreased FoxP3, and inversely if blockade with some

→ IL21 as therapy?

# Surgery vs. endovascular repair in Takayasu's arteritis

- Surgery vs. percutaneous endoluminal repair
  - Retrospective study on 79 consecutive patients (age 39, females 80%) who underwent 104 surgical procedures and 62 surgery
  - Follow-up 6.5 years, 74 complications (restenosis 42)
  - **Surgery vs. PTA arterial complication-free rate**
    - At 5 yrs: 60% vs. 49%
    - **At 10 yrs: 57% vs. 29% (p<0.05) almost x4!!**
    - Multivariable analysis: PTA had OR=3.61 of complications
    - Higher CRP, ESR and fibrinogen also associated with complications
- **More arterial complications with PTA**

# Tocilizumab for LVV and PMR

- 8 mg/kg/month
  - 7+3=10 patients
    - 7 GCA, 2 TA, 1 PMR
    - Mean disease duration 18 months
    - Mean follow-up on TCZ 7.5 months
  - **At 8 weeks, effective in all** on ESR, CRP, decrease of PDN<5 mg OD (7 off PDN)
  - 1 flare, 2 months after cessation of TCZ
  - Mild neutropenia (2/7) and transaminitis (3/7)
- when to stop and outcomes post-cessation?

# Tocilizumab for LVV

- 8 mg/kg/month for 6 months
- 6 patients
  - 2 new TA: followed by MTX
  - 1 relapsing GCA, 2 TA, 1 aortitis+RPF: on top off MTX (3) and MMF (1)
- **Effective in all** on ESR, CRP, Kerr and/or ITAN scores
- 5/6 with >3 months of follow-up post-cessation of TCZ
  - **2 relapsed**

# ANCA associated vasculitides

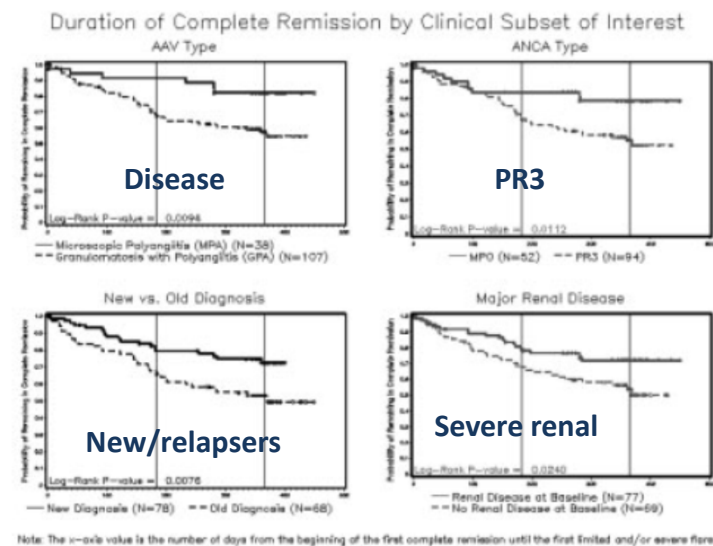


# Descriptive Epidemiology of GPA, MPA, PAN and antiGBM in the USA

- **USA:** HIPPA-compliant Thomson-Reuters MarketScan Commercial Claims and Encounters and the Medicare Supplemental and COB databases
- Around **86 million insured employees and their dependents**
- ICD9 code (GPA [446.4]; MPA [446.20, 446.29]; PAN [446.0] and GS [446.21]) between 2008-2009
- **Unadjusted incidence rate**
  - GPA 15.6/million (95%CI: 14.2, 17.1),
  - MPA, 13.4/million (95%CI: 12.1, 14.8),
  - PAN and GS were 6.9/million (95%CI: 6.1, 8.0) and 1.6/million person-years (95%CI: 1.2, 2.1)
- Age-standardized incidence rates
  - GPA 14.9/million
  - MPA 12.2/million
  - Unchanged for PAN and GS
- Gender-specific rates were higher in females for all diseases except GS
  - highest female preponderance for MPA (F/M ratio: 2.43)
- Incidence peaked in the 8th decade for GPA (38.9/million), the 6th decade for MPA (18.1/million), and the 8th and 9th decades for PAN (21.1/million) and GS (5.1/million)
- **Year 2008–2009 prevalence**
  - 123/million (95%CI: 118, 128) for GPA
  - 78.3/million (95%CI: 74, 83) for MPA
  - 51.0/million (95%CI: 47.7, 54.7) for PAN and 8.8/million (95%CI: 7.5, 10.4) for GS

# Extended RAVE follow-up

- 197 patients ANCA+ (49% new, 51% relapsers)
- CR (NS)
  - At M6: 64% RTX vs 53% CYC/AZA
  - At M12: 47% RTX vs 39% CYC/AZA
  - At M18: 39% RTX vs 33% CYC/AZA
- Higher risk of relapse
  - Relapsers
  - No renal disease
  - PR3+
  - GPA
- Flares occurred only after B cell reconstitution in RTX arm



# Rituximab severely reduces Ig in AASV

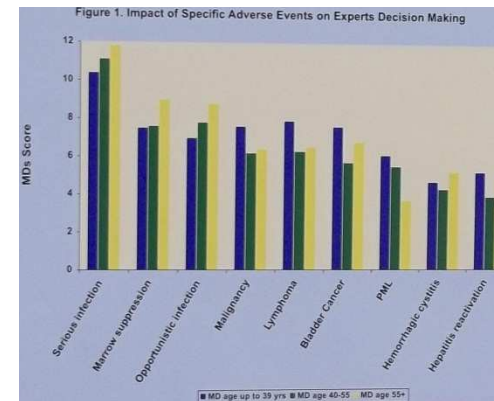
- 26 AASV on CYC - 29 RTX - 15 CYC then RTX
- IgG, M and A decreased in all groups
  - But **mainly in the CYC then RTX group**
  - e.g., IgM level post treatment: 0.88 – 0.81 – 0.52 g/l
- Post-RTX (mean 1.8-1.9 g cumulative), follow-up showed no increase of Ig at M24

→ No correlation study with infections...

# Ig level at baseline and during RTX or CYC induction (RAVE)

- 56/197 (28.4%) had a low Ig of any isotype at baseline (36 (64%) relapsers)
- **Similar decrease** in IgG, then M, A during Rx in both groups (among the 124 who completed M18 – 61/63)
- At 6 and 18 Months, more patients had low Ig levels of all isotypes
  - IgG 18.2→65.1→44.9% CYC  
21.3→55.8→31.7% RTX
  - IgM 16.2→59→39.1% RTX
  - IgA 5.1→30.1→27.5%
- **Not correlated with infections**
  - IgG 1.86 (N) versus 1.23 (Low at any time) infection per p. per year RTX  
1.16 (N) versus 1.38 (Low at AT) infection per p. per year CYC
- B cell reconstitution earlier in the RTX arm
- Mainly URT tract infections

# CYC versus RTX in practice



- MaxDiff Scaling (MDS) survey to rheumatologists at 2010 ACR
  - Including 23 AEs associated with either RTX and/or CYC, in different combinations of 4 items
  - how much each AE influences the decision about which medication to prescribe for a 50 year old post-menopausal woman with newly diagnosed severe AASV and pulmonary-renal syndrome
  - respondents to choose the most important item
  - hierarchical Bayes modeling to generate the mean relative importance score for each AE
  - association between physician characteristics and ratings by multivariate linear regression models
- 118 physicians completed the survey; mean age (SD) 48 years (10); 68% male; 81% spend the majority of time in clinical practice; 39% work in an academic setting; 46% see between 1 and 5 patients with AAV per year; 22% see between 6 and 10 patients with AAV per year, and 25% see more than 10 patients with AAV per year
- **Treatment decisions were most strongly influenced by the risk of infection**
  - Older physicians were more strongly influenced by the risks of infection (SE 0.29, p=0.004) and less by that of cancer (SE -0.25, p=0.02) compared to younger (after adjusting for gender, work setting and number of patients per year)

# Treatment of AASV in practice

- 145 invited experts to complete a web-based survey on Rx for 3 scenarios for 4 profiles (22 and 62 W, 22 and 62 M)
  - Newly diagnosed severe AAV without co-morbidities
  - recurrent severe AAV (prior use of oral CYC) without co-morbidities
  - recurrent severe AAV (prior use of IV CYC) without co-morbidities
- multinomial generalized estimating equation analysis
- 50 completed the survey; 77% male, 49% rheumatologists, 39% nephrologists; 90% attending and 4% trainees; 67% in clinical practice, 31% in clinical research, 2% in basic research.; 71% in a university setting; 24% from US, 61% from Europe
- Preferences for treatment of newly-diagnosed young women (52% with RTX) differed significantly ( $p=0.001$ ) from those for older men (76% with CTX) and older women (74% with CTX)
- 60% or more of respondents preferred RTX for recurrent disease regardless of patients' age or sex
- Efficacy, toxicity and cost were all important reasons underling experts' choices
- Uncertainty regarding the efficacy of AZA and RTX to maintain remission had much less influence and for young men

Table. Treatment Preferences for AAV

	Newly Diagnosed AAV: Treatment Naïve*				Recurrent AAV: Received PO CTX - on AZA			Recurrent AAV: Received IV CTX - on AZA		
	PO CTX	IV CTX	RTX	No Preference	CTX	RTX	No Preference	CTX	RTX	No Preference
Young Woman	2%	30%	56%	12%	2%	92%	6%	5.9%	88.2%	5.9%
Older Woman	10%	64%	10%	16%	17.6%	70.6%	11.8%	19.6%	60.8%	19.6%
Young Man	2%	48%	36%	14%	4%	84%	12%	10%	78%	12%
Older Man	12%	64%	10%	14%	16%	72%	12%	18.4%	61.2%	20.4%

Cozmula et al. (Connecticut) #2367

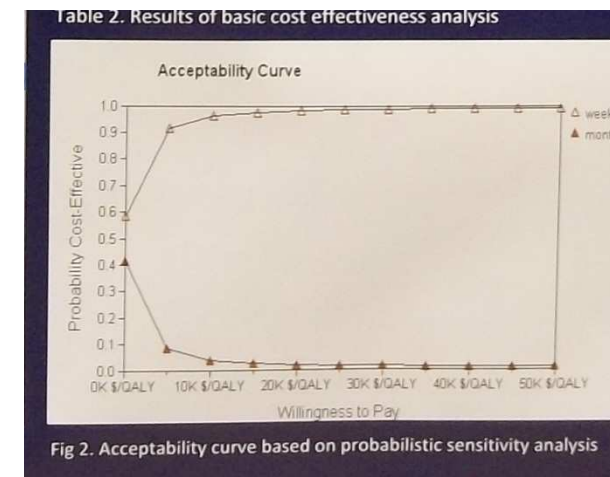
\* Treatment preferences for a young woman differ significantly from those of an older woman and older man.

# Cost-effectiveness of weekly CBC monitoring in GPA patients given CYC

- Weekly compared to monthly CBC in GPA receiving oral CYC
- Decision analysis model (TreeAge Pro 2009™) - societal perspective.
  - Prevalence of leukopenia, infections, and outcomes from Cleveland registry (130 patients) and literature review
  - Costs in dollars (2010) and effectiveness as quality-adjusted life-years (QALYs)
  - Univariate sensitivity analyses and probabilistic sensitivity analysis (PSA) to check for robustness of parameters included in the analysis
  - base case patient = 45 years old, but also ages 25–65 years

Strategy	Weekly CBC	Monthly CBC	Gain with weekly CBC
Cost (\$)	1571	2070	489
Effectiveness (QALY)	18.74	18.52	0.22

Table 2. Results of basic cost effectiveness analysis



- The expected gain of weekly CBC is 0.22 QALYs and incurs \$489 lower cost per patient
- Results were not sensitive to changes in patient age

# Biomarkers of ANCA disease activity

- 28 serum markers before and at M6 of Rx + ESR, CRP in 186 RAVE patients
  - 186 severe vs 68 healthy controls; 137 active at enrollement vs in remission at M6; 25 mildly active vs 137 in remission at M6
  - Among the 137 in remission at M6
    - 24/28 markers decreased
    - ROC analyses **CXCL13, MMP3, TIMP1 active vs remission with AUC>0.8**
  - Active vs healthy controls
    - Same markers
  - Multivariable analysis: **severe vs. remission**
    - **ACE (low)+GMCSF+MMP3+TIMP1+ESR**
    - Not good to distinguish mild vs. remission
- Look propectively (predictive of relapse???)
- CXCL13 as potential new target?

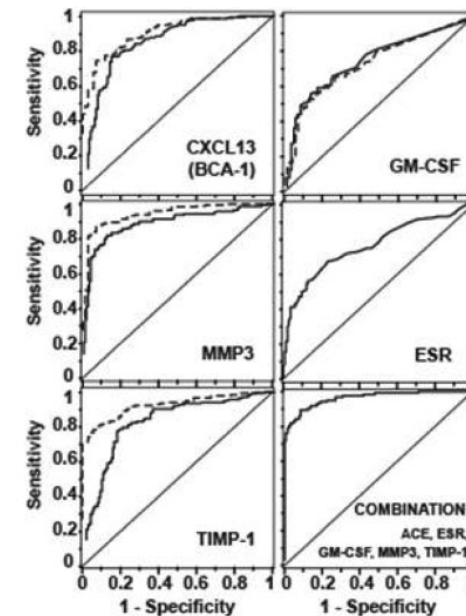


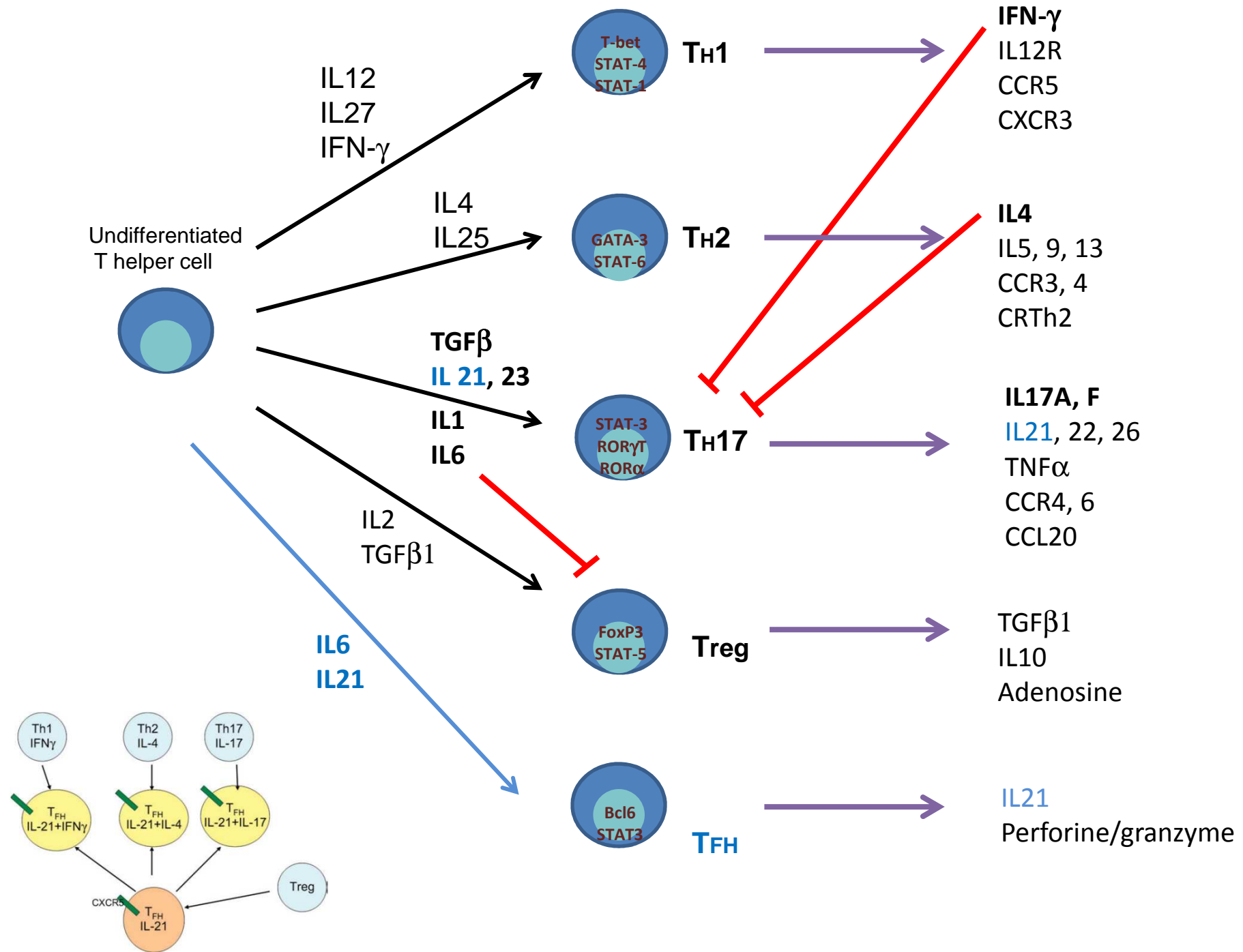
Figure. Receiver operating characteristic (ROC) curves for 5 individual markers and for a combination of 5 markers, comparing active vasculitis to remission (solid curves) or to healthy controls (dashed curves, not done for ESR or the combination of markers).

# Circulating mitDNA copy numbers as a disease and activity marker in AASV

- PMN and PMeO release extracellular traps (NETs); those NETs may contain mtDNA, which binds to TLR9
- 54 AASV, 31 HC or intervertebral hernia or OA
- PCR of plasma for nuclear DNA and mtDNA copy numbers
- **HC 15,400/ml mtDNA copies vs. AASV 449,683/ml mtDNA copies**
- nDNA low in both and not significantly different and not correlated with BVAS
- Multivariable analysis
  - Only **BVAS++ and CRP were associated with copy numbers of mtDNA** (not ANCA levels)
  - BVAS was influenced by mtDNA and neutrophil count
- ROC 0.97 with cut-off at 178,000 copies/ml, Se=87.5%, Sp=100%, LHR=27.1
- mtDNA distinguish AASV from controls, irrespectively to disease activity
- In AASV, mtDNA “correlates” with disease activity (BVAS and CRP)

# Increased frequency of T<sub>FH</sub> in GPA

- Follicular Th cells characterized by production of IL21, influencing B cell differentiation and production of Abs (induced by IL6/IL21; Bcl6 as main transcription factor; produce IL21)



# Increased frequency of T<sub>FH</sub> in GPA

- Follicular Th cells characterized by **production of IL21**, influencing B cell differentiation and production of Abs (induced by IL6/IL21; Bcl6 as main transcription factor; produce IL21)
- 33 GPA in remission (21 ANCA+, 12 ANCA-), 22 HC
- PBMCs+PMA+Calcium ionophore+ BrefeldinA
- Intracellular FACS IL21, IL17 (to distinguish from Th17 cells which also produce some amount of IL21); measurement of IgG after stimulation of GPA-PBMCs with IL21/BAFF for 12 days; IL21 receptor expression on B cells
- **% of T<sub>FH</sub> cells higher in GPA (for ANCA+ but not ANCA- patients), expression of Bcl6 higher in GPA (but no difference in TH17 RoRgc)**
- IL21/BAFF increases IgG production in vitro by GPA-PBMCs
- Role of treatment?
- IL21 as a potential therapeutic target?

# In situ IC MPO-antiMPO and C3 cause glomerular capillary injury

- 317 glomeruli from 20 patients with antiMPO GN
  - Number of infiltrating MPO+ cells, MPO expression and extracellular MPO, C3; colocalisation of MPO, IgG, C3 and CD34
  - All showed a weak but positive staining for IgG, often with MPO deposition along the capillary glomerular membrane
  - Double positive MPO IgG 14%
  - Double positive MPO C3 13%
  - Triple positive MPO, IgG, CD34 in 5% of the studied glomeruli, on capillary wall, predominantly in early stage of disease
  - Role of these IC in the pathogeny?
- Correlation with clinical presentation?

# Infertility and vasculitis

- VCRC Contact Registry → internet-based questionnaire
- 2 groups at the time of diagnosis: childbearing completed or not
- 450 participants completed the questionnaire
- **Among the 343 women**
  - 221 women had completed childbearing at Dx, age at diagnosis 47.9 years → infertility 11.6%
  - 122 women had not, age at diagnosis 27 years → infertility 17% (NS)
  - **Among those diagnosed <40 years, those who received CYC had ~3-fold higher rate of infertility (24.3% vs 8.8%, p=0.01)**
  - Discussion of the impact of CYC on fertility recalled by 67.8% of women
  - 17 (43%) received ovarian protection with GnRH-agonists (7), OC (8), both (1), depot medroxyprogesterone (1)
- **Among the 107 men**
  - 83 men had completed childbearing at Dx, age at diagnosis 53.7 years → infertility 9.6%
  - 24 men had not, age at diagnosis 27 years → infertility 33.3% (p<0.01)
  - **Receiving CYC had no impact**
  - Discussion of the impact of CYC on fertility recalled by 83.3% of men
  - 50% of them stored sperm (cryopreservation)

# Pregnancy in men and women with vasculitis

- VCRC Contact Registry → internet-based questionnaire
- 65 pregnancies after a diagnosis of vasculitis reported by women
  - Rate of pregnancy loss was statistically higher after the Dx of vasculitis compared to prior to Dx (34% vs 23%,  $p=0.03$ ).
  - Non-significant increase in preterm births after vasculitis than before (23% vs 13%,  $P=0.1$ )
  - 59% reported that vasculitis activity was not impacted by pregnancy, 23% reported improvement in vasculitis during pregnancy, 18% reported worsening of disease during pregnancy
- For men, the pregnancy loss rate was 59% in 17 pregnancies after vasculitis, compared to 75% of 130 pregnancies prior to vasculitis ( $p=0.7$ ). Pregnancy outcomes and vasculitis activity in pregnancy did not differ significantly between diagnoses for men or women
- 24 pregnancies were exposed to prednisone (39% of the pregnancies after Dx of vasculitis)
  - loss and preterm birth rates did not statistically differ with or without PDN exposure
- 7 pregnancies were exposed to AZA → 1 elective abortion, 2 miscarriages, 2 live term births, with 2 pregnancies ongoing
- 2 pregnancies were exposed to MTX → 1 electively aborted, 1 miscarriage
- 1 pregnancy just after exposure to CYC → 1 live term birth
  - loss rate was not elevated in the 15 pregnancies conceived by women with prior exposure to CYC

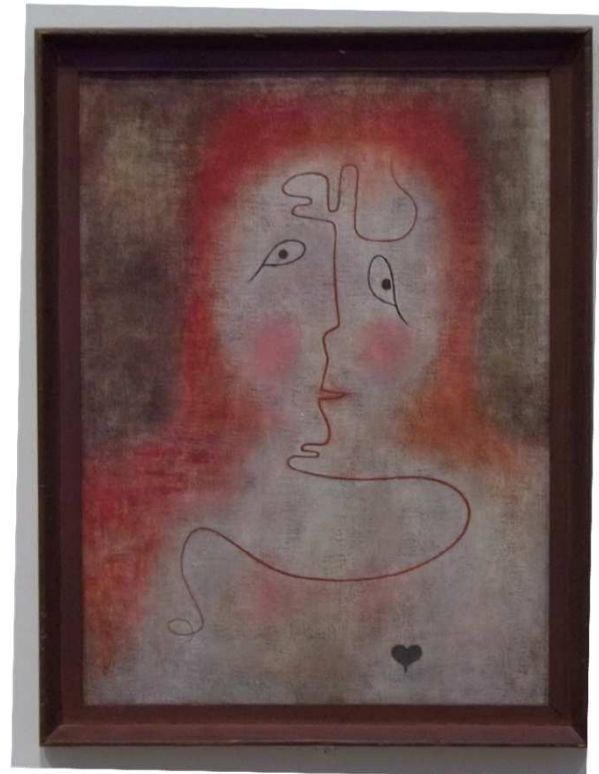
# Few pregnancies after CYC despite “preservation” ovarian function

- Survey of women with rheumatic disease who received CYC <35 years + chart review for doses
- **23 women**, aged 32.9 [21-45]; 19 SLE, 2 GPA, 1 SSC, 1 SSC/SLE
- Received CYC at the age of 25.1 [12-35]
  - Dose 21 g [0.5-88]; 3 Oral, 16 IV, 4 both routes
  - <6 mo. for 5; >1 year for 11 (!!)
- **Cessation of menses = 10**
  - 2 prior to CYC + 8 after CYC (at 32.9 years, i.e. 7.8 years after CYC)
  - **mean CYC 22.2 g** (vs. 14.4 g)
- **Menstrual cycle continued = 13**
  - 8 resumed regular cycles + 5 resumed irregular cycles
  - **mean 14.4 g** (vs. 22.2 g)
- 7 received leuprolide + 3 oral contraceptive
  - **60% continued cycles vs. 15.4% (p=0.02) in the absence of ovarian protection**
- **Pregnancies**
  - **10 had no pregnancy**; 13 had a total of 41 pregnancies (!!!)
  - Only 6% of the women diagnosed prior to the age of childbearing had the number of child desired (vs. 57% of those diagnosed later)
  - Data for 39 pregnancies: 33 before + **6 (uneventful) after CYC** – no differences in studied obstetrical parameters

# Childhood GPA

- Classification criteria for childhood WG (cWG) include the airway stenosis
- Retrospective chart review on patients <18 years old in 2004-2010.
- 28 patients; mean follow-up 3.1 years
- **Laryngotracheobronchial disease = 50% of patients**
  - present at diagnosis in 36%
  - developed on immunosuppressive therapy 14%
- **Medical management was ineffective for airway disease in 71%**
  - All patients underwent (successful) endoscopic intervention

# Other vasculitides and miscellaneous (vasculitis borderlines)



# Immunosuppressants reduce the VTE relapses in Behcet's disease

- Venous disease 14% to 39% of patients
- Cohort of 820 BD patients satisfying ICBD, 296 patients (36.7%) had venous thrombosis
  - 73.6% of male
  - median (Q1-Q3) age 30 (24–36) years
- Total of 582 venous thrombosis events
  - 555 deep thrombosis (limbs (55.1%), cerebral veins (13.1%), pulmonary embolism ( 9.7%), vena cava (10.7%), Budd Chiari syndrome (2.4%) and cervical veins (2.2%)
  - 27 superficial thrombosis.
  - mortality rate = 6.4% (n=19) after a median follow up of 4.75 [Q1-3, 2–7] years
  - Univariable analysis = death associated with male gender (p=0.0088), cardiac involvement (p=0.026) and Budd Chiari syndrome (p=0.004)
  - Multivariable analysis = factors preventing relapses of VTE = immunosuppressants [HR 0.27 (0.14–0.52), p<0.001] and corticosteroids [HR 0.62 (0.40–0.97), p = 0.058]

# FVSG Churg-Strauss syndrome patients

- 383 patients 1957-2009
- ANCA tested on 348 → 31% ANCA+
- ANCA+ patients had more frequent ENT, renal disease, mononeuritis multiplex, weight loss + trend for purpura, higher BVAS, higher CRP level, vasculitis features on histology
- ANCA- had more frequent cardiomyopathy
- ANCA+ had a higher mortality rate (12.5% vs 5.6%) but a lower mortality rate (35.2% vs 22.5%)
- Predictors of mortality: cardiomyopathy (HR 4.22), older age and Dx < 1996
- Predictors of relapse: lower Eosino count (ANCA+ and skin involvement in model 2 without eosinophils)

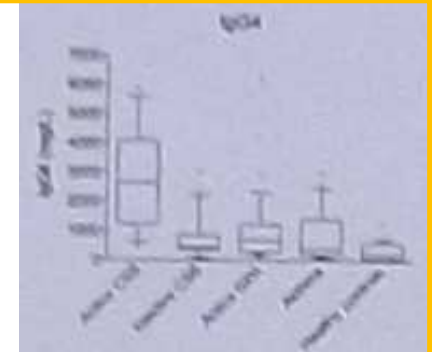
# AASV patients from clinical trials vs those followed in observational cohorts

- 423 cohort patients (167 FVSG, 256 VCRC) vs 220 trial patients (159 WEGENT, 61 WEG91)
  - All systemic GPA or MPA with FFS $\geq$ 1
- **Trials patients were older** (56.6 vs 46.5 years), had **more frequent and severe renal involvement** (80.9% vs 53.7%), and **more frequent lung** (78.2% vs 65.6%) **and cardiovascular** (17.5% vs 6.0%) manifestations at Dx
- **Trial patients  $\rightarrow$  higher mortality (22.3% vs 3.3%), mainly during the first 2 years, but a lower relapse rate (45.9% vs 60.5%)**
- Relapse-free survival rates at 5 years post-diagnosis were eventually comparable (38.4% (95% CI, 29.0–47.6, FVSG) vs. 39.5% (95% CI, 32.5–46, trials))

# T cell clonality in CSS

- 24 CSS (37.5% ANCA+) and 19 IHES
- 9/24 (37.5%) CSS patients showed positive TCR g- and d-chain gene rearrangements
  - 2 of them were ANCA+
  - 3 had histological necrotizing vasculitis
- Positive TCR g- and d-chain gene rearrangements in 11 (57.8%) of IHES ( $p=0.22$ )
- No correlation between TCR gene rearrangements and eosinophilic count, IL2, IL4 or IL5

# IgG4 in CSS



- TH2 responses in allergic diseases enhance the production of IgG4
- 34 CSS (22 active, 12 quiescent); 18 GPA; 20 HC
- Serum IgG, IgM, IgA and IgE, IgG subclass and stained tissue biopsies from CSS for IgG4
- Active CSS and GPA both showed increased total IgG as compared to HC
- CSS (mean  $272 \pm 40$  mg/dl) but not GPA (mean  $90 \pm 17$  mg/dl) showed increased serum IgG4 as compared to HC (mean  $35 \pm 7$  mg/dl;  $p < 0.001$ )
- Serum IgG4 levels correlated with the number of organ manifestations ( $p < 0.05$ ) and with disease severity, as assessed with FFS or BVAS
- IgG4 levels were normal in CSS patients in remission
- Heart involvement and peripheral neuropathy were more frequent in IgG4-high ( $>135$  mg/dL) CSS patients ( $p = 0.13$  and  $p = 0.056$ , respectively)
- In 3/9 CSS tissue biopsies, intense IgG4-producing plasma cell infiltration were detected

# RTX for IgG4-Related Disease

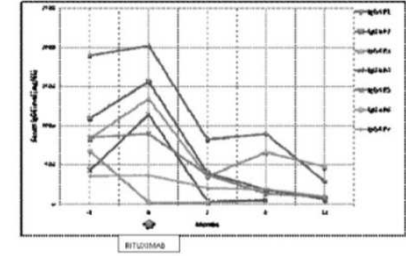


Figure. The graph is showing the serum IgG4 concentrations of 7 out of 10 patients with IgG4-RD who had elevated serum IgG4 levels at baseline 2 month prior to rituximab treatment to 12 months after treatment.

- 10 IgG4-RP patients refractory to PDN and DMARDs → RTX 1g x 2 fortnightly
- 7/10 had increased IgG4 at baseline
- **9/10 had striking response within 1 month**
- 1/10 with thyroid fibrosis and other organs did not improve but stabilized
- All patients stopped PDN and DMARDs
- **ONLY IgG4 subclass decreased**
- 4 retreated at 6 months (2 with recurrent symptoms and IgG4 increase, 2 systematically), effectively

# Prednisone vs tamoxifen in idiopathic retroperitoneal fibrosis

- Open-label RCT
- 40 patients (4 with high IgG4 levels, 3 in the tamoxifen group)
- All 1 mg/kg/d prednisone, then those who achieve remission at M1 are randomised to continue PDN over 8 months with tapering dose or to receive tamoxifen (0.5 mg/kg/d) for 8 months and stop PDN within 2 weeks + 18 months of follow-up
- PE=relapse rate at month 8
- 36/40 achieved remission with PDN
- Relapses 6% PDN vs. 39% tamoxifen (p=0.04)
- At M26, 17% PDN vs. 50% tamoxifen (p=0.04)
- Greater reduction in size of RPF with PDN
- PDN more effective (opposite as previous series)

# French CryoVas survey: prognosis and causes of deaths

- Survey on Rx for non-infectious MCV (possibly LNH, hemopathy but not MC gammopathy – not type I)
- 242 patients from 81 centers, diagnosed between 1995-2010 with W/M 2.2 and mean age 62.6
- Purpura 75%, PNS 52%, arthralgias 44%, GN 35%, Raynaud's 26%, skin ulcers 16%, GI 5%, CNS 2%
- Mean follow-up: 54 mo. → 42 (17%) died
  - Infections, n=21
  - Vasculitis, n=8
  - CV disease, n=5
  - Global degradation, n=2
  - Unknown, n=7
- 1-, 5- and 10-year mortality = 91%, 79% and 65%
- Predictors of mortality: age>65 (HR 1.04), GI (HR 2.29), male (HR 2.13), GFR<60 ml/min (HR 1.90) → Prognostic score (CryoVas score)
- CVS=0 → HR for death = 1
- CVS=1 → HR for death = 8.2
- CVS ≥2 → HR for death = 26.8

# French CryoVas survey: efficacy of treatments

- Survey on Rx for non-infectious MCV (possibly LNH, hemopathy but not MC gammopathy – not type I)
- 242 patients from 81 centers, diagnosed between 1995-2010
  - 202 with >6 months follow-up and data
  - Mainly idiopathic, then blood neoplasm, SAI (Sjogren)
- During follow-up: CS all; CYC (n=95); RTX (80); PE (43); other (31)
- Efficacy
  - Remission RTX+CS (HR 3.7, p=0.01) > CS alone
  - CS<10 mg at 6 months RTX+CS (HR 2.5, p<0.01) (and CY+CS) > CS
  - Renal response (HR 31.6, p=0.03) > CS
  - Immunological response (HR 33.8, p=0.001) (and CY+CS) > CS
- Safety
  - (serious) Infections RTX+CS > CS (HR 9, p<0.001)
  - Mainly if CS > 50m/d
  - Infections CYC+CS < CS !!!
  - No difference in mortality

# Systemic vasculitis as a rare cause of retinal vasculitis

- Review of 1,390 uveitis patient charts (Oregon center) 1985-2010
- Perivascular exudates, intraretinal hemorrhage or cotton wool spots or angiographic occlusion or leakage
- 207 (14.9%) with retinal vasculitis
  - 35 primary retinal vasculitis
  - Pars planitis (36), infection (29), sarcoidosis (13), BCR (9)
  - 14 Behcet
  - 3 (1.4%) with systemic vasculitis (+ 1 but with CMV) among a total of 11 uveitis patients with systemic vasculitis (3GPA, 4 PACNS, 2 CSS, 1 LCV, 1 Lung V)