ACR 2013

Updates on vasculitis

Dr. Christian Pagnoux
Mount Sinai Hospital
cpagnoux@mtsinai.on.ca

Disclosures

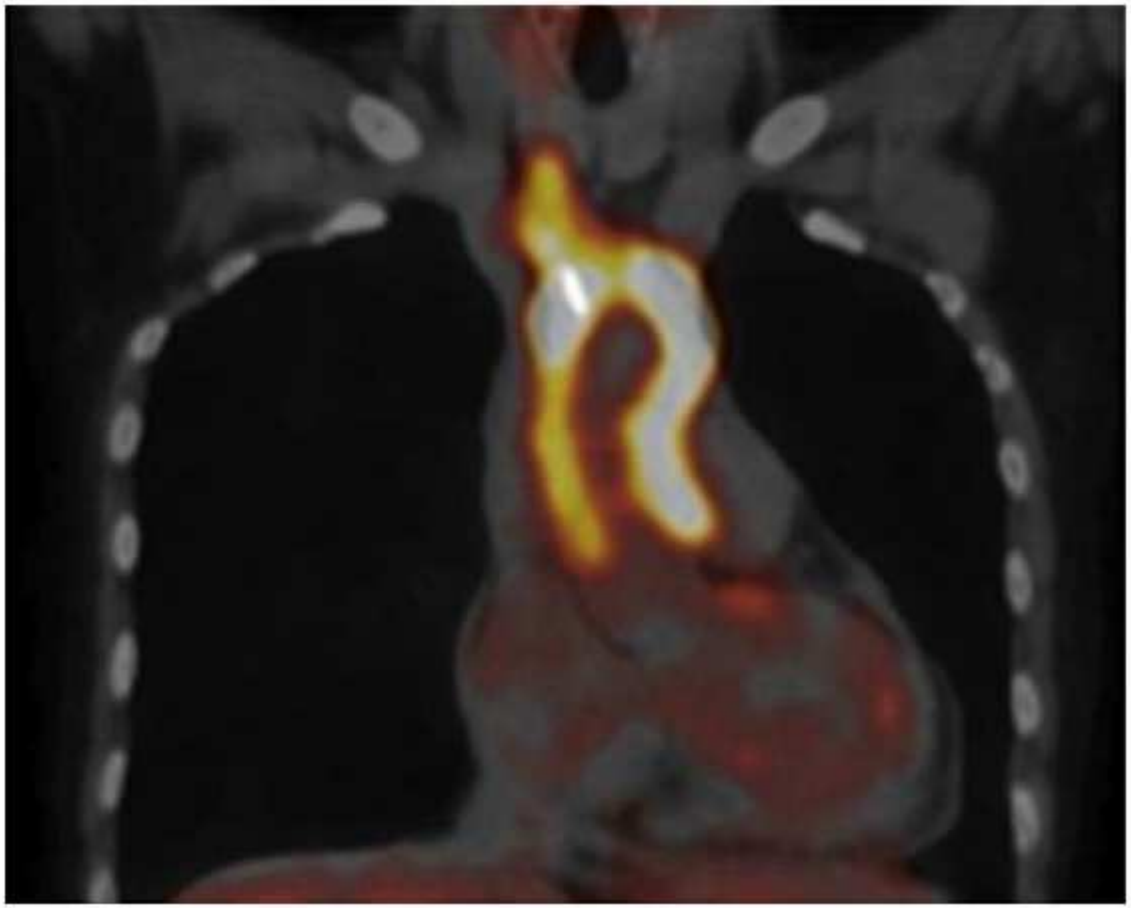
- Consulting and speaker fees
  - Hoffmann-La Roche
  - BMS
- Advisory boards
  - Hoffmann-La Roche
  - GSK
- Educational subventions (CanVasc)
  - Hoffmann-La Roche
  - Abbott Immunology
  - Pfizer-Amgen
  - Janssen-Cilag
  - Euroimmun

Objectives

- Review the main ACR 2013 abstracts on vasculitis

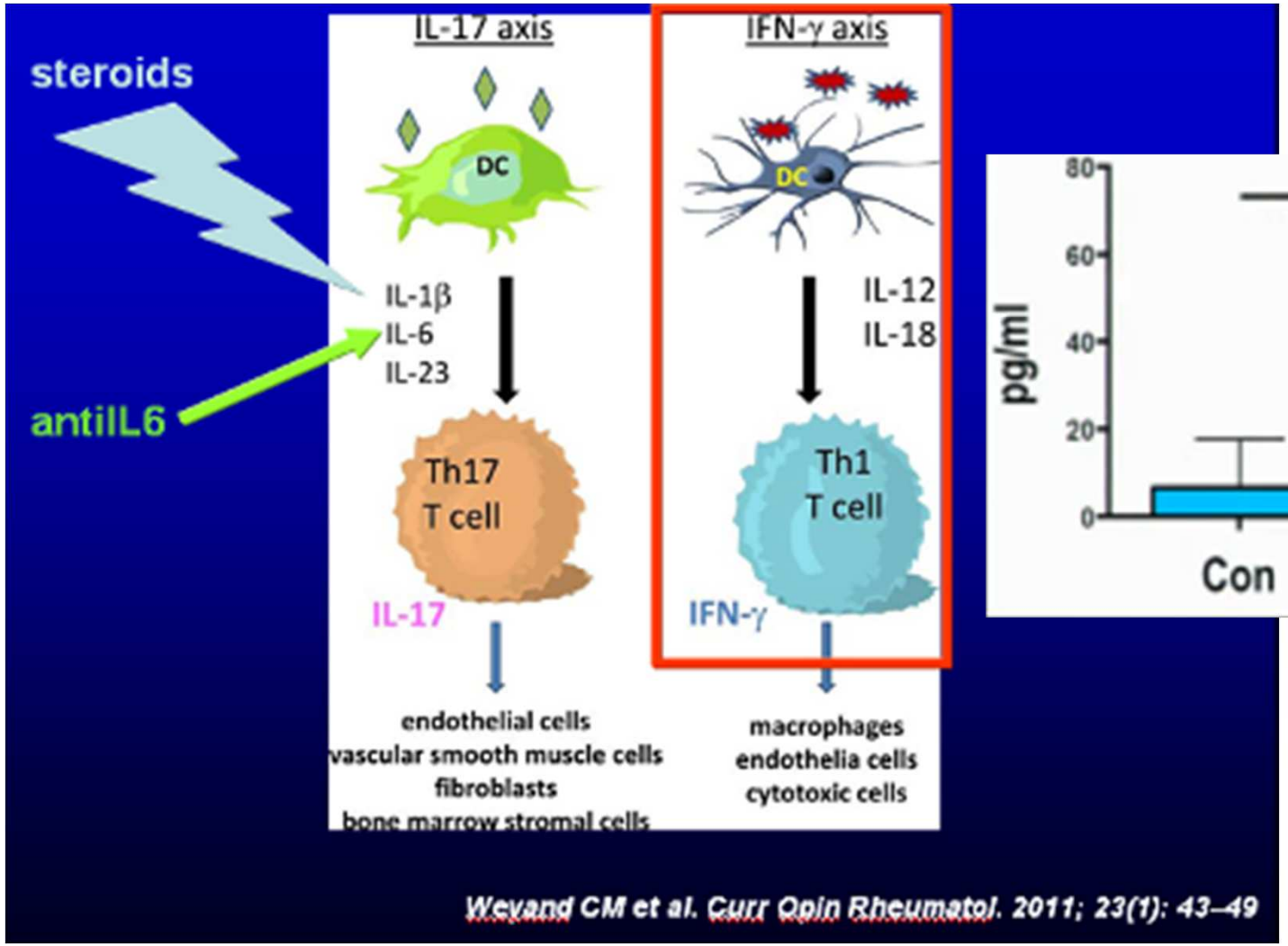
- Discuss whether, why and how these new findings may impact our practice

Large vessel vasculitis

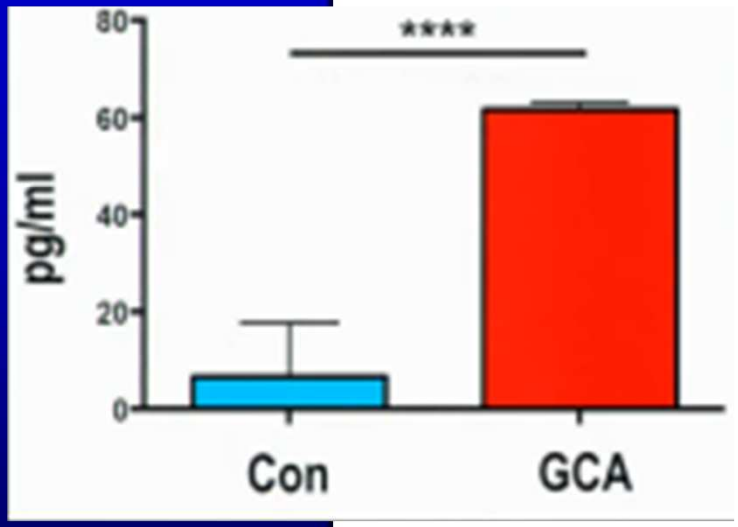


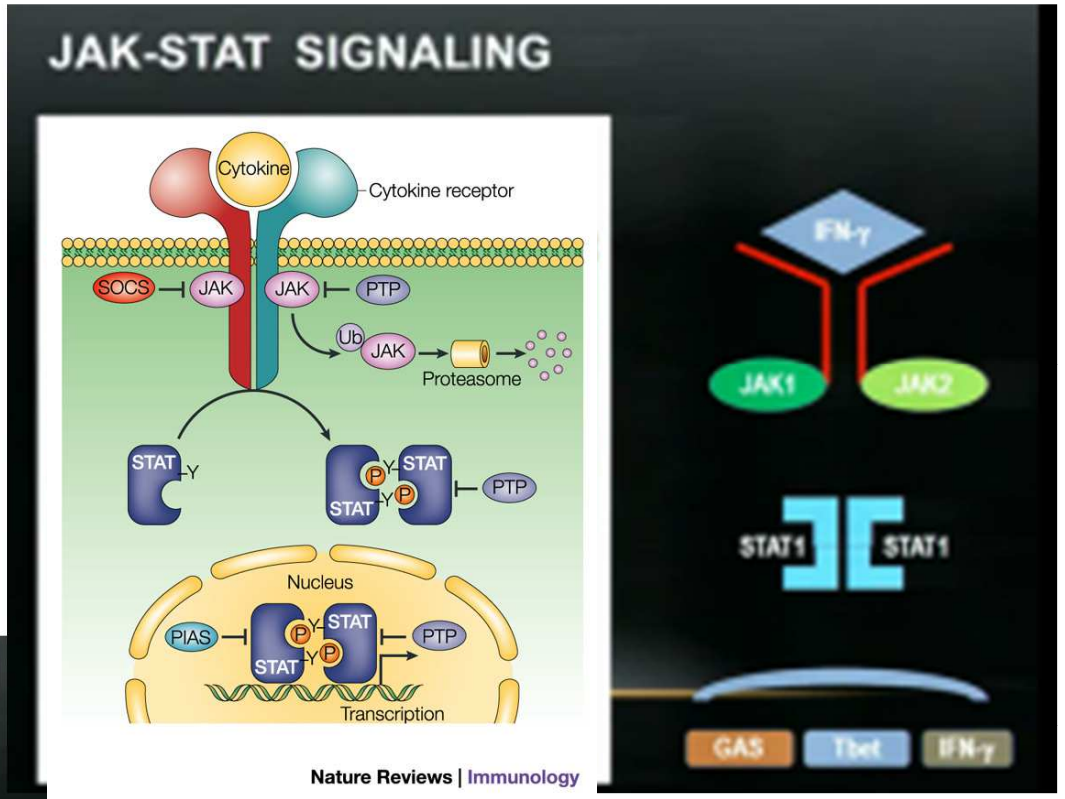
PLENARY - The STAT1 Signaling Pathway In Giant Cell Arteritis

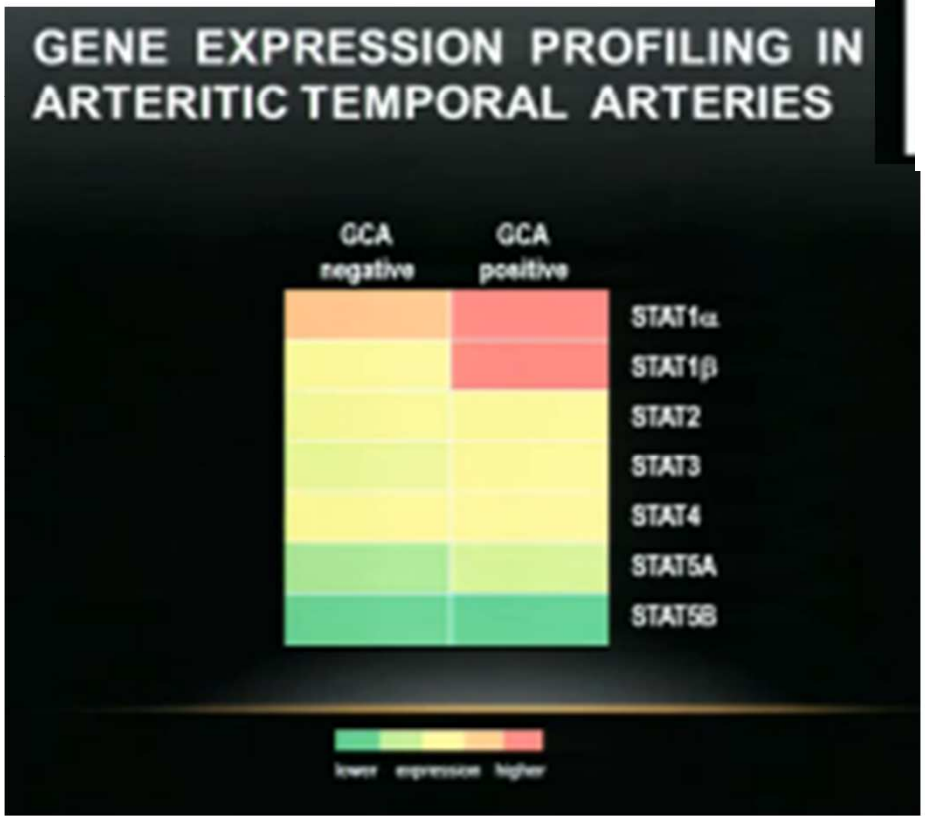
B Hartmann, J Liao, MH Weisman, KJ Warrington, JJ Goronzy, CM Weyand



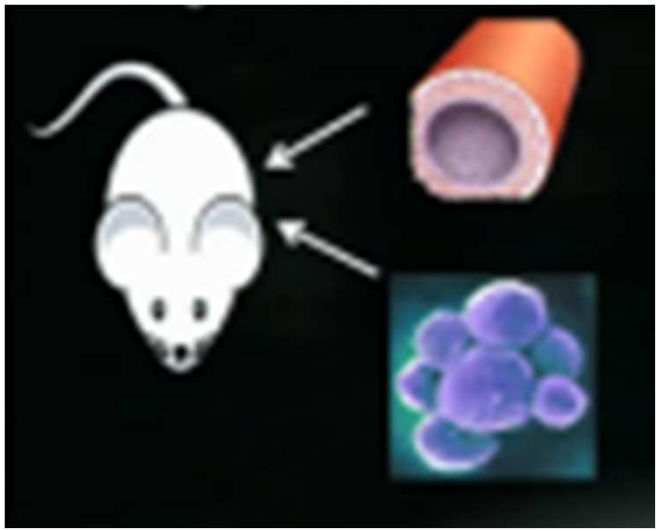
IFN-gamma




JAK-STAT SIGNALING
Cytokine
Cytokine receptor
SOCS
JAK
JAK
PTP
Ub
JAK
Proteasome
STAT
Y
STAT
STAT
PTP
Nucleus
PIAS
STAT
STAT
PTP
Transcription
Nature Reviews | Immunology
IFN-γ
JAK1
JAK2
STAT1
STAT1
GAS
Tbet
IFN-γ


GENE EXPRESSION PROFILING IN ARTERITIC TEMPORAL ARTERIES
GCA negative
GCA positive
STAT1α
STAT1β
STAT2
STAT3
STAT4
STAT5A
STAT5B

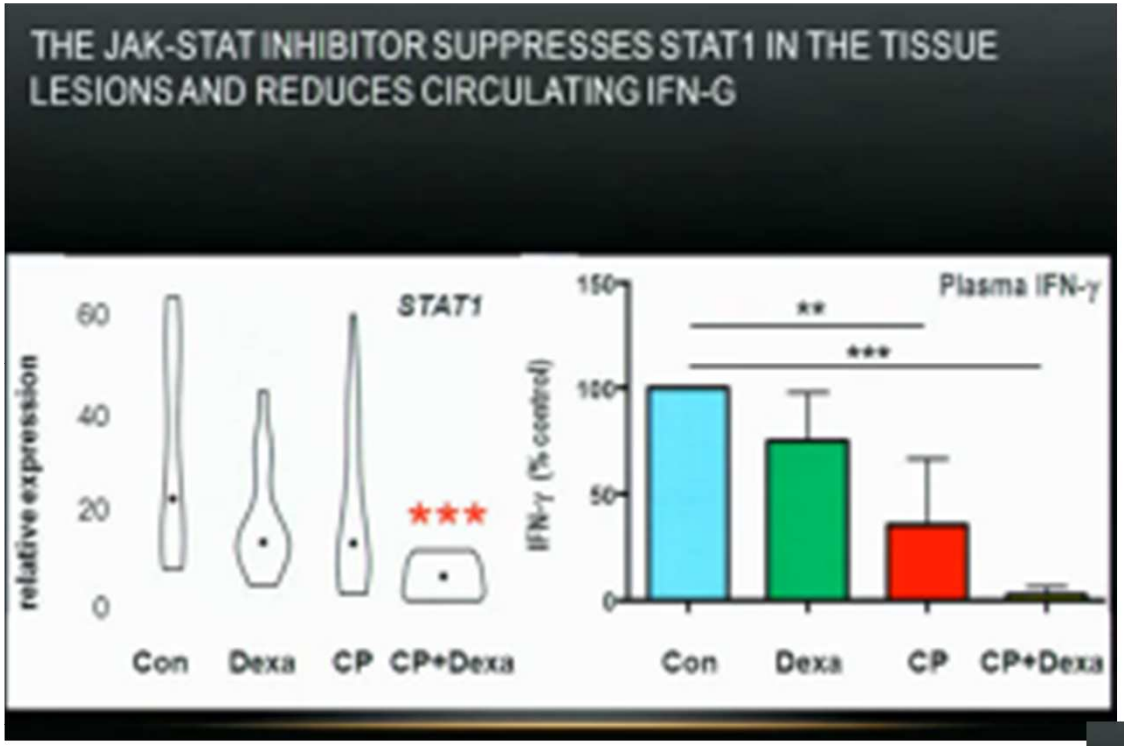
NOD.Cg-*Prkdcscid Il2rgtm1Wjl*/SzJ
mice (NSG) mice



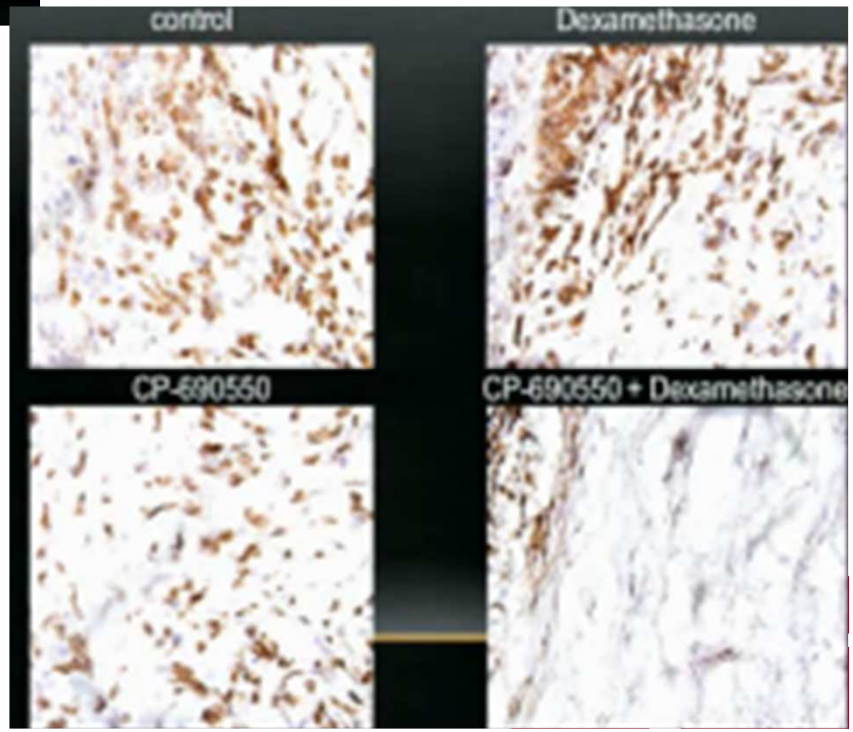
engrafted with human
medium-sized arteries

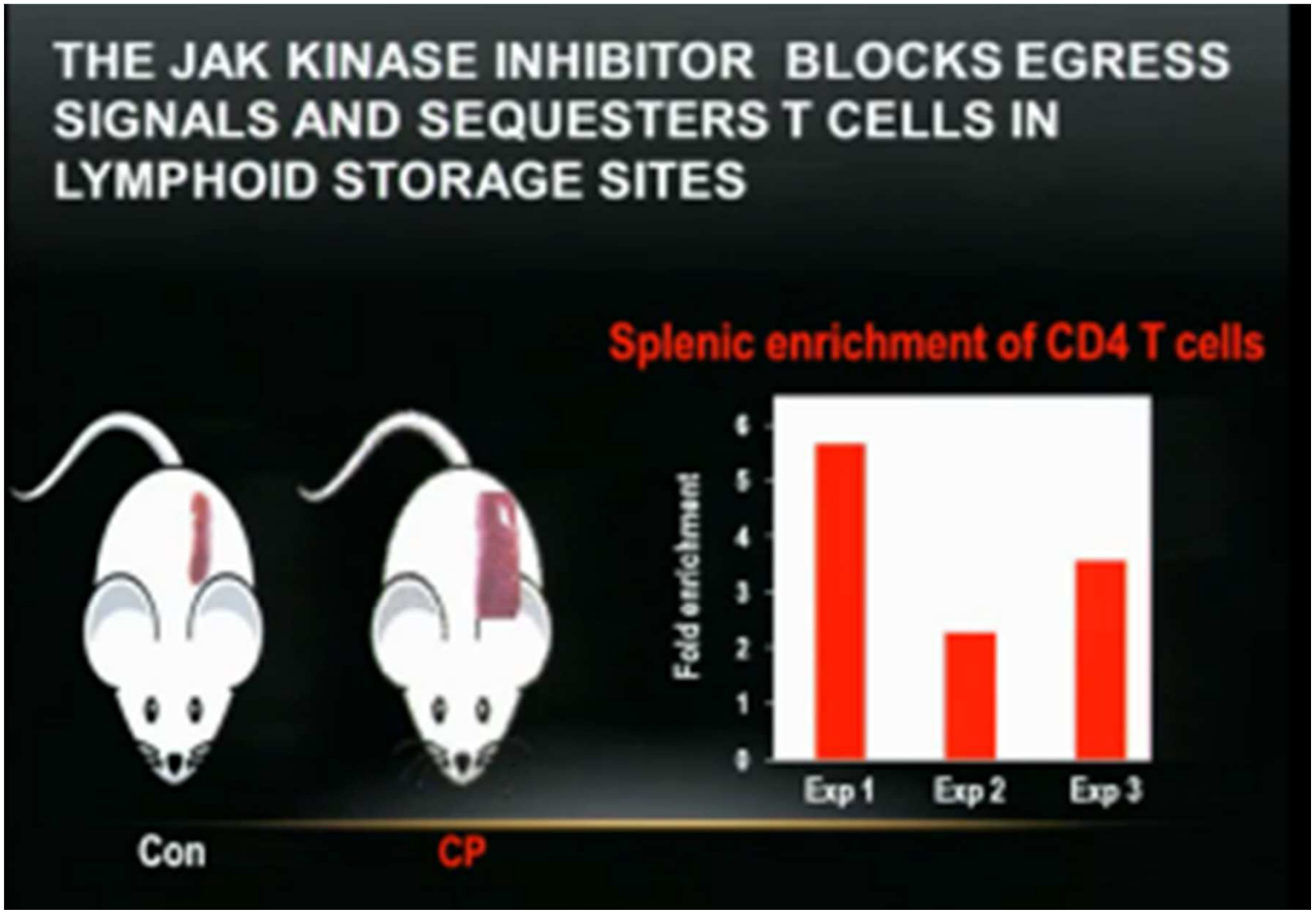
reconstituted at D7 with PBMC
from patients with biopsy-
proven GCA

dexamethasone (15 mg/kg)
or
tofacitinib (4 mg/kg) JAK 1 and 3 inhibitor
or
both → for 5 days (D15-20)
or
control



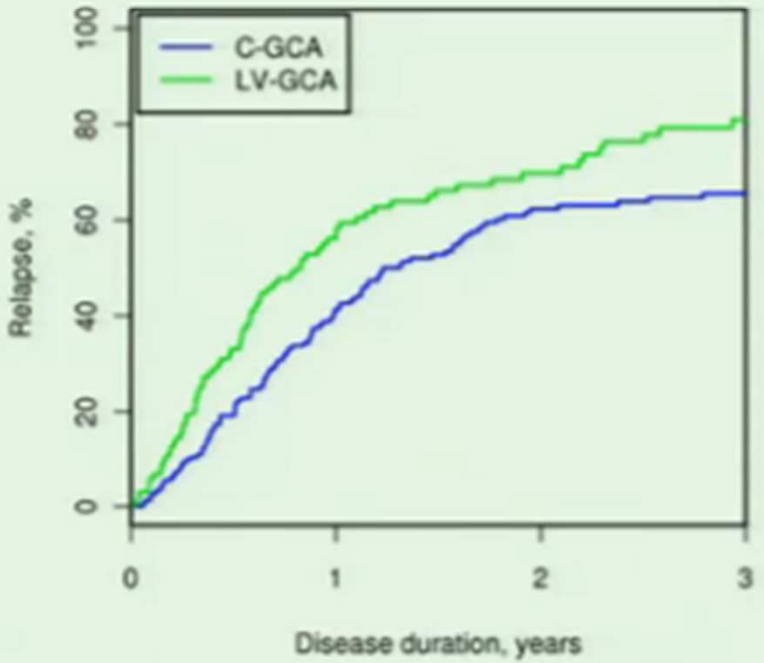
JAK-1 inhibition decreases Th1 cell recruitment




THE JAK KINASE INHIBITOR BLOCKS EGRESS SIGNALS AND SEQUESTERS T CELLS IN LYMPHOID STORAGE SITES
Splenic enrichment of CD4 T cells
Fold enrichment
0
1
2
3
4
5
6
Exp 1
Exp 2
Exp 3
Con
CP

LV-GCA
Treatment Course

- Compared to C-GCA
  - Same disease course[1]
  - More relapses[2]
  - Higher cumulative steroid dose
  - Longer to reach 0 mg



1 Schmidt WA. Rheumatology (Oxford). 2008 Sep;47(9):1406-8.

2 Muratore F et al. Arthritis Rheum. 2012 Oct; 64(10):S994. # 2358

MAYO CLINIC

The Relative Risk Of Aortic Aneurysm In Patients With Giant Cell Arteritis Compared With The General Population

J Robson, A Kiran, J Maskell, A Hutchings, NK Arden, B Dasgupta, Wi Hamilton, A Emin, D Culliford, RA Luqmani

GCA and aortic aneurysm

- 18 per 1000 person years (retrospective reviews)
- 22% by 5 years (screening study)
- 17 x more thoracic and 2.4 x more abdominal aortic aneurysms than normal population
- Meta-analysis, 2-8% developed thoracic AA (cohort without systematic screening)

The Relative Risk Of Aortic Aneurysm In Patients With Giant Cell Arteritis Compared With The General Population

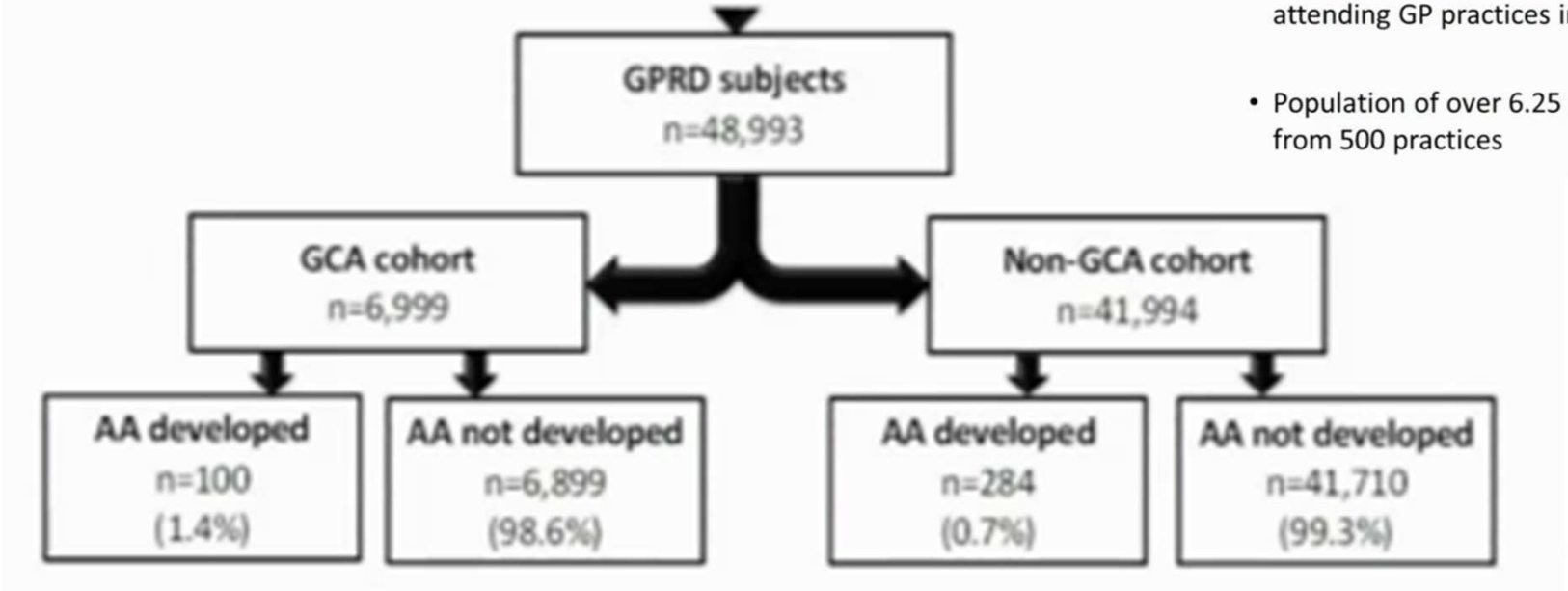
J Robson, A Kiran, J Maskell, A Hutchings, NK Arden, B Dasgupta, Wi Hamilton, A Emin, D Culliford, RA Luqmani

Parallel cohort study / General Practice Research Database (GPRD)

6,999 men and women with GCA matched on a 6:1 ratio on the same GP practice, year of birth (/ 3 years) and gender

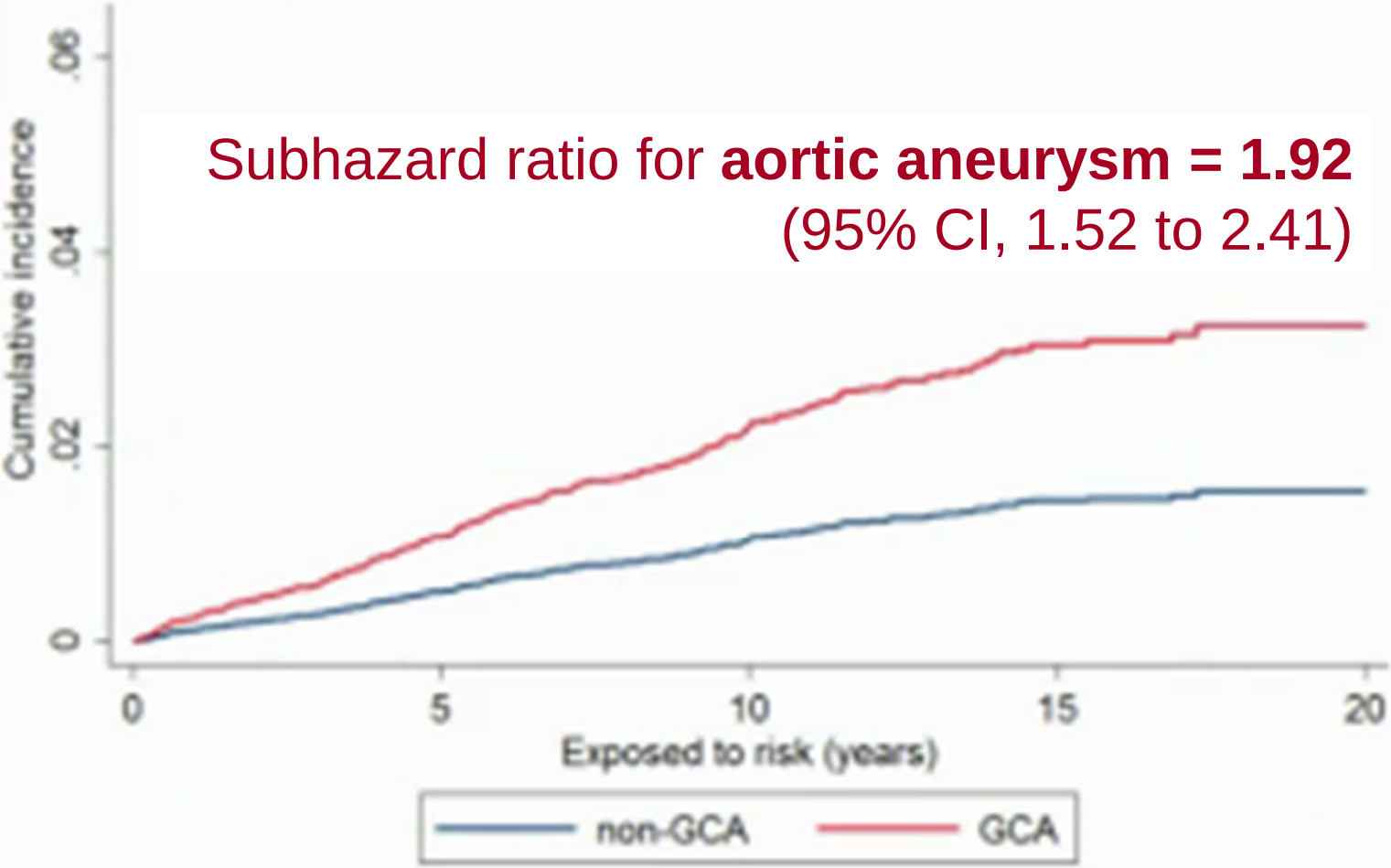
A competing risk model using aortic aneurysm as the primary outcome and death as the competing, after adjustment for cardiovascular risk factors (BMI, smoking, alcohol, hyperlipidaemia, HTN, diabetes, CVD, stroke, PVD)

- Medical records of a sample of patients attending GP practices in the UK
- Population of over 6.25 million patients from 500 practices

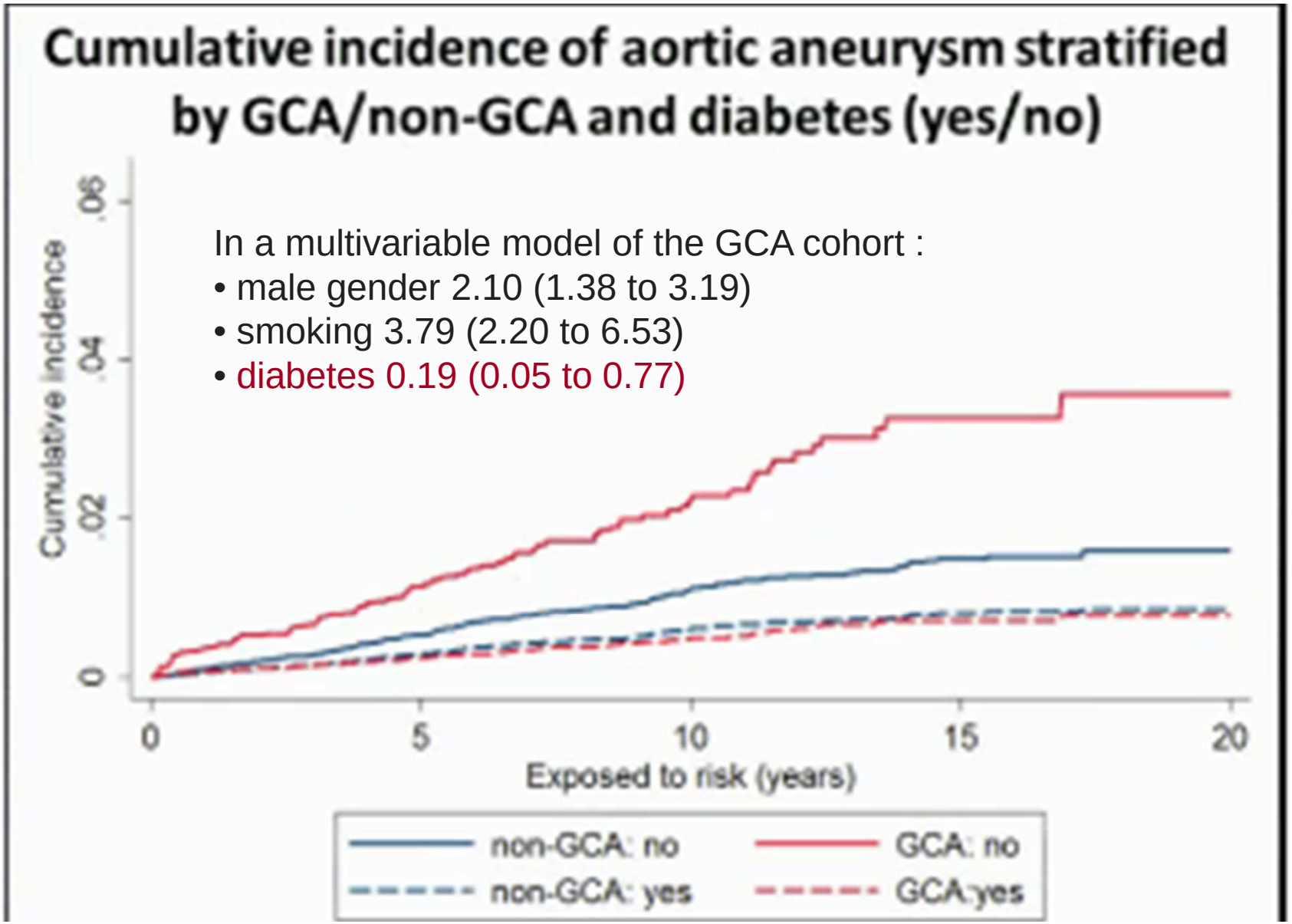


Cumulative incidence of aortic aneurysm stratified by GCA or non-GCA

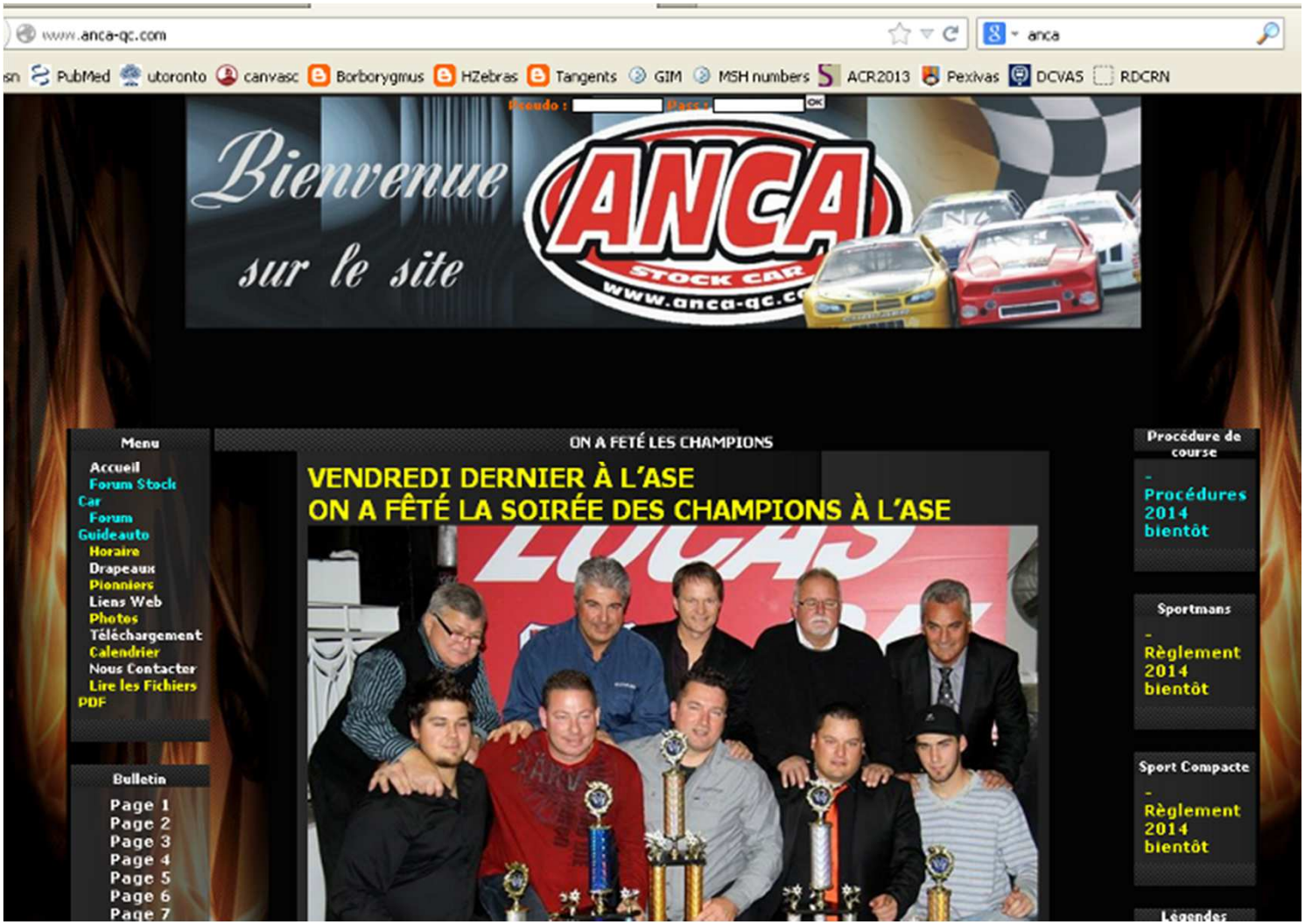
Subhazard ratio for **aortic aneurysm = 1.92**
(95% CI, 1.52 to 2.41)



Cumulative incidence of aortic aneurysm stratified by GCA/non-GCA and diabetes (yes/no)



Small vessel & ANCA vasculitis



Efficacy Of Methotrexate For Remission Induction and Maintenance In Granulomatosis With Polyangiitis In Routine Clinical Practice

ML Krause, M Baqir, R Cartin-Ceba, T Peikert, K Keogh, U Specks

Single center retrospective study of patients of GPA treated with methotrexate for either induction or maintenance between January 1997-December 2012

74 GPA (39 c-ANCA/PR3 +, 22 (30%) p-ANCA/MPO + , 13 (17%) ANCA -)

mean age 48.6 +/- 15.3; 26 (35%) male

Bx-proven in 47 patients (77%)

At Dx, BVAS/WG 7.0 +/- 3.9).

56 MTX for induction → effective in 45 (35 newly-diagnosed, 10 relapsing GPA)

18 MTX for maintenance

Efficacy Of Methotrexate For Remission Induction and Maintenance In Granulomatosis With Polyangiitis In Routine Clinical Practice

ML Krause, M Baqir, R Cartin-Ceba, T Peikert, K Keogh, U Specks

56 MTX for induction → effective in 45
18 MTX for maintenance

Median follow up 3.5 years (IQR, 1.6–10.3)

19 relapsed (30%)

15 (31%) in the induction group
4 (28%) in the maintenance group

At the time of conclusion of follow-up, 37 (50%) remained on MTX
5 (6.8%) discontinuations due to side effects (LFTs and GI + 1 PCJ)

Efficacy Of Glucocorticoids To Treat Limited Flares In ANCA-associated Vasculitis

E Miloslavsky1, U Specks, PA Merkel, P Seo, RF Spiera, CA Langford, GS Hoffman, CGM Kallenberg, EW St. Clair, N Tchao, L Ding, DIkle, B Jepson, P Brunetta, JH Stone

Patients with a 1st limited flare in the RAVE trial
(BVAS/WG 3 and no major BVAS/WG items)

→ Treated per protocol, by increasing PDN to a dose selected by investigatord, for 1 month before resumption of a protocol-specified taper with endpoint = 0mg

47 patients (24%) experienced limited flares (25RTX, 22 CYC)

38 patients (81%) were PR3-ANCA+ and 29 (62%) were previous relapsers

→ first limited flare on average 7.6 months (range 1.8–17.2) after entry
- 28 patients (60%) were off PDN at the time of the flare
- mean CS dose at flare 7.1 mg (2.5–20.0) for those on PDN
- 9% of the CYC/AZA patients were still on CYC, 86% were on AZA

Efficacy Of Glucocorticoids To Treat Limited Flares In ANCA-associated Vasculitis

E Miloslavsky1, U Specks, PA Merkel, P Seo, RF Spiera, CA Langford, GS Hoffman, CGM Kallenberg, EW St. Clair, N Tchao, L Ding, DIkle, B Jepson, P Brunetta, JH Stone

→ average follow-up of 7.0 months (0.7–16.3)

PDN dose used to treat limited flares 19.5 mg OD (2.5–80)

36 patients (77%; 18 RTX, 18 CYC) achieved remission again,
an average of 2.5 months after the increase in PDN

BUT 22 patients (47%) had recurrent flares
13 limited (8 RTX, 5 CYC), 9 severe (5 RTX, 4 CYC)

→ Only 11 patients (23%) who experienced limited flares were able to achieve remission, discontinue PDN, and maintain remission through month 18

→ Alternative approaches including continuing CS indefinitely or increasing or changing concomitant IS must be considered

Safety Of Remission Induction With Rituximab Versus Cyclosphosphamide In Patients 65 and Older With Severe ANCA-Associated Vasculitis

E Miloslavsky, U Specks, PA Merkel, PSeo, RF Spiera, CA Langford, GS Hoffman, CGM Kallenberg, EW St. Clair, N Tchao, L Ding, D Ikle, B Jepson, P Brunetta, JH Stone

55 RAVE patients ≥ 65 years old (36 RTX, 19 CYC/AZA)
vs. 142 patients < 65 years old (63 RTX, 79 CYC/AZA)

Treatment regimens achieved similar efficacy in both age groups

Patients ≥ 65 had more SAEs (Grade 3) - cytopenias
All 4 deaths during the study period occurred in patients ≥ 65 (2 RTX, 2 CYC)

	Under 65 (95% CI)	65 and Older (95% CI)
Mean baseline BVAS/WG	7.84	8.51
Mean baseline creatinine	1.33	1.74
PR3-ANCA	74.6%	45.5%
MPO-ANCA	25.4%	54.5%
Achieved complete remission at 6 mos	61.3%	50.9%
Remained in complete remission at 18 mos	37.3%	32.7%
Mean total prednisone dose (g)	7.07	5.73
Total adverse events/patient year	10.51 (10.07–10.97)	11.50 (10.73–12.3)
Severe adverse events (Grade ≥3)/ patient year	0.52 (0.42–0.63)	1.06 (0.83–1.32)
Severe infections/patient year	0.10 (0.06–0.16)	0.21 (0.12–0.34)
Severe cytopenias/patient year	0.03 (0.01–0.06)	0.23 (0.14–0.37)
Deaths	0	4

Safety Of Remission Induction With Rituximab Versus Cyclosphosphamide In Patients 65 and Older With Severe ANCA-Associated Vasculitis

E Miloslavsky, U Specks, PA Merkel, PSeo, RF Spiera, CA Langford, GS Hoffman, CGM Kallenberg, EW St. Clair, N Tchao, L Ding, D Ikle, B Jepson, P Brunetta, JH Stone

No differences comparing the 2 treatment arms

→ **OK for rituximab in patients ≥ 65 years old**

… but WHY rituximab???

Retreatment With Rituximab In The Rituximab In ANCA-Associated Vasculitis (RAVE) Trial

E Miloslavsky, U Specks, PA Merkel, P Seo, RF Spiera, CA.Langford, GS Hoffman, CGM Kallenberg, EW St Clair, N Tchao, L Ding, D Ikle, B Jepson, P Brunetta, JH Stone

Methods

- Patients with severe flare were eligible to receive open-label RTX (OLR) between 6 and 18 mos
  - Severe flare - BVAS/WG > 3 or one major item
  - 375mg/m^2 weekly x 4

- Outcomes
  - Complete remission – BVAS/WG = 0 and prednisone = 0
  - Complete response – BVAS/WG = 0 and prednisone < 10mg
  - Remission – BVAS/WG = 0
  - Limited flare – BVAS/WG ≤ 3
  - Severe flare – BVAS/WG > 3 or one major item

Baseline characteristics of patients receiving OLR

	N=17
Originally assigned to RTX	16 (94%)
PR3-ANCA positive	14 (82%)
GPA	15 (88%)
Relapsing disease at entry	11 (65%)
Received CYC prior to study entry	9 (53%)
Mean time to OLR* (range in days)	367 (225-556)
Mean prednisone dose at OLR (n=5)	8.5 (2.5-15mg)
BVAS/WG at OLR (range)	5.3 (3-11)*
Renal flare	5 (29%)
Diffuse alveolar hemorrhage	1 (6%)
Detectable B-cells at flare	15 (94%)
Rising ANCA at flare	14 (82%)

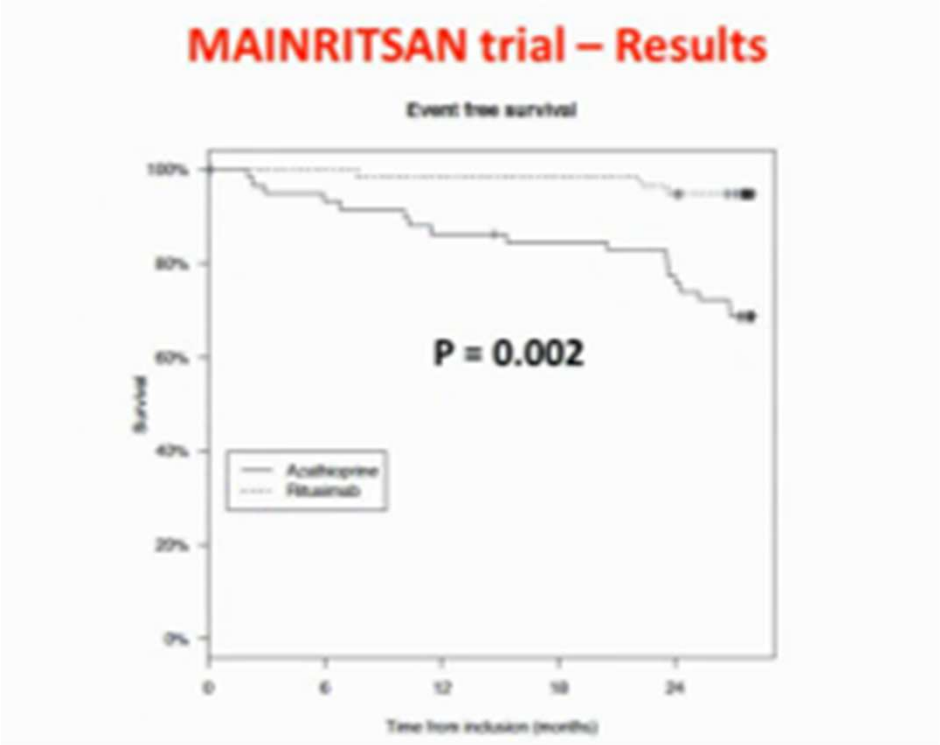
OLR – Open label rituximab

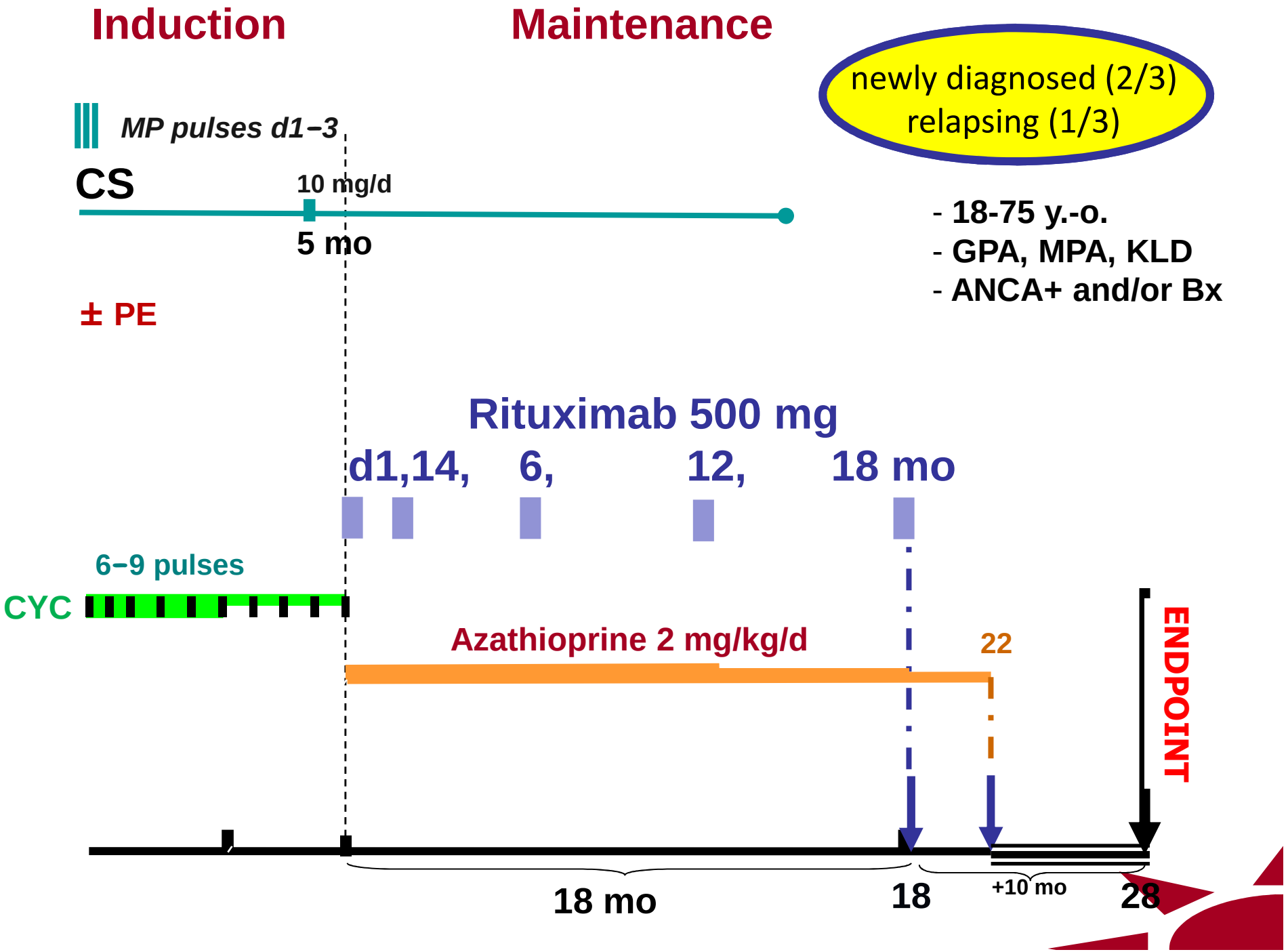
Outcomes

Remission	15 (88%)
Time to remission (days)	57 (27-181)
Complete response (pred < 10mg)	12 (71%)
Time to complete response (days)	142 (95-256)
Complete remission	8 (47%)
Time to complete remission (days)	182 (121-256)
Flares within 1 year after OLR	4 (27%)
BVAS/WG at flare	2.5 (2-3)
Time to flare from OLR (days)	244 (78-428)

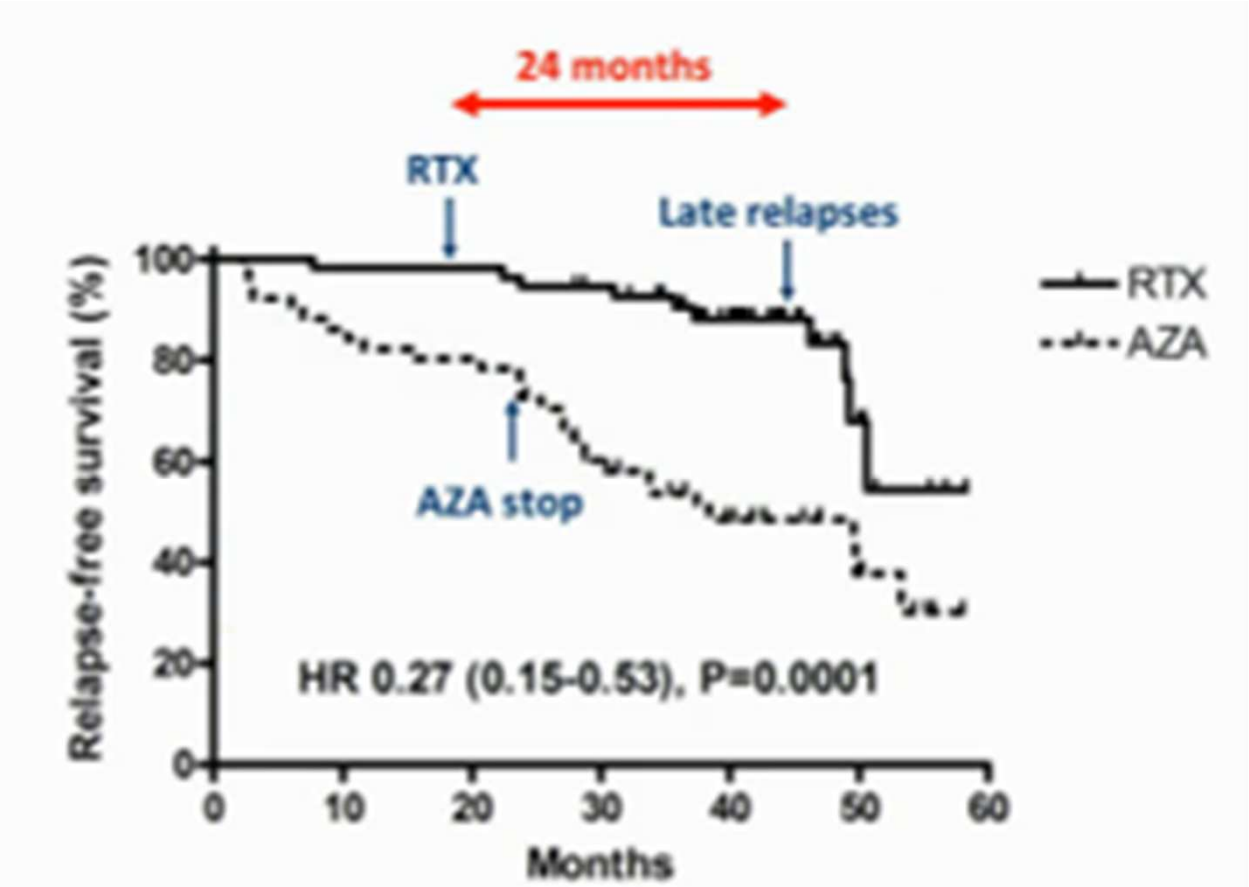
Rituximab Versus Azathioprine For Maintenance In Antineutrophil Cytoplasmic Antibodies-Associated Vasculitis: Follow Up At 39 Months

B Terrier, C Pagnoux, A Karras, CKhouatra,O Aumaıˆtre, P Cohen, F Maurier, O Decaux, H Desmurs-Clavel, P Gobert, T Quemeneur, C Blanchard-Delaunay, P Godmer, X Pue惡hal, L Mouthon, L Guillevin




Induction
Maintenance
newly diagnosed (2/3)
relapsing (1/3)
MP pulses d1–3
CS
10 mg/d
5 mo
± PE
- 18-75 y.-o.
- GPA, MPA, KLD
- ANCA+ and/or Bx
Rituximab 500 mg
d1,14, 6, 12, 18 mo
6–9 pulses
CYC
Azathioprine 2 mg/kg/d
22
ENDPOINT
18 mo
18
+10 mo
28

Median duration of follow-up = 43.6 months (IQR, 38.0-49.5)



MAJOR RELAPSE

28/54 = 51.9% in the AZA arm

10/55 = 18.2% in the RTX arm

Behcet’s disease

Is Complete Remission a Realistic Target With Current Therapeutic Options in Behcet's Disease?

F Alibaz-Oner, G Mumcu, Z Kubilay, G Ozen, G Celik, A Karadeniz, M Can, SY Oner, N Inanc, PAtagunduz, T Ergun, H Direskeneli

Multi-systemic disorder with a remitting-relapsing nature

→ Retrospective study on **258 patients** (ISG criteria)

F/M: 130/128, mean age: 41.1 +/- 11,5 years

125 (48.4%) with mucocutaneous type

133 patients (51.6%) with major organ involvement

≥1 of any disease manifestations = active

Mean follow-up duration was **45.8 +/-36.5 months** (2–165)

→ 1757 visits

Is Complete Remission a Realistic Target With Current Therapeutic Options in Behcet's Disease?

F Alibaz-Oner, G Mumcu, Z Kubilay, G Ozen, G Celik, A Karadeniz, M Can, SY Oner, N Inanc, PAtagunduz, T Ergun, H Direskeneli

Mean follow-up duration was 45.8 +/-36.5 months (2–165) → 1757 visits

19.8–43.9% of the patients were on IS
35.3–59.3% under colchicine or NSAIDs
6.4–45% were noncompliant patients (without any treatment)

Patients clinically active in 67.2% (n=1182) of the total visits

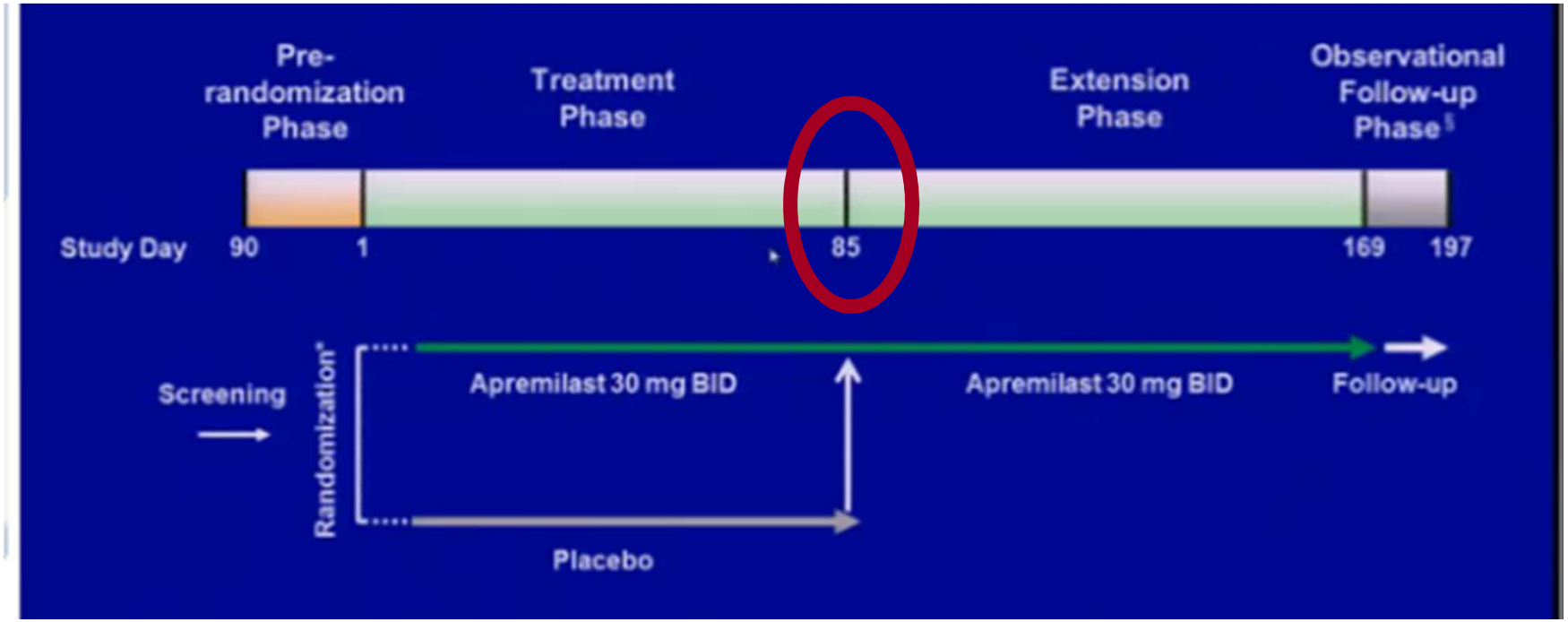
Major cause of activity = aphthous ulcers (39.4–63.2%)

- genital ulcer: 3.5–27.1%
- erythema nodosum: 8.2–22.5%
- papulopustular lesions: 18.2–33.7%
- arthritis: 21.3–33.5%
- uveitis: 0.5–8.5%
- vascular involvement: 2.5–10.8%

No difference IS vs non-IS therapies…

PLENARY - Apremilast For The Treatment Of Behcet's Syndrome: A Phase II Randomized, Placebo-Controlled, Double-Blind Study

G Hatemi, M Melikoglu, R Tunc, C Korkmaz, BT Ozturk, C Mat, PA Merkel, K Calamia, Z Liu, L Pineda, RM Stevens, H Yazici, Y Yazici



Inclusion criteria

>18 years old

Behcet's based on ISG criteria

Active ulcer (oral or genital) in the past 28 d

≥2 oral ulcers at the time of randomisation

Exclusion criteria

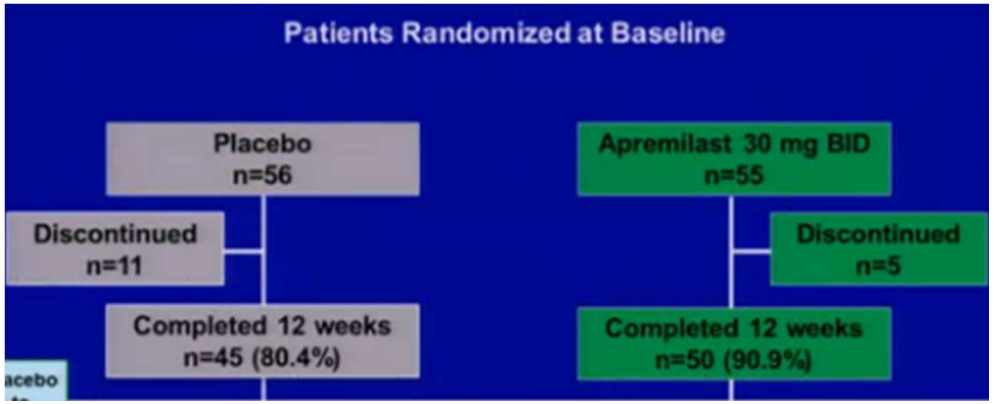
No active uveitis

No active major organ disease in past 12 mo

No concomitant IS, topical CS

No colchicine in any arm

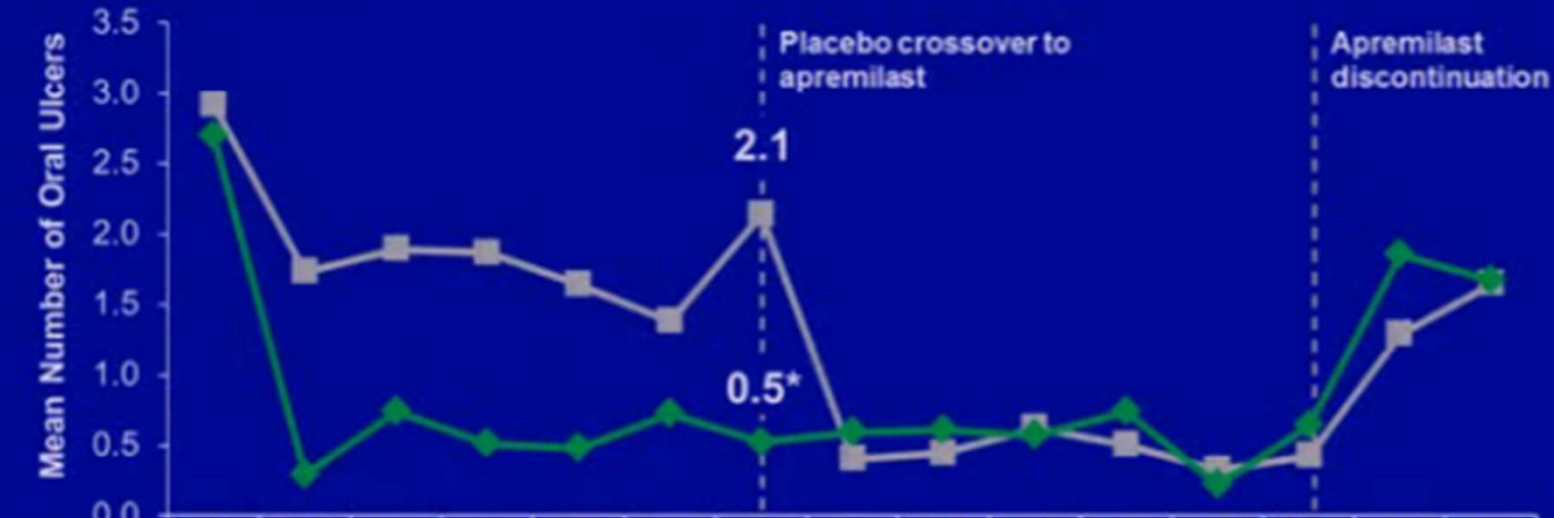
- 3 Turkish + 1 US sites
- Endpoint = n of oral ulcers at week 12



	Placebo n=56	Apremilast n=55
Male	32%	29%
White	98%	96%
Duration of disease, yr	5.7	4.9

Primary End Point: Mean Number of Oral Ulcers at Week 12

Intent-to-Treat Population, LOCF (N=111)



	wk0	wk2	wk4	wk6	wk8	wk10	wk12	wk14	wk16	wk18	wk20	wk22	wk24	wk26	wk28
Placebo	2.9	1.7	1.9	1.9	1.6	1.4	2.1	0.4	0.4	0.6	0.5	0.3	0.4	1.3	1.6
30 mg BID	2.7	0.3	0.7	0.5	0.5	0.7	0.5	0.6	0.8	0.6	0.7	0.2	0.8	1.9	1.7

*$P<0.0001$ vs. placebo.

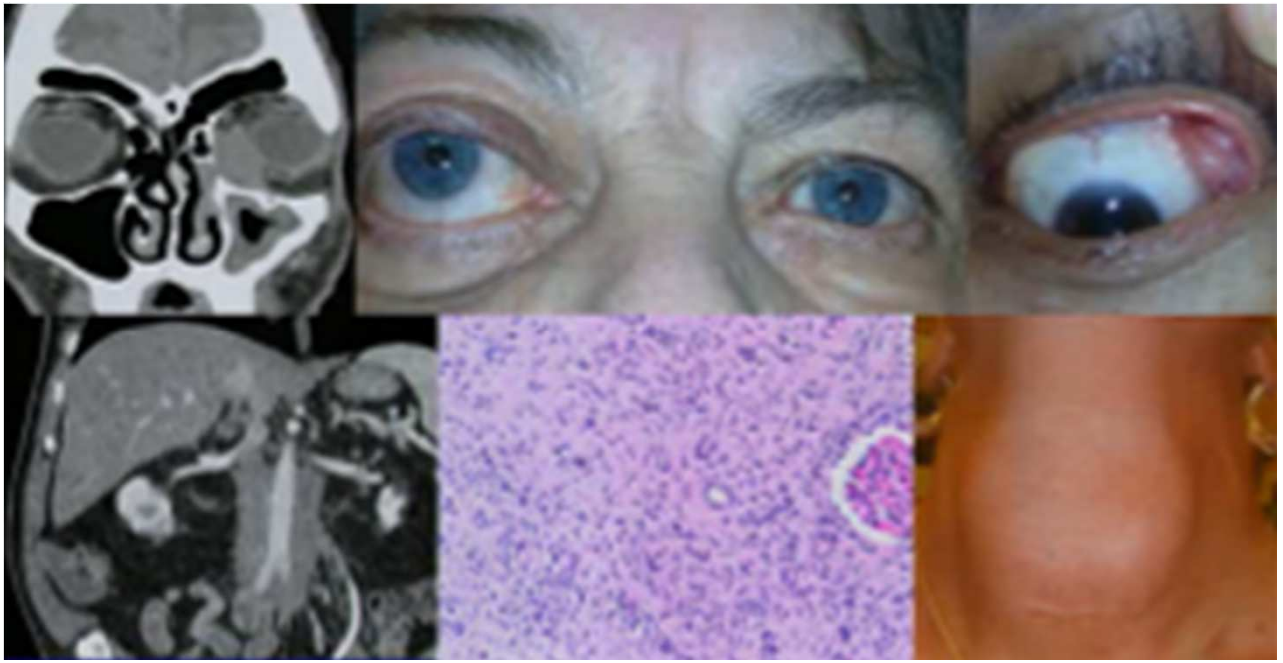
- Reduced oral ulcer burden over 12 weeks was corroborated on an individual patient basis
  - Mean oral ulcer AUC for apremilast was 1/3 of the mean oral ulcer AUC for placebo ($P<0.0001$)

- Significant improvement in oral ulcer pain
- Significant clearance of genital ulcers (100% vs 50%)
- Similar and low SAE rate (3.6% vs 5.4%), mainly headache, nausea, diarrhea

IgG4 related disease

PLENARY - Rituximab For The Treatment Of IgG4-Related Disease: A Prospective Clinical Trial

M. Carruthers, M. Topazian, A Khosroshahi, T Witzig, J Oakley, PHart, L Kelly, L Bergstrom, S Chari, JH Stone



63% achieve remission with CS

Open label study

RTX 1g x 2

EI = disease response (decline of IgG4 score ≥2)
and off PDN at month 6

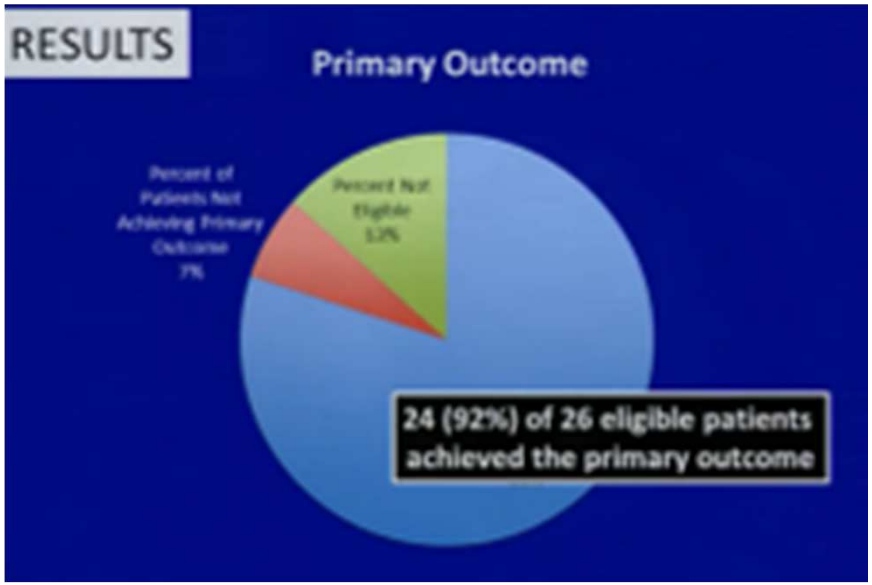
30 patients (16 MGH, 14 Mayo)

Mean age 63 (42-82)

87% M

10/30 had high IgG4 serum level at Dx

RTX alone when possible → alone in 26/30

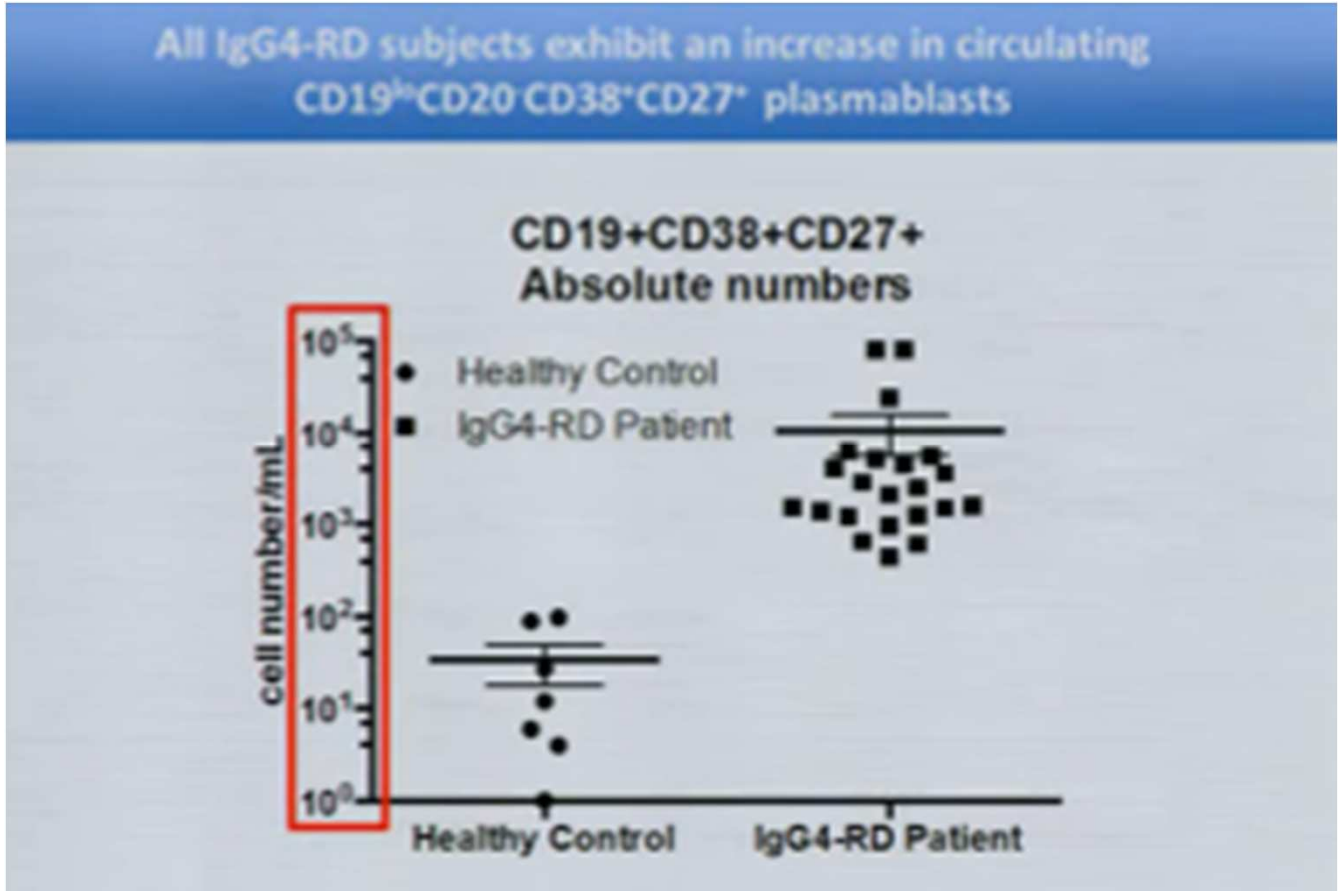


92% achieve the EI

3 required additional CS (→ 2 CR, 1 CS-depdt)

5 relapses (only 1 before 6 months)

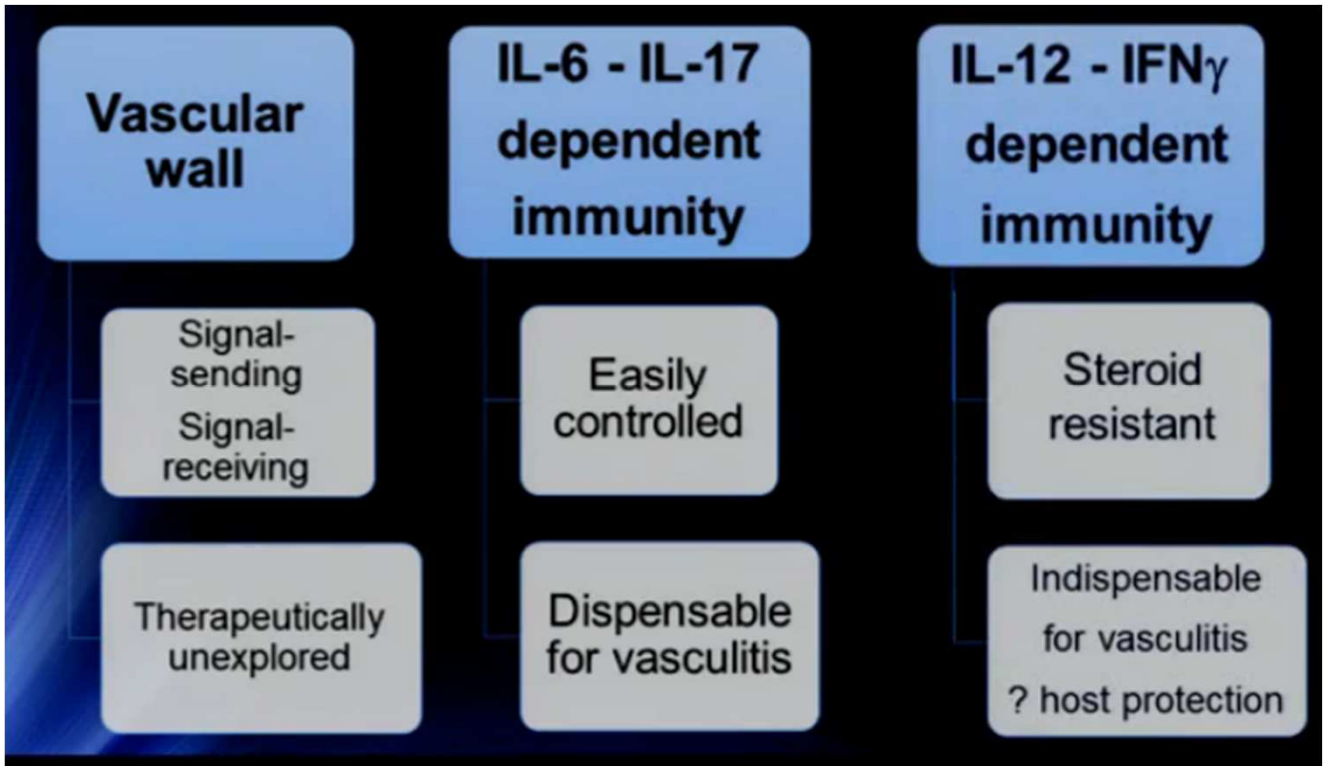
7 SAE but none attributed to RTX



PLASMABLASTS

Conclusions, 1/3

Role of TH1 pathway in GCA → IFN-gamma → STAT1 ; NOTCH → triple hit model



Conclusions, 2/3

Rituximab, again…

- for patients >65 years old
- to re-treat if relapses
- for maintenance

BUT… *for how long?*

Conclusions, 3/3

- Two “outsiders” did pretty well
  - Behcet’s disease and apremilast
  - IgG4-related syndrome and rituximab