ACR 2017 SAN DIEGO HIGHLIGHTS - VASCULITIS

Nikolaos Marketos

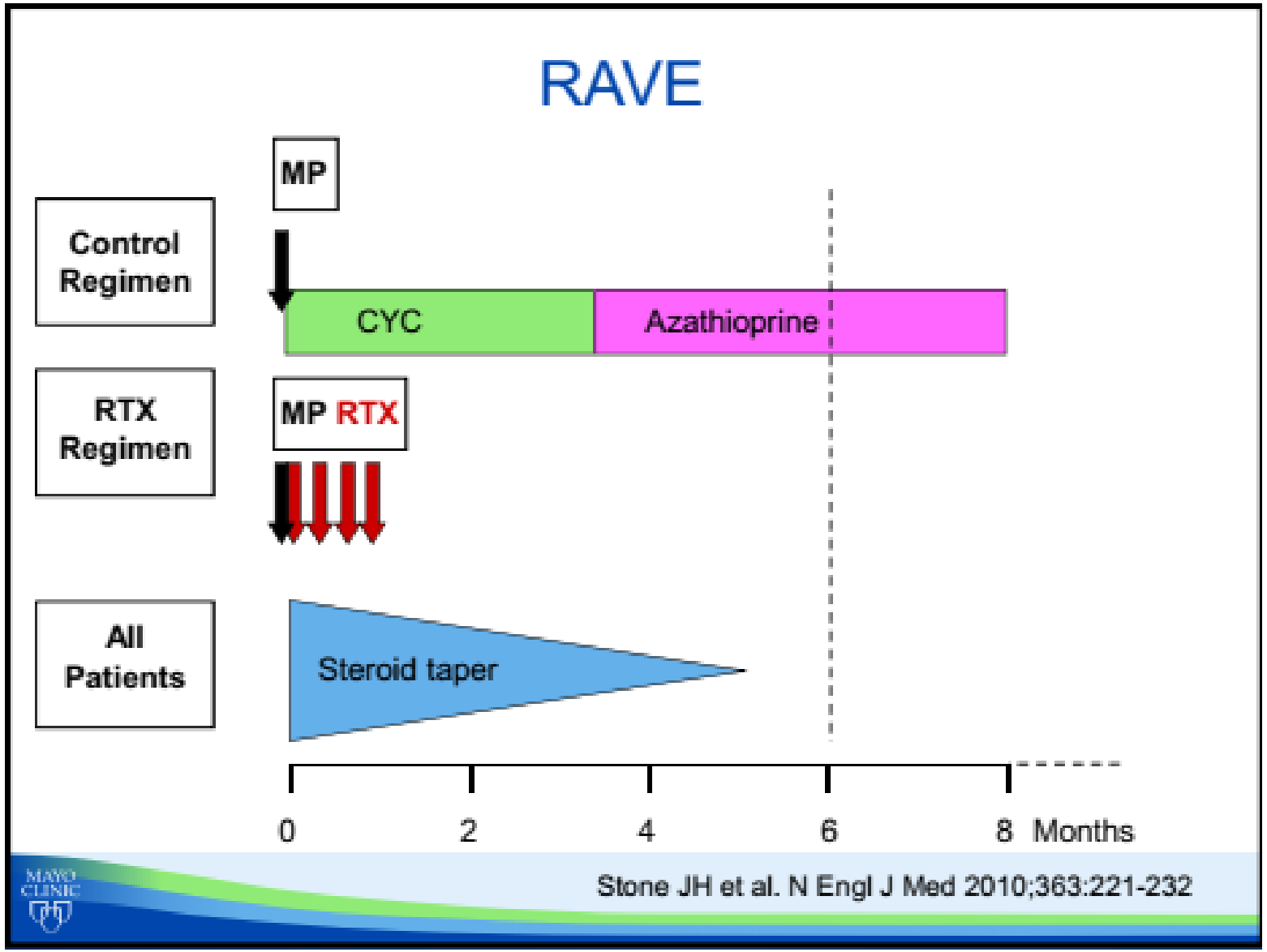
Rheumatologist

Volos, 1-6-2018

- No disclosures

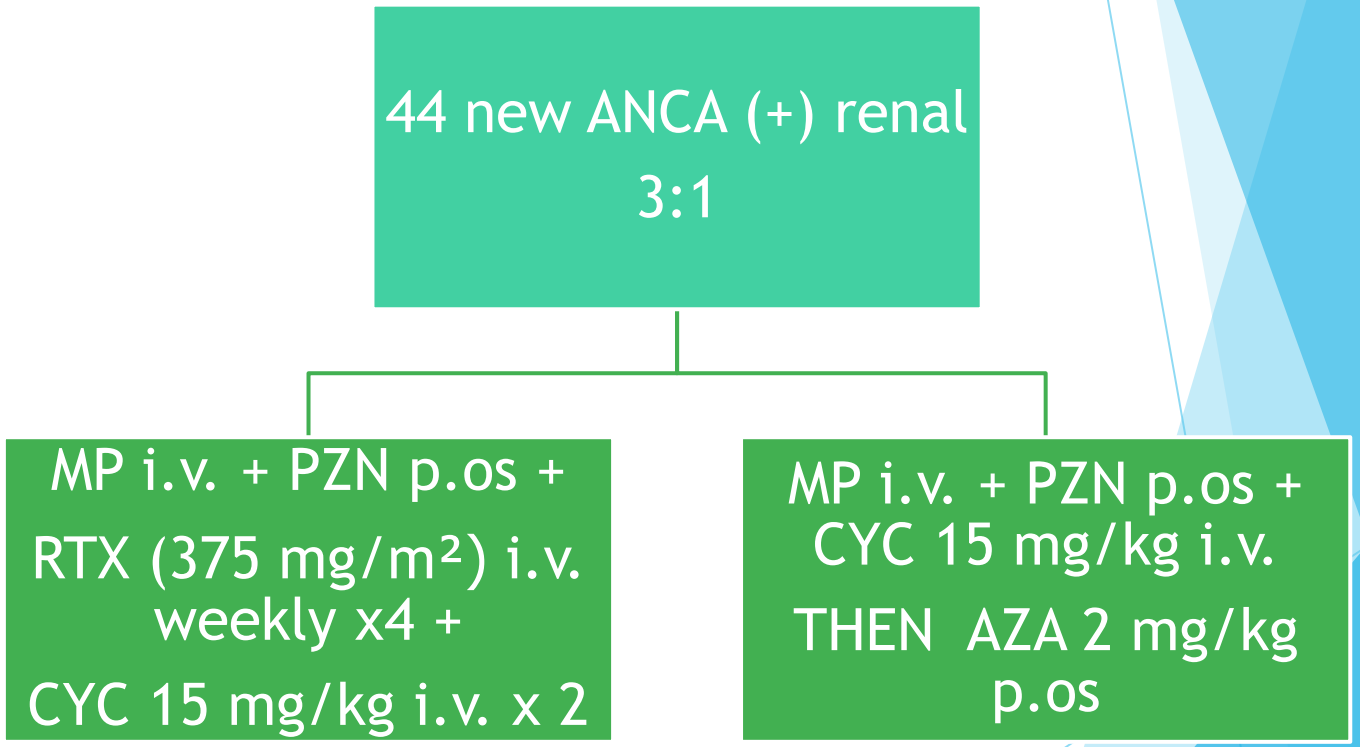
Vasculitis, mainly large vessel

- Update on ANCA-associated – prognosis & treatment
- GCA vascular complications and treatment


RAVE
MP
Control Regimen
CYC
Azathioprine
RTX Regimen
MP RTX
All Patients
Steroid taper
0
2
4
6
8 Months
Stone JH et al. N Engl J Med 2010;363:221-232

RITUXVAS: RTX vs CYC in ANCA-Associated Renal Vasculitis

- RTX not superior to CYC
- Similar AEs



Jones RB et al. N Engl J Med 2010;363:211-220.

RTX profile

- Young patient / fertility
- Cytopenias
- Malignancy history
- Urological problems
- Non-compliant
- Difficulty lab follow-up

WEGENT: AZA vs MTX maintenance

- 2 year relapse-free survival: MTX 74,5% vs AZA 71,8% = no difference
- AEs: MTX 46% vs AZA 56%

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

IMPROVE: AZA vs MMF maintenance

- Open label, 2002 – 2009, all new, CYC i.v. + PZN
- If remission: AZA 2mg/kg vs MMF 2000 mg/d
- AEs: MMF 42/86 (18 major) vs AZA 30/80 (10 major). Adjusted HR 1,80

Hiemstra, T. F. et al. JAMA 2010;304:2381-2388

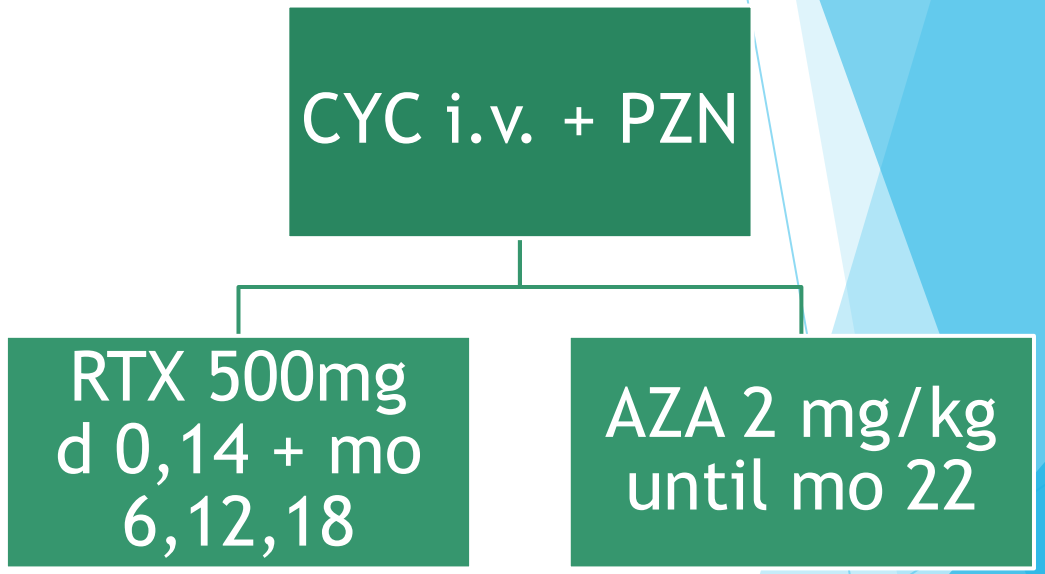
RTX maintenance – Mayo data

- 10 year, 53 pts refractory GPA, median RTX x 4
- All relapses after B cell comeback
- Along with or before ANCA rise
- No association IgG levels & infection

Cartin-Ceba et al. A & Rheumatism Vol. 64, No. 11, November 2012, pp 3770–3778

MAINRITSAN

- Relapse: 29% AZA vs 5% RTX (Hazard Ratio 6,61)
- AEs: No difference
- After 1 yr: AZA reduction to 1,5 then 1mg/kg/d



L Guillevain et al. N Engl J Med 2014;371:1771-80.

Other therapies

- Non threatening – limited – non-renal = MTX + PZN

Jayne DR et al. J Am Soc Nephrol. 2007;18(7):2180

- Plasma exchange in severe renal: MEPEX trial = reduced ESRD in 1 yr, result not sustained
- PEXIVAS ongoing, results in a few years
- TAPIR: ongoing, PZN tapering or not

Walsh M et al. Kidney Int. 2013; Aug;84(2):397-402

- CYC: iv (less dose accumulated) or pos (less relapses)???
- RTX + CYC for the very sick

Treatment summary (Pagnoux)

- **INDUCTION:** **CYC** pulse 15mg / kg on D1, 15, 29 then /3w alternatively orally 2mg/kg/d

OR

- **RTX** 375 mg/m^2/wk x 4 (or 1g on D1 & 15)

AND

- **GC** tapering in 3 – 6 mo
- +/- PEX??

- **MAINTENANCE (>18 mo???):** AZA 2mg/kg/d **OR** MTX 0,3 mg/kg/wk **OR** LFN 20mg/d OR MMF 2g/d

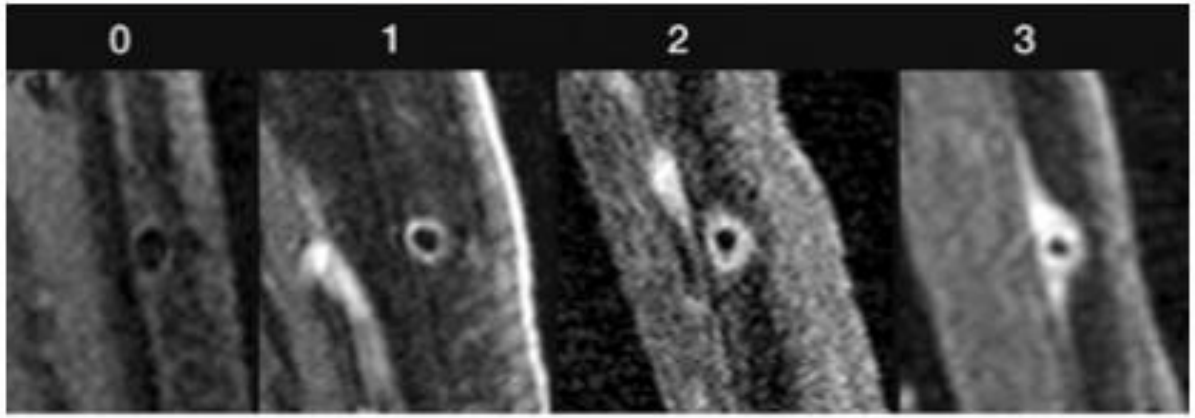
OR

- **RTX** 500 – 1000 mg q 4-6 mo or 'on demand'

Giant cell arteritis

MRI

Temporal Artery MRI



Sensitivity 78-85%, Specificity 86-90%,

0-1 days GC: Sens 85%

>4 days GC: Sens 56%

Klink et al. Radiology 2014

Hauenstein et al. Rheumatology 2012

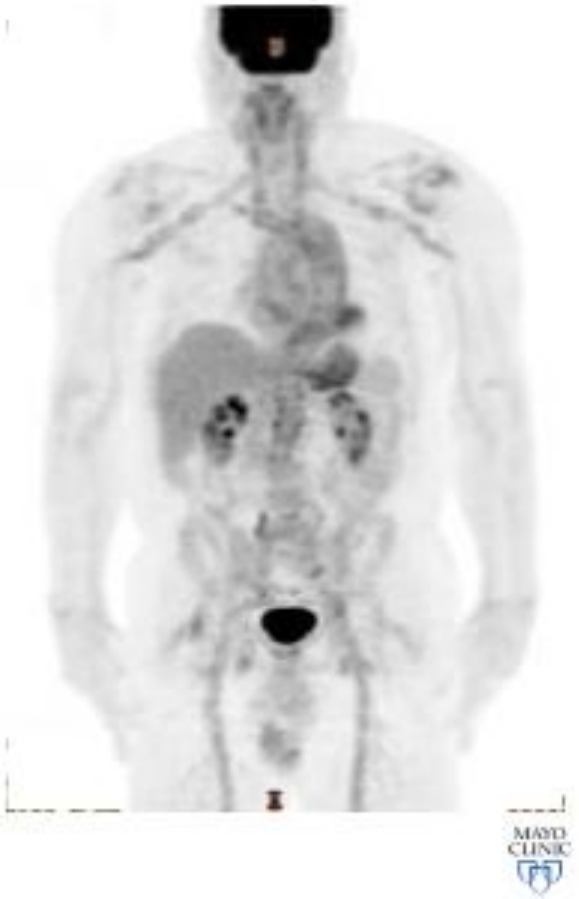
MAYO CLINIC

PET / CT

PET/CT

- Positive in up to 83%
- Pooled Sen 93%, Spec 90%
- Cannot assess temporal arteries
- Lack of standardized evaluation criteria
- Cost/availability
- Best uses: FUO, GCA aortitis

Blockmans D Arthritis Rheum 2006
Lee YH et al. Z Rheumatol 2016
Soussan M Medicine 2015



Injection of the substance in the feet: Less obscure than from carotid vein = better CT pictures!

Clinical Features

Older

Cranial symptoms

Vision loss

Younger

Often absent

Arm Claudication

Vascular findings

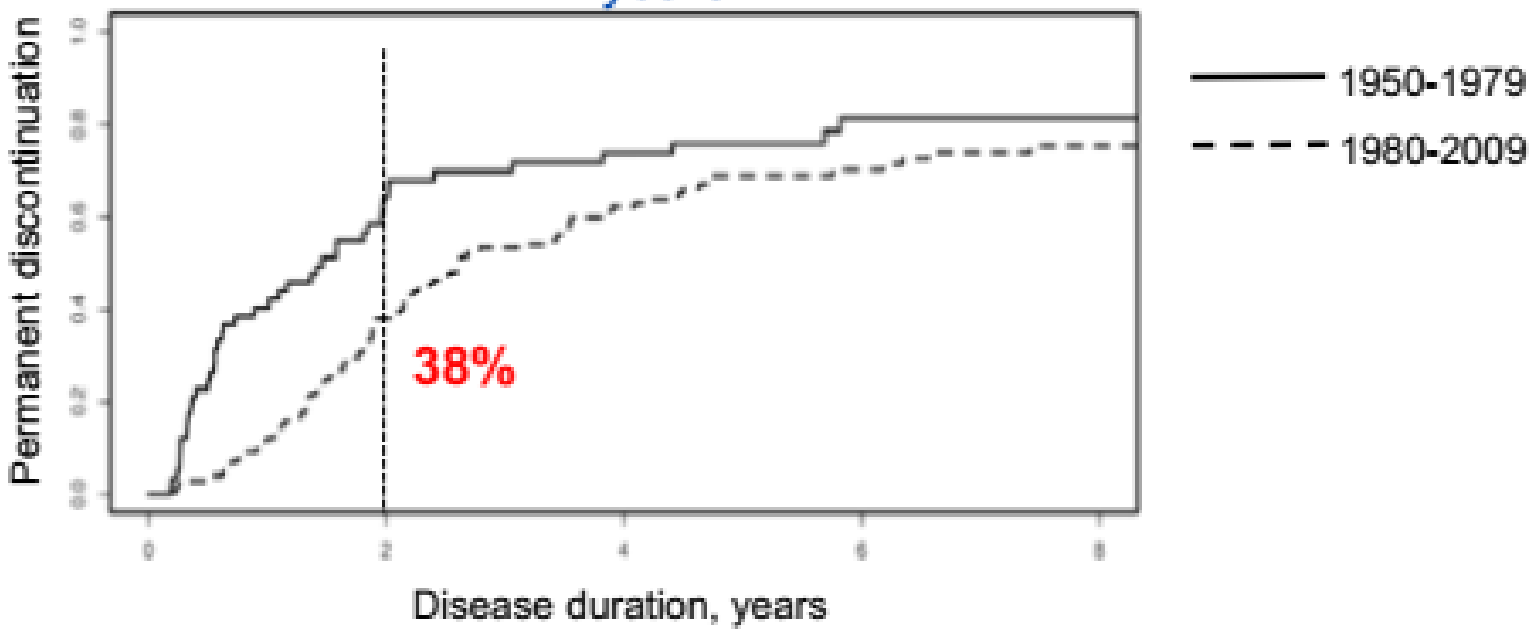
Schmidt WA Rheumatology (Oxford). 2008 Jan;47(1):96-101

Prieto-Gonzalez S, et al. Ann Rheum Dis 2012;71:1170–6

Muratore F et al Rheumatology (Oxford). 2015 Mar;54(3):463-70.

GCA – Olmsted Cohort

Median time to discontinuation (1980-2009) was 2.6 years



Chandran A et al. Clin Exp Rheumatol 2015

MAYO CLINIC

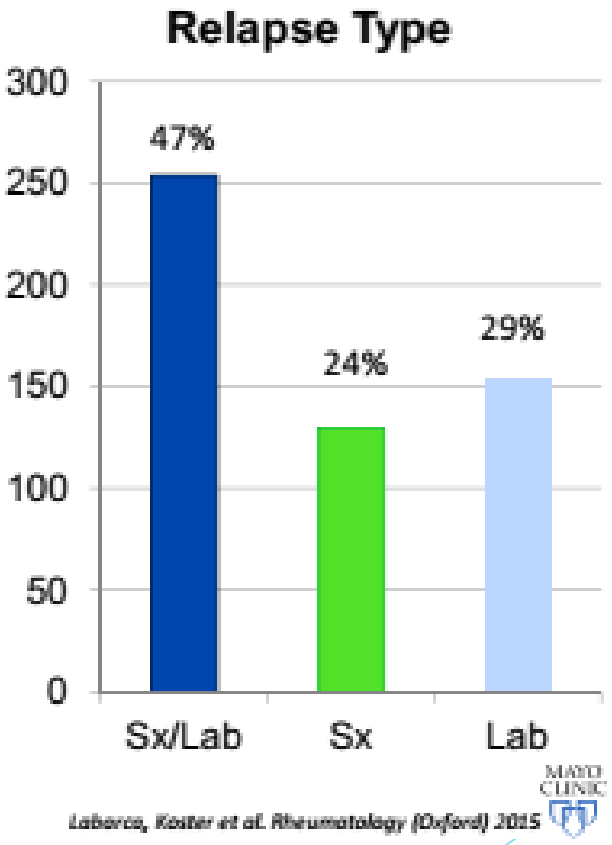
- High relapse rate: female, HT, DM
- > vs < 40mg/d initially = better chance off PZN in 3 yrs
- Relapse symptoms: PMR,headache, fatigue, tenderness **NO VISION LOSS**

Mayo Biopsy (+) Cohort - Relapse

Relapse	Patients, N (%)
0	73
1	80
2	51
≥3	82

75% of patients relapsed

30% had ≥ 3 relapses



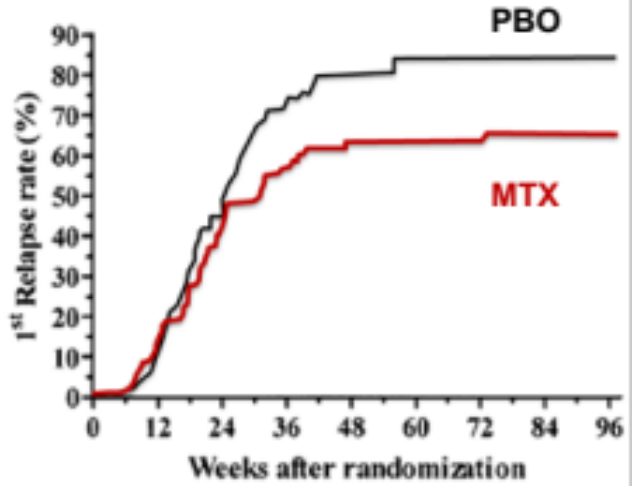
Laborca, Koster et al. Rheumatology (Oxford) 2015

MTX & Relapse

- MTX 7,5 – 15 mg/w
- **BUT:** After 9 mo PZN

GCA - Methotrexate

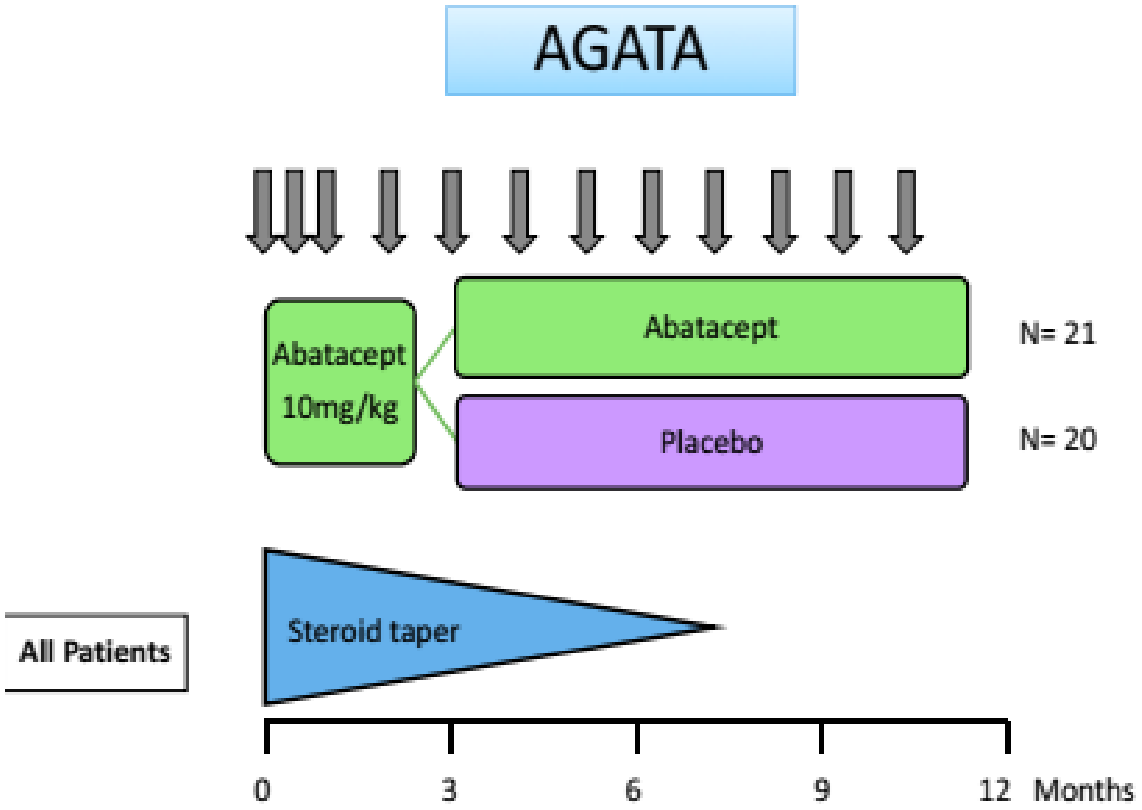
- MTX reduced:
  - Risk of 1st relapse by **35%**
  - Risk of 2nd relapse by **51%**
  - Exposure to steroids



Mahr A et al Arthritis Rheum. 2007 Aug;56(8):2789-97.

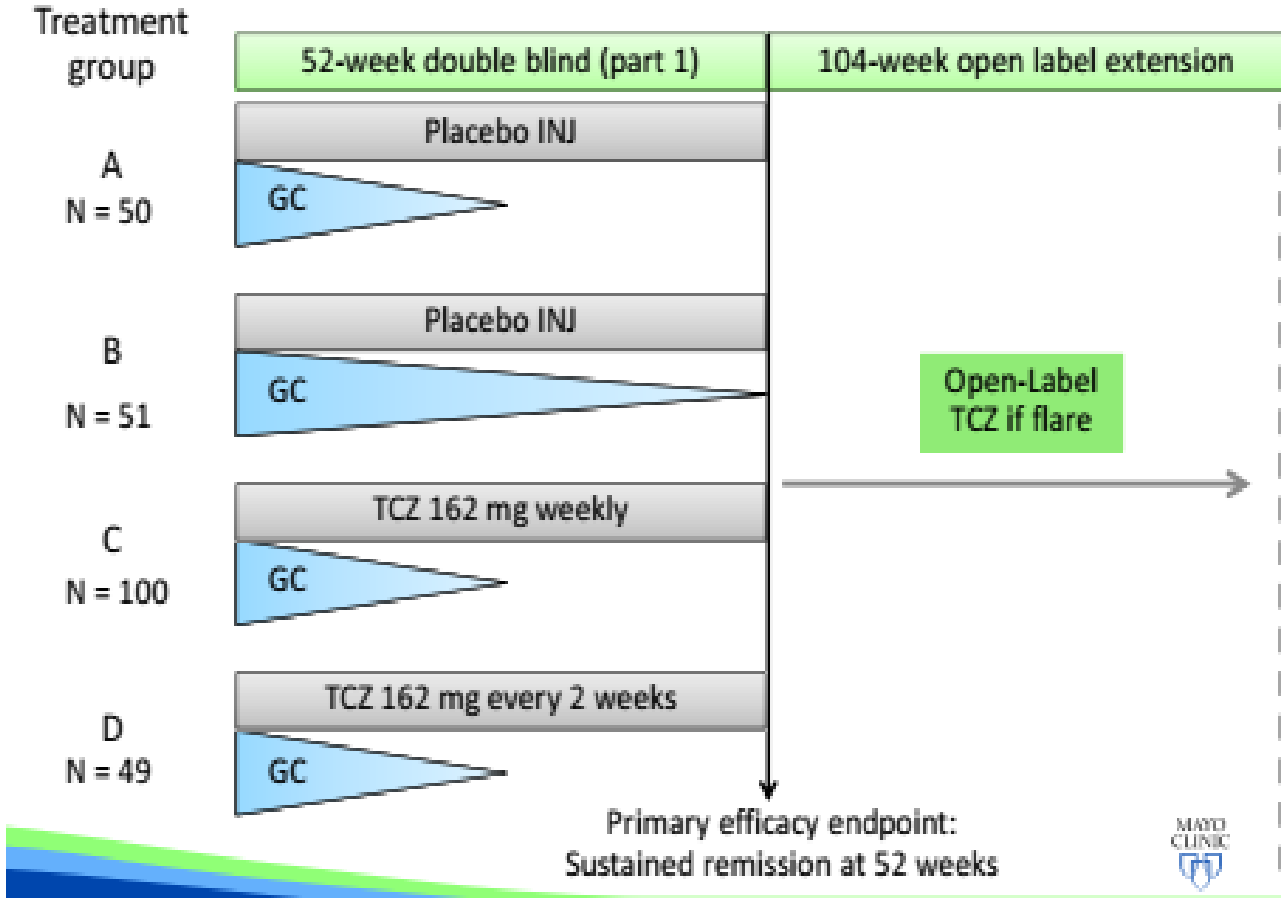
Abatacept for GCA

- All ABA + GC, mo 3 ABA vs PLC
- 48% vs 31% relapse free at 12 mo
- No difference in severity or frequency of AEs

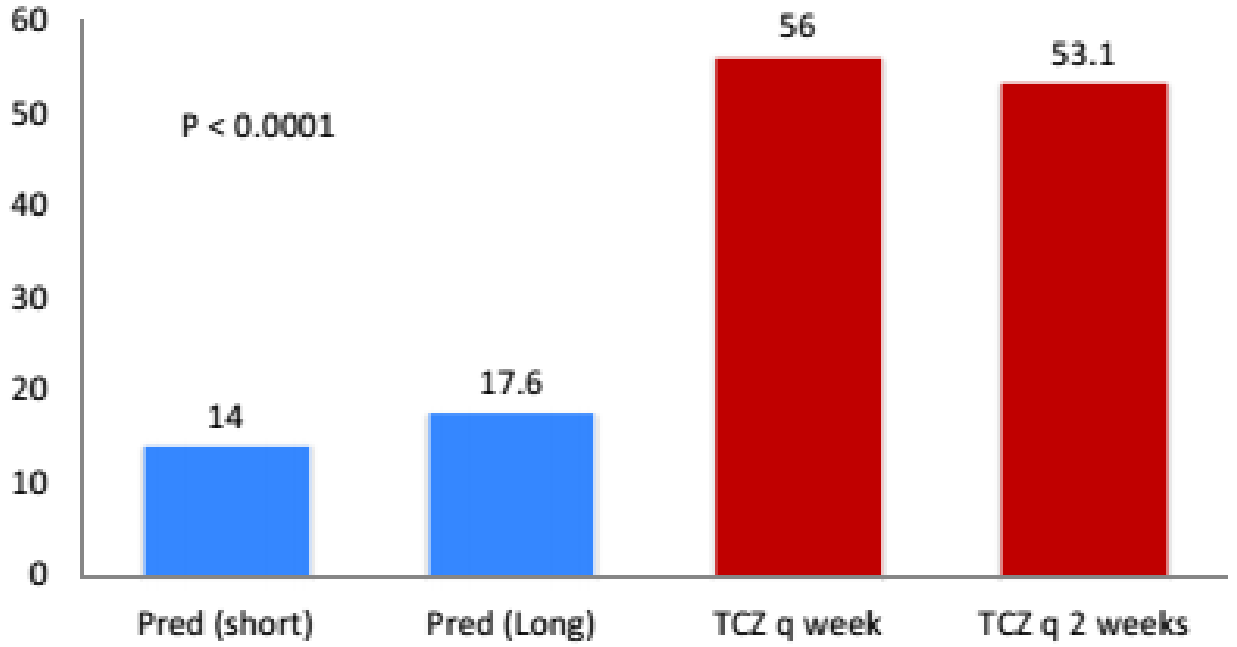


Langford CA et al. Arthritis Rheumatol; Jan 2017

GiACTA study design



Primary Endpoint: Patients in sustained remission at 52 weeks, (%)



Stone JH et al. N Engl J Med. 2017 Jul 27;377(4):317-328

MAYO CLINIC

Future Therapies

Baricitinib in relapsing GCA: phase II, open-label pilot study

Inclusion criteria

-Diagnosis of GCA

-Relapse with active GCA
Symptoms ***AND***
ESR ≥30 mm/hr ***OR*** CRP ≥10mg/L

Other therapy

- TNF inhibitors
  - Clinical trial data - No efficacy
- Aspirin
  - May reduce ischemic events
  - Generally recommended
  - Retrospective data
    - Conflicting evidence
- Statins
  - No evidence of benefit

Hoffman et al., Arthritis Rheum 2004; 50: 2296-2304
Salvarani C, et al. Rheumatology (Oxford). 2009 Mar;48(3):250-3
Schmidt et al. J Rheumatol. 2013 Jun;40(6):910-5.

Ongoing in Mayo Clinic

Complications: Aortic aneurysm

- 17,3 x risk, 12-33% incidence in 10yr, aortic regurgitation as clinical predictor?

- CT / MRI every 2-5yrs or ECHO

Evans JM et al. Ann Intern Med 1995;122(7):502-7

Robson JC. Ann Rheum Dis. 2013 Oct 4

Kermani TA, Warrington KJ, et al. Ann Rheum Dis. 2012 Dec 19.

García-Martínez A, et al Ann Rheum Dis. 2013 Jul 19

Salvarani C et al Lancet. 2008 Jul 19;372(9634):234-45

Mackie SL et al. Ann Rheum Dis. 2012 Dec 22

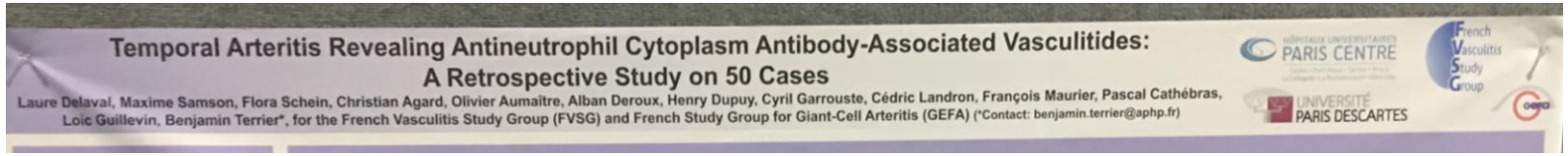
Bienvenu B. Rev Med Interne. 2016 Mar;37(3):154-65

Mayo proposal

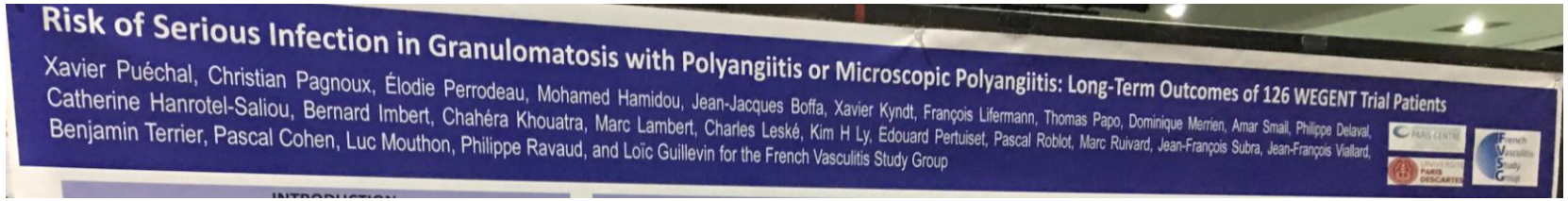
- Important to know type of aortitis: IgG4 = RTX, GCA = TCZ
- If TCZ for 1-1,5 year & no relapse: either reduction of dose (mg/kg/mo) or space out dose intervals.

- IL-1 (inhibited by PZN) promotes one pathway, IL-6 (inhibited by TCZ) promotes the other = **BOTH NEEDED!!!**

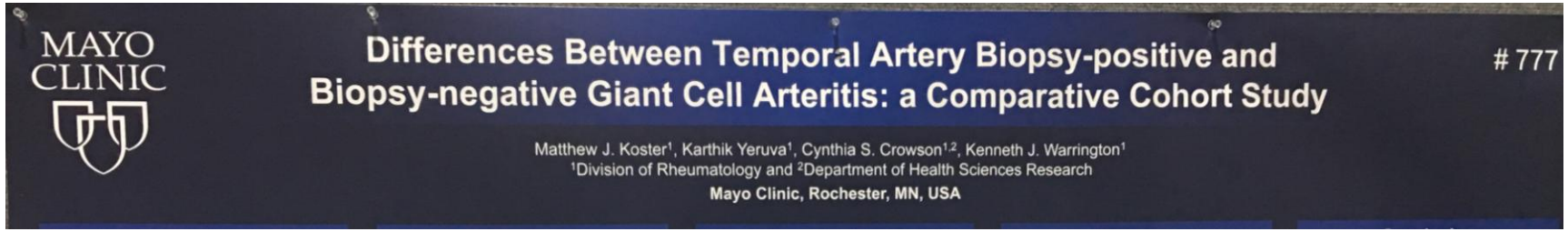
ANCA Poster



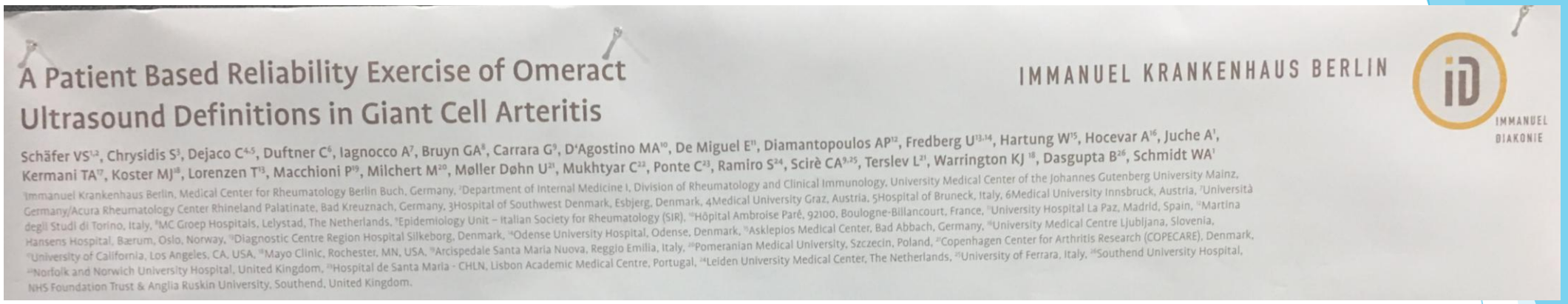
- French study: 50 pts with cranial symptoms, 2000-2001. 33 screened for ANCA with 62% MPO, 38% PR3. 2/3 GPA, 1/3 MPA, few EGPA.
- 14 relapses in 42 mo of follow-up // Peripheral neuropathy, lung, renal, ear, nose, throat involvement more often.
- Necrosis instead for granuolomatosis.



- Older age & previous cumulative CYC dose as prognostic factors of serious infections in 124 WEGENT pats.



- TAB (-): Younger at diagnosis
- Shorter time from symptoms to diagnosis
- Seldom fulfill ACR GCA classification criteria
- Frequent scalp tenderness, arm claudication, anorexia & fatigue
- Seldom jaw claudication – PMR
- Lower CRP
- Later GC discontinuation



A Patient Based Reliability Exercise of Omeract Ultrasound Definitions in Giant Cell Arteritis

IMMANUEL KRANKENHAUS BERLIN

IMMANUEL DIAKONIE

Schäfer VS[1,2], Chrysidis S[3], Dejaco C[4,5], Duftner C[6], Iagnocco A[7], Bruyn GA[8], Carrara G[9], D'Agostino MA[10], De Miguel E[11], Diamantopoulos AP[12], Fredberg U[13,14], Hartung W[15], Hocevar A[16], Juche A[1], Kermani TA[17], Koster MJ[18], Lorenzen T[13], Macchioni P[19], Milchert M[20], Møller Døhn U[21], Mukhtyar C[22], Ponte C[23], Ramiro S[24], Scirè CA[9,25], Terslev L[21], Warrington KJ [18], Dasgupta B[26], Schmidt WA[1]

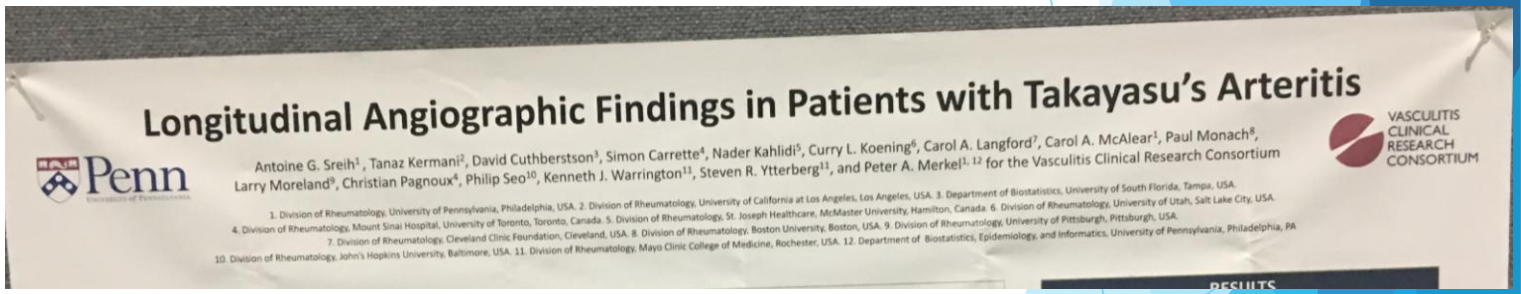
[1]Immanuel Krankenhaus Berlin, Medical Center for Rheumatology Berlin Buch, Germany, [2]Department of Internal Medicine I, Division of Rheumatology and Clinical Immunology, University Medical Center of the Johannes Gutenberg University Mainz, Germany/Acura Rheumatology Center Rhineland Palatinate, Bad Kreuznach, Germany, 3Hospital of Southwest Denmark, Esbjerg, Denmark, 4Medical University Graz, Austria, 5Hospital of Bruneck, Italy, 6Medical University Innsbruck, Austria, [7]Università degli Studi di Torino, Italy, [8]MC Groep Hospitals, Lelystad, The Netherlands, [9]Epidemiology Unit – Italian Society for Rheumatology (SIR), [10]Hôpital Ambroise Paré, 92100, Boulogne-Billancourt, France, [11]University Hospital La Paz, Madrid, Spain, [12]Martina Hansens Hospital, Bærum, Oslo, Norway, [13]Diagnostic Centre Region Hospital Silkeborg, Denmark, [14]Odense University Hospital, Odense, Denmark, [15]Asklepios Medical Center, Bad Abbach, Germany, [16]University Medical Centre Ljubljana, Slovenia, [17]University of California, Los Angeles, CA, USA, [18]Mayo Clinic, Rochester, MN, USA, [19]Arcispedale Santa Maria Nuova, Reggio Emilia, Italy, [20]Pomeranian Medical University, Szczecin, Poland, [21]Copenhagen Center for Arthritis Research (COPECARE), Denmark, [22]Norfolk and Norwich University Hospital, United Kingdom, [23]Hospital de Santa Maria - CHLN, Lisbon Academic Medical Centre, Portugal, [24]Leiden University Medical Center, The Netherlands, [25]University of Ferrara, Italy, [26]Southend University Hospital, NHS Foundation Trust & Anglia Ruskin University, Southend, United Kingdom.

- 4 pts vasculitic lesions axillary & temporal, 2 normal
- 12 sonographers, 2 rounds
- 1 day UK, 3 day inclusive US training

- Before training: poor to fair inter – observer reliability
- After training: moderate to perfect

Takayasu

- 128 Japanese pts, 3,5 yr median follow up. 25% damage in 6 mo, 75% later, most 1st yr.



- Most pts without clinical or laboratory findings prior / during flare. Carotid & subclavian most likely to respond to therapy.

TCZ even in PMR???


The Efficacy and Safety of the Anti-IL-6 Receptor Antibody Tocilizumab for Polymyalgia Rheumatica Patients with Resistance or Intolerance to Glucocorticoids and Methotrexate

- 8 pts in Japan, refractory / non-responders to GCs & MTX that received TCZ = all managed to taper GCs.

Behcet

- IFX effective in relapsing retinal Behcet – Spanish study of 103 pts
- Apremilast for mucocutaneous ulcers: very good results where other therapies & biologics have failed in 14 Spanish pts.

IgA

- 52 adult pts from centra in Turkey, 50% follow-up for 2 years. 45% FFS>1, 30% at least one damaged item.
- Late onset disease associated more frequently with renal involvement in a French study of 260 pts.

ACR 2017 SAN DIEGO HIGHLIGHTS – SJÖGRENS SYNDROME

Nikolaos Marketos

Rheumatologist

Volos, 1-6-2018

ΑΤΥΠΗ ΚΛΙΝΙΚΗ ΕΙΚΟΝΑ SJÖGREN (20%)

- Οροθετική πολυαρθρίτις
- Ρευματική πολυμυαλγία
- Λευκοκυτταροκλαστική αγγειίτις
- Απομυελινωτίκή νόσος
- Περιφερική νευροπάθεια
- Φλεγμονώδη μυοσίτις
- Διόγκωση σιελογόνων αδένων
- Προοδευτική τερηδόνα
- Νεφρική σωληναριακή οξέωση
- Πυρετός αγνώστου αιτιολογίας
- Σύνδρομο χρονίου πόνου
- Αυξημένη ΤΚΕ
- ANA / Rf σε ασυμπτωματικό ασθενή
- Διάτρηση κερατοειδούς

* F. Vivino F, *Medscape Rheumatology 5(2)*, 2004.

** FB Vivino, P Minerva, CH Huang, SE Orlin . *J Rheumatol*, 28, 379, 2001.

ΔΙΑΦΟΡΙΚΗ ΔΙΑΓΝΩΣΗ

- Αμυλοείδωση
- Χρόνια σιαλαδενίτις
- ΣΔ
- Δυσαυτονομία
- Σύνδρομο ηωσινοφιλίας – μυαλγίας
- Σύνδρομο μοσχεύματος – ξενιστή
- Ηπατίτις C
- IgG 4 σχετιζόμενες νόσοι
- Ξηρότητα σχετιζόμενη με φάρμακα
- Αναπνοή από το στόμα
- Σκλήρυνση κατά πλάκας
- Μετά ακτινοβολία
- Σαρκοείδωση
- Σιαλαδένωση
- HIV – DILS (Διάχυτο διηθητικό λεμφοκυτταρικό σύνδρομο)
- Νόσος από σιλικονούχα προθέματα στήθους
- Σύνδρομο Sjögren (1^{ο} παθές, 2^{ο} παθές)
- Υπερλιπιδαιμία τύπου V

ΚΡΙΤΗΡΙΑ ΤΑΞΙΝΟΜΗΣΗΣ

- 1965 – 2017: 13 διαφορετικά σετ!! Αλγόριθμος? Τέστ?
- American-European Consensus Group Criteria (AECGC) - 2002: ξηροστομία, ξηροφθαλμία, παθολογικά τέστ δακρύων, σιέλου, anti-SSA/SSB, βιοψία χείλους (4/6).

(Vitali C et al., *Ann Rheum Dis, 2002*)

2016 ACR – EULAR κριτήρια

- Βιοψία χείλους (FS>1/4 mm^2) = **3**
- Anti Ro = **3**
- OSS > 5 (van Bijsterfeldt>4) = **1**
- Schirmer < 5mm / 5min = **1**
- Unst. salivary flow <0,1ml/min = **1**

9

Positive score 4/9

Shiboski C et al. *Arthritis & Rheum,* 2017

Αυτοαντισώματα

- ANA 70-90%
- Rf 60-90%
- Anti – SSA (Ro) 40-60%
- Anti – SSB (La) 20-40%
- Anti-CCP 7-19%
- Anti – centromere 4-13%
- Anti – M3R 62-90%
- Anti – a fodrin 1-50%
- Anti CA-6 ??
- Anti –SP1 ??
- Anti PSP??

Sjo – kit or Early Sjögren profile, commercially available

SICCA REGISTRY – NIH

2003 - present

- **S**jögren **I**nternational **C**linical **C**ollaborative **A**lliance (9 sites)
- Συλλογή κλινικών πληροφοριών & βιοδειγμάτων
- Παροχή πόρων για έρευνα
- Εξέλιξη νέων κριτηρίων

ACR – SICCA κριτήρια ταξινόμησης 2012

1. **Ορολογικά:** SSA ή SSB (+) ή Rf (+) / ANA> 1:320
2. **Ιστολογικά:** Βιοψία με Focus score > ¼ mm^2
3. **Ξηρά κερατοεπιπεφυκίτις:** Ocular staining score >3 (έναν οφθαλμό)

- Ασθενείς με θετικά αντισώματα είχαν 12x συχνότερα θετική βιοψία (95% CI // 9,3 – 15,5)
- Αυτοί με θετικές βιοψίες 4x συχνότερα ocular staining score (95% CI // 3,1-5,3)
- Αυτοί με θετικό OSC 4,8x συχνότερα αντισώματα (95% CI // 3,6-6,4)

- **Πλεονεκτήματα**
  - Απλό
  - 90-95% ευαισθησία & ειδικότητα
  - Βασισμένο σε αντικειμενικά τέστ
  - Καλύτερη εκτίμηση της οφθαλμικής επιφάνειας
- **Μειονεκτήματα**
  - Σε μεγάλο βαθμό εξάρτηση από βιοψία
  - Ειδικές χρώσεις οφθαλμού μόνο σε κέντρα

Shiboski S et al, *Arthritis Care Res*, 2012

Διαγνωστική χρησιμότητα anti – SSB??

- 3514 συμμετέχοντες
- 3297 δεδομένα (9/2013)
- **Προσοχή** στην ερμηνεία anti-SSB σε ασθενή με πιθανό Sjögren
- Επιπρόσθετα στοιχεία, όπως βιοψία χείλους αναγκαία

Baer A et al. *Ann Rheum Dis, 2015*

Πολυκλωνική ενεργοποίηση Β-λεμφοκυττάρων
Λέμφωμα

- 5% ασθενών με NHL εντός 10ετίας
- Συχνότερα σε σιελογόνους αδένες // MALT ή Marginal Zone B cell lymphoma
- 23-33% θνησιμότητα

RTX??

- Κρυοσφαιριναιμική αγγειίτις
- Αγγειίτις
- Έντονη διόγκωση παρωτίδων
- Φλεγμονώδης αρθρίτις
- Πνευμονική νόσος
- Περιφερική νευροπάθεια, ειδικά μονονευρίτις

Carsons S et al. *Arthritis Care Res*, 2016.

ΚΑΤΕΥΘΥΝΤΗΡΙΕΣ ΟΔΗΓΙΕΣ ΟΔΟΝΤΙΑΤΡΩΝ - ΟΦΘΑΛΜΙΑΤΡΩΝ

- Τοπική χρήση φθοριούχων σκευασμάτων
- Διαλύματα επιμετάλλωσης

Zero D et al. *JADA*, 2016

- **Μηχανισμός ξηροφθαλμίας:** Μειωμένη παραγωγή (ανεπάρκεια δακρύων) ή αυξημένη εξαέρωση (δυσλειτουργία αδένων του Meibom)???

- **Τάξης 1:** Τεχνητά δάκρυα, gel
- **Τάξης 2:** Αντιφλεγμονώδεις σταγόνες, Ω-3 λιπαρά, εκκριταγωγά // αζιθρομυκίνη, ερυθρομυκίνη
- **Τάξης 3:** Αυτόλογα δάκρυα, φακοί επαφής, καυτηρίαση δακρυικού πόρου
- **Τάξης 4:** Χειρουργική επέμβαση

Foulks G et al. *Ocular Surface*, 2015

Take home messages

- Βιοψία χείλους // αντισώματα αναγκαία για διάγνωση
- Σημαντικά τα αντικειμενικά ευρήματα.
- DMARDs – PLQ για μυοσκελετικό πόνο.
- Κόπωση συχνή, άσκηση η λύση.
- RTX σε ασθενείς με βαρύτερη, πολυσυστηματική νόσο.
- Φθορισμός οδόντων σε όλους.
- Διερεύνηση μηχανισμού ξηροφθαλμίας για καλύτερη αντιμετώπιση.


Thank you!
SAMSUNG
5 STAR
NO