ACR-EULAR UPDATE 2021-2022 SLE and RA

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OUTLINE : SLE & RA

- Pathogenesis.
- Diagnosis.
- Clinical aspects.
- Treatment

SLE

Pathogenetic Hints

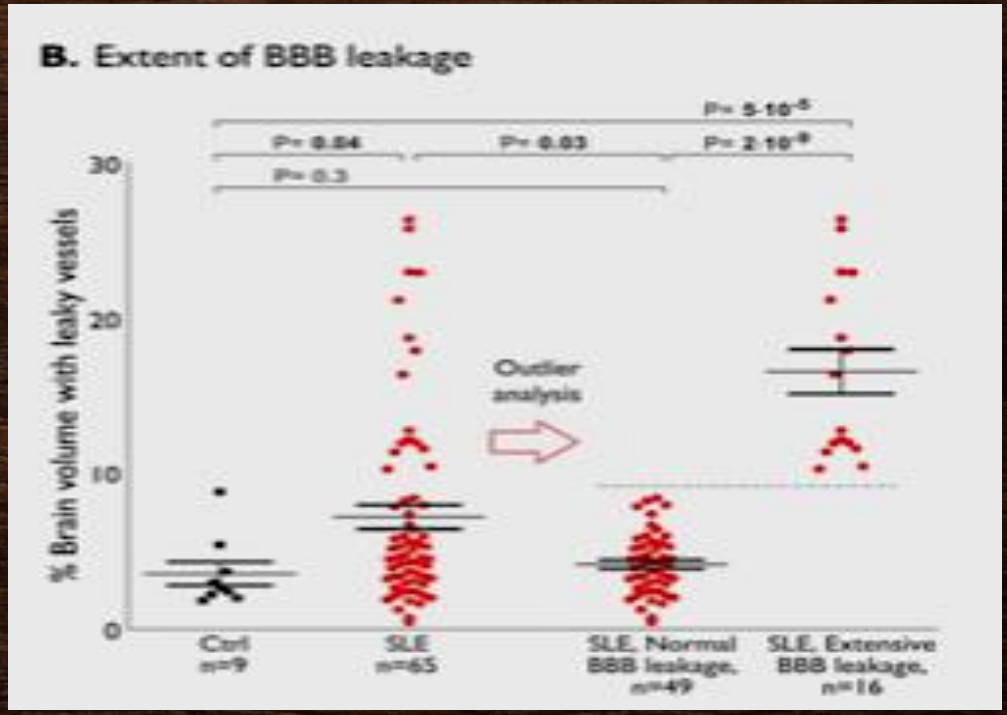
Blood-brain barrier leakage in SLE is associated with gray matter loss & cognitive impairment

Kamintsky l, Beyer s, et al. A&R 2020. 72(suppl 10) abs 1580

- 65 ambulatory SLE pts & 9 controls
- Dis Duration: 15.1 yrs
- Quiescent SLE
- Cognitive Impairment in 1 of 5 domains in 47.7% of SLE patients

- Increased BBB leakage-shown by contrast MRI

- **Extensive leakage (>9% of brain volume) in 24.6% with lower gray matter volume and lower cognition**



Percentage of brain volume with quantified BBB-leakage

Diagnosis

Anti-ganglionic nicotinic acetylcholine antibody (gAAchR) for lupus enteritis

aso k, kono m, et al. A&R 2021. 73(Suppl 10): abs0344

- N=144 SLE; 14.6% had lupus enteritis
- Retrospective
- Anti-gACHRα3 - antibody (20.1%) overall
- Lupus enteritis (37.9%) vs no LE (8.7%)

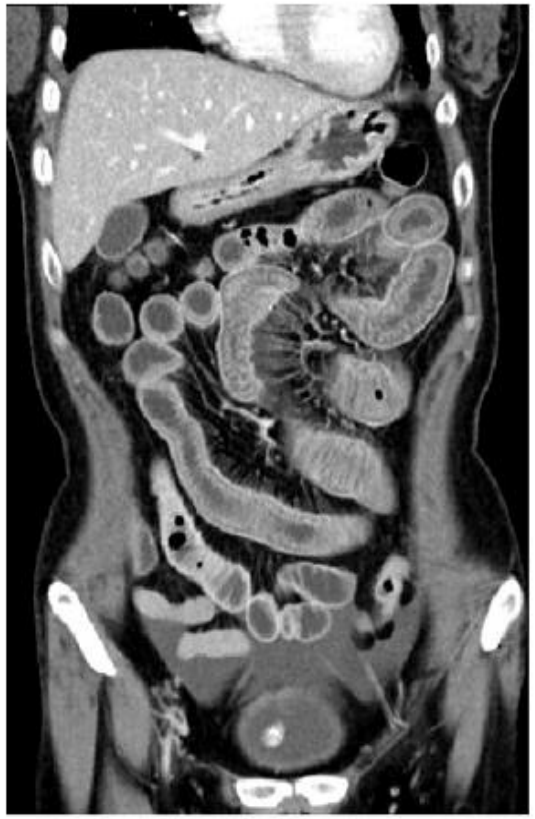


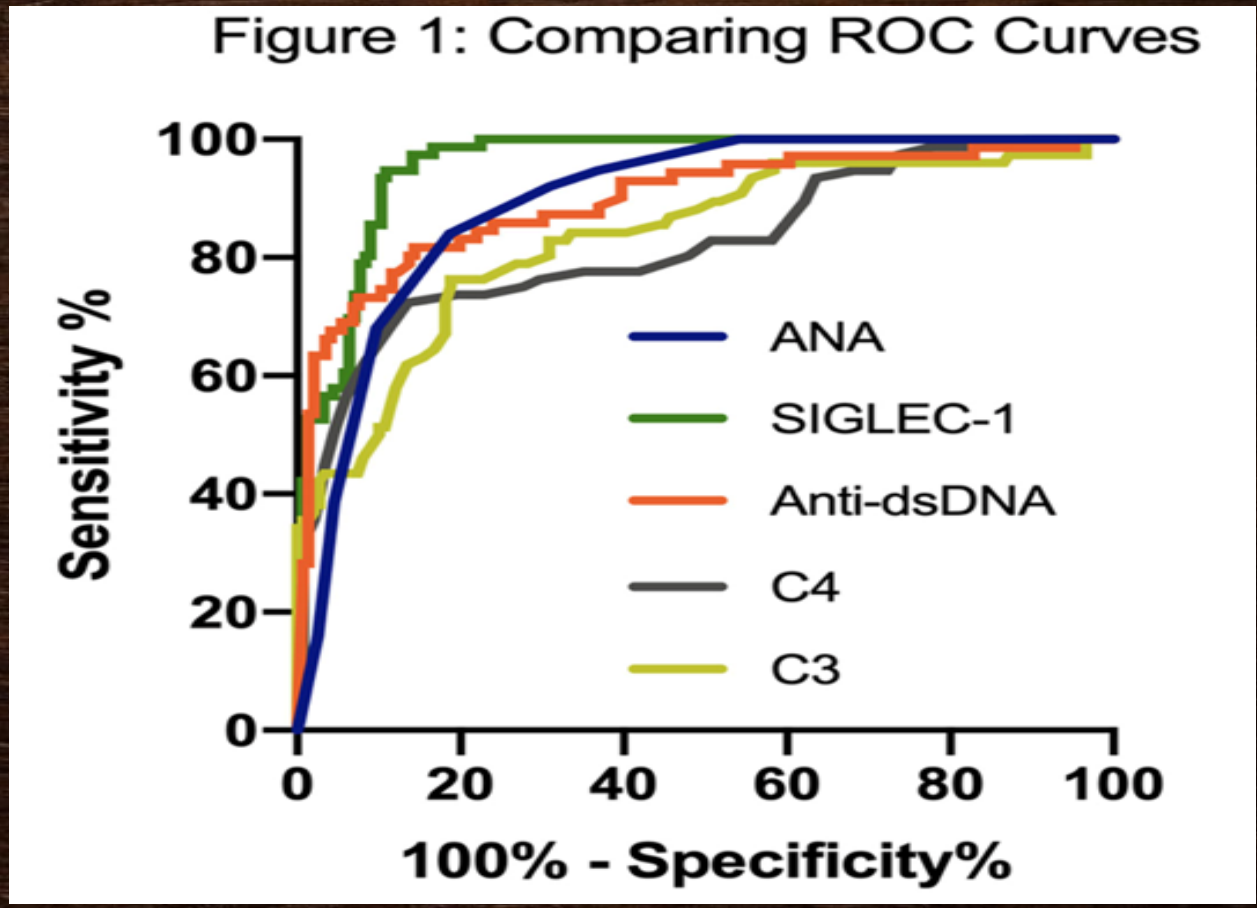
Figure. Lupus enteritis

A negative interferon biomarker (CD169/siglec-1) rules out SLE

zorn-pauly l, von stuckrad asl, et al. ard. 2021. 80 (suppl 1): 623 (abs POS0744)

- 232 controls compared with 76 SLE pts (do not know the diagnosis of these non-SLE pts)
- Siglec-1/CD169 are cell markers for macrophages that promote inflammation and IFN1
- **Negative Predictive value: >99.9%** while Positive Predictive value of only 0.2% among this group of pts. (Not tested against other defined disease)

Conclusion: An interferon biomarker may have a real place in the diagnosis of SLE, although much work is still needed.

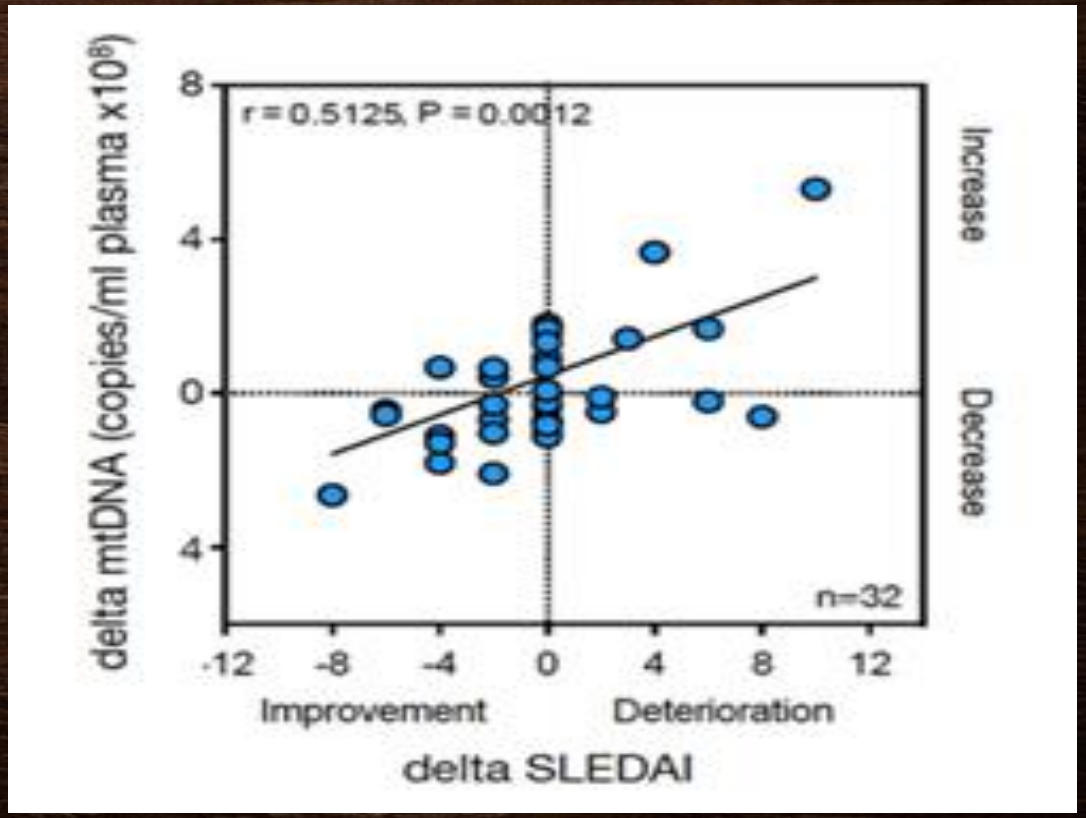


Pathogenetically logical

Plasma mitochondrial dna as a biomarker in diagnosis & follow-up of SLE

Giaglis s, daoudlarian d, et al. ard 2021. 80 (Suppl 1): 265 (abs POS0108)

- Mitochondrial ROS participate in the formation of neutrophil extracellular traps. Extruded mitochondrial DNA reflects inflammation in SLE.
- N=103 SLE and 56HC
- Quantitation of mitochondrial DNA in plasma
- Diagnostic Validity (vs normal):
  - Sensitivity: 87.4%
  - Specificity: 94.6%
  - Not tested vs other rheumatic disease



Conclusion: Mitochondrial DNA reflects NETS and may reflect an aspect of the pathogenesis of SLE.

Clinical

Depression in SLE is persistent & independent of disease activity

Kellahan s, Huang x, et al. A&R 2020. 72 (suppl 10): abs 1291

- N= 144, 91% female, 56.3% Afro-American (AA)
- F/U: 40.2 months
- CESD-R-nml <16: depressed 16-21; major depression >21
- Trajectory modeling
- AA more major depression): 37; 72.7%
- NO RELATIONSHIP TO SLEDAI-2K
- 61.2% indicated persistent depression

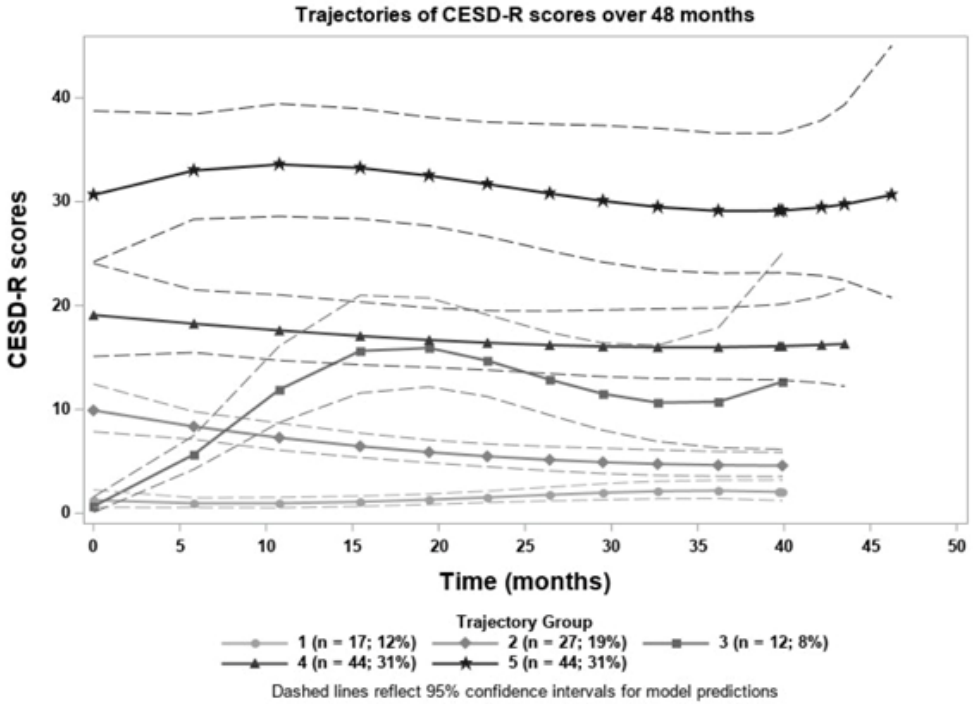


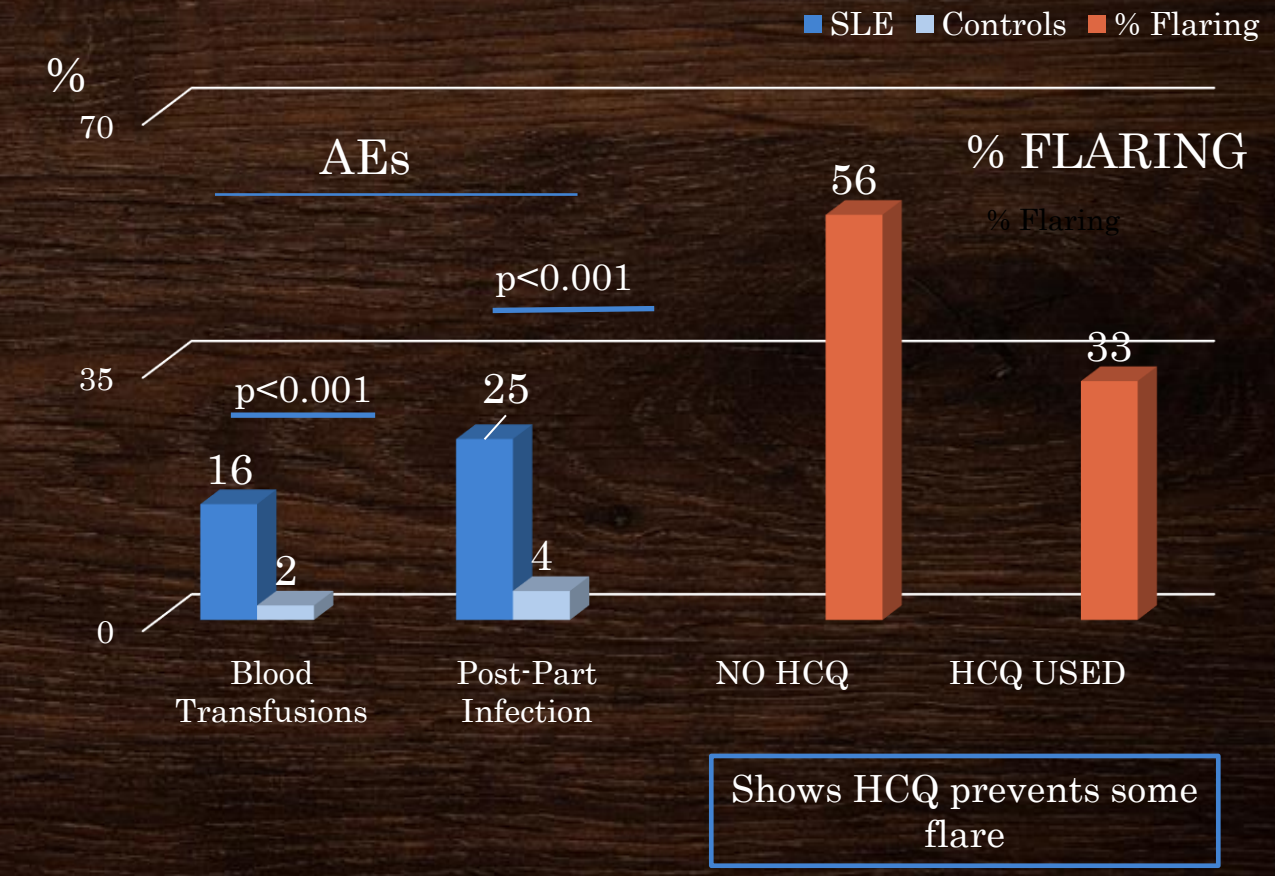
Figure 1. Identified trajectories of depression scores over time

Conclusion: Depression was common, persistent & not related to SLEDAI-2K

Post-partum adverse events in sle

bernado a, hubbard j, et al. a&R 2021. 73(suppl10): abs 1466

- From EMR
- SLE identified by an algorithm with positive predictive value of 90%
- N=178 SLE pregnancies identified by chart review to confirm SLE
- **No data on meds or extent of disease**
- N=250 non-autoimmune controls, also confirmed by chart review
- Controls had no autoimmune disease by ICD9 or ICD10



Conclusion: SLE patients have more AEs post-partum and HCQ decreases the number of flares

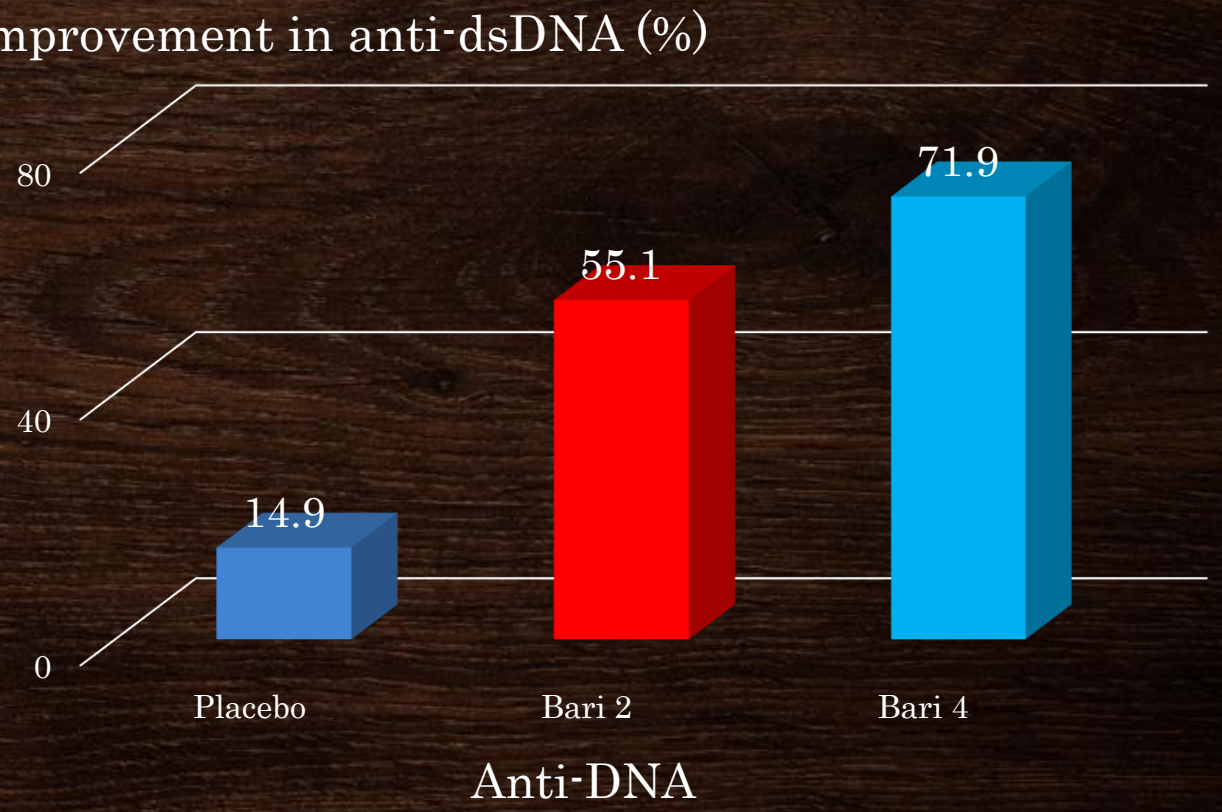
Treatment

Marketed medications

Baricitinib decreases anti-dsDNA in SLE: phase 2 DB-RCT vs placebo

Dorner T, Von Vollenhoven R, et al. A&R 2020. 72 (suppl 10): abs 0686

- 24 week
- Placebo (N=51), Bari 2 mg (N=56), Bari 4 mg (N=53)
- PTS: dsDNA positive, low C3 & C4
- No clinical data

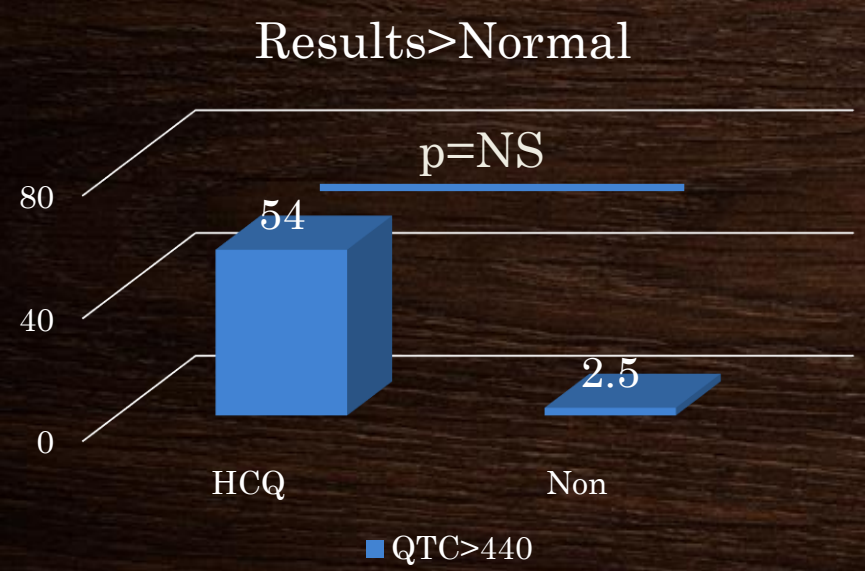


Conclusion: Baricitinib improves dsDNA in SLE- but does it change SX?

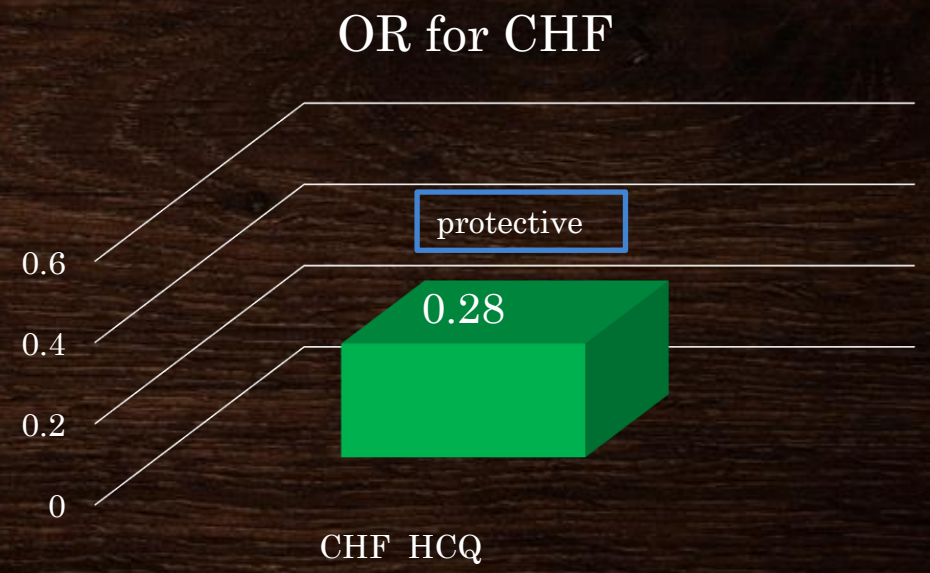
HCQ looks good in the heart in SLE/RA

Park e, Giles j, et al. A&R, 72 (Suppl 10): abs 0431;
Rua-Figueroa I, Rua-Figueroa d, et al.ARD, 80 (suppl 1): POS0721

Park: retrospective; n=681 RA/SLE QTC intervals



Rua-Figueroa: retrospective; N=117 SLE/CHF vs 3506 SLE no CHF—multi-variate analysis of CHF



95% CI: 0.17-0.46

Conclusion: NO increase in QTc plus protective against CHF

HCQ and retinal toxicity

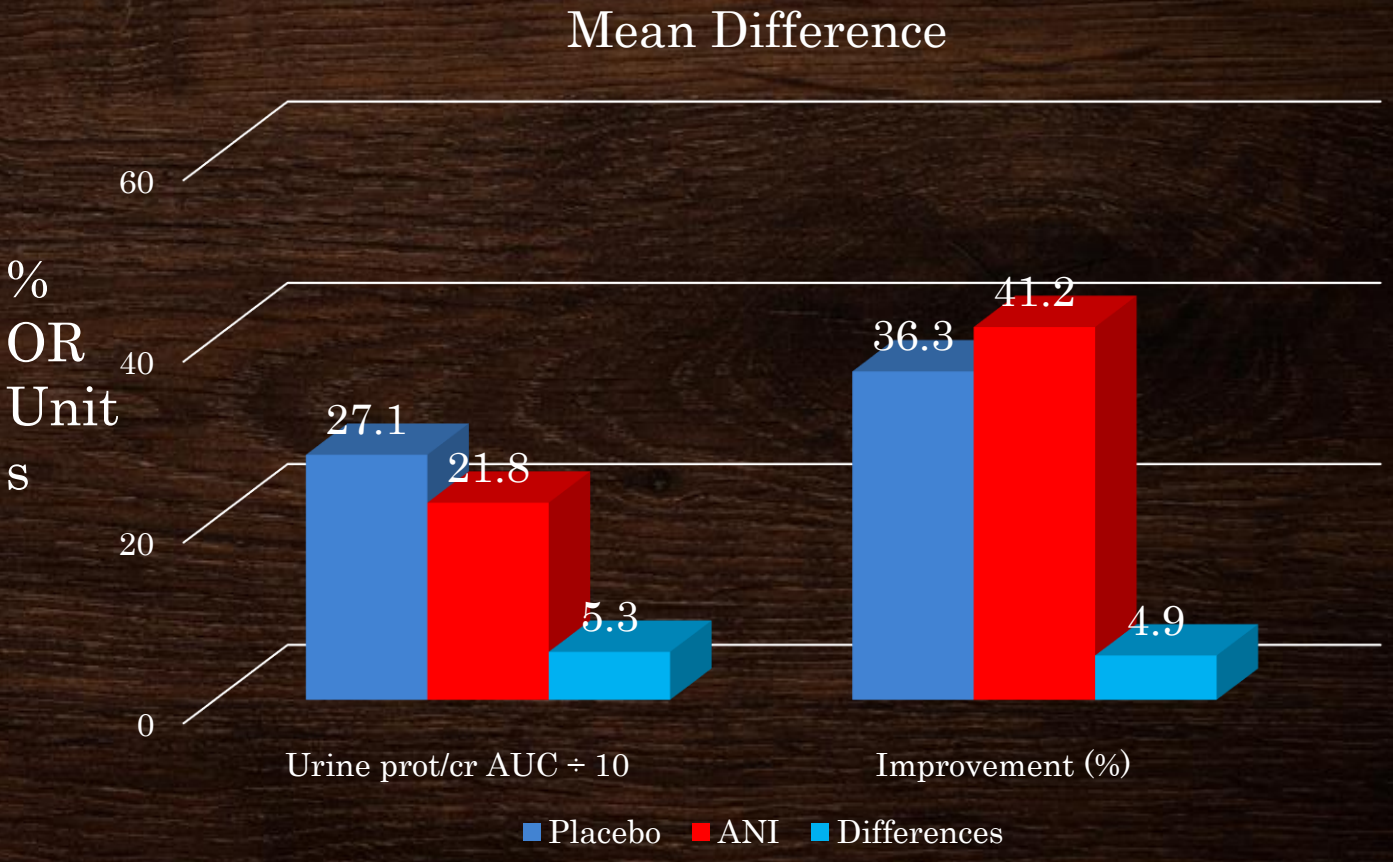
- Do S, Du JH, et al. ARD 2021, 80 (Suppl 10): abs OP0133
  - 676 pts >5 years HCQ
  - Retinal Tox: 6.8%
  - >10 yrs use—OR: 4.32 (1.99-12.5)
  - ≳ 2000 grams—OR: 15
- Alameda-Brasil C, Hanley J, et al. A&R 72 (Suppl10)
  - 1460 pts
  - Retinal tox: 1/1000 pt yrs at mean: 8.8 yrs
  - Cumulative tox: 1% at 10 yrs then increases by 1% per year

New compounds

Anifrolumab and SLE in Renal SLE

Morand ef, Furie r, et al. ARD 2021. 80 (Suppl 1): abs POS0691

- TULIP 1&2: 48 wk DB, placebo controlled trials
- Anifro: 300 mg IV q4 wks
- N=99 renal (N=45 anifrol; 54 placebo)
- Urine protein to creatinine ratio (UPCR mg/mg)>0.5 defined renal disease; improvement is >0.5 to ≤0.5 mg/mg
- Numerical, not statistical, differences



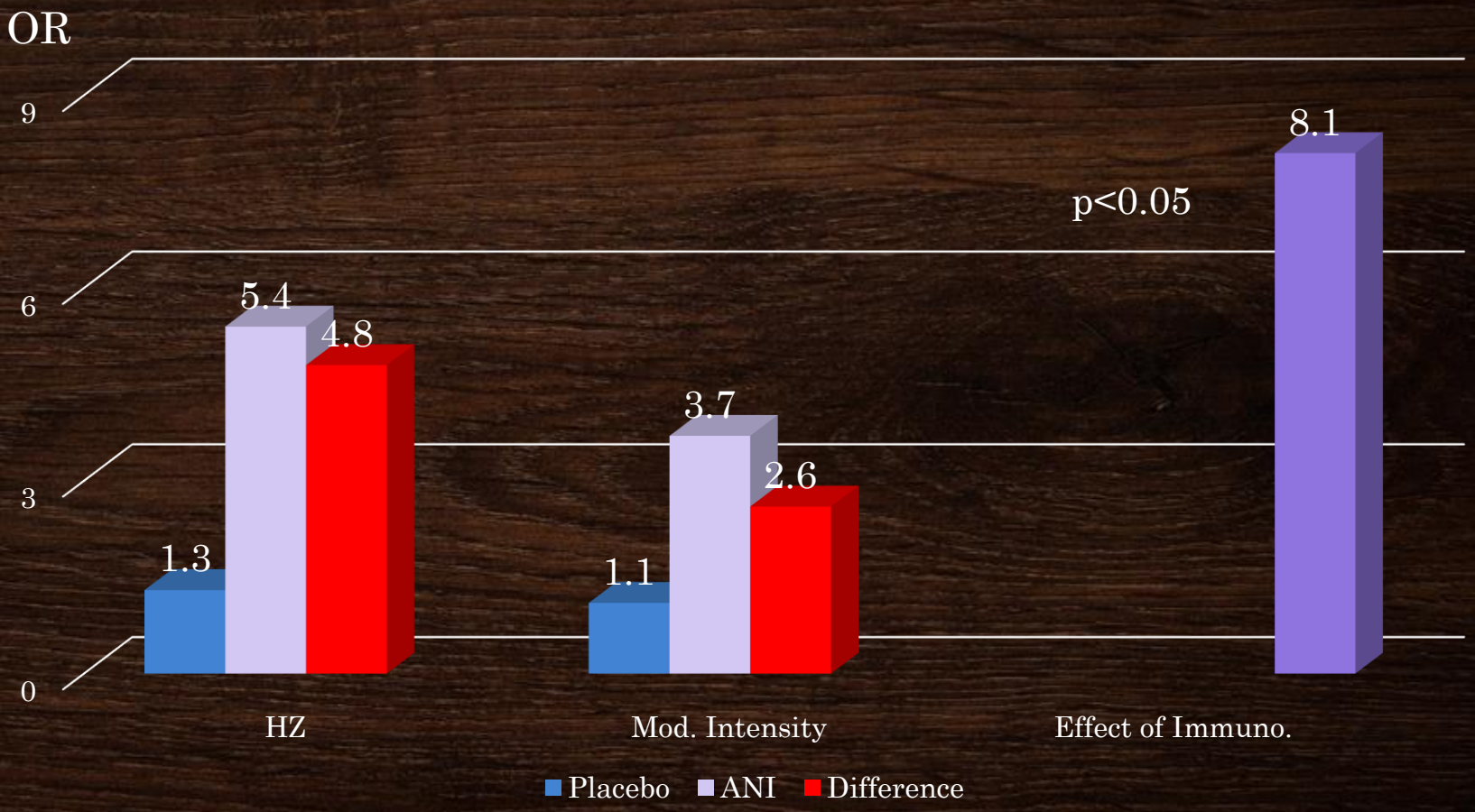
95% CI -161 to 54 -21 to 30.9

Conclusion: Numerical but NOT statistical evidence that Anifrolumab may affect the kidneys in SLE

Anifrolumab is associated with h. zoster in SLE

Merrill j, Kalunian k, et al. A&R 2020. 80 (suppl 1). abs 0849

- Phase 2 (MUSE) and Phase 3 (TULIP 1&2)
- N=459 ANI vs 466 Placebo

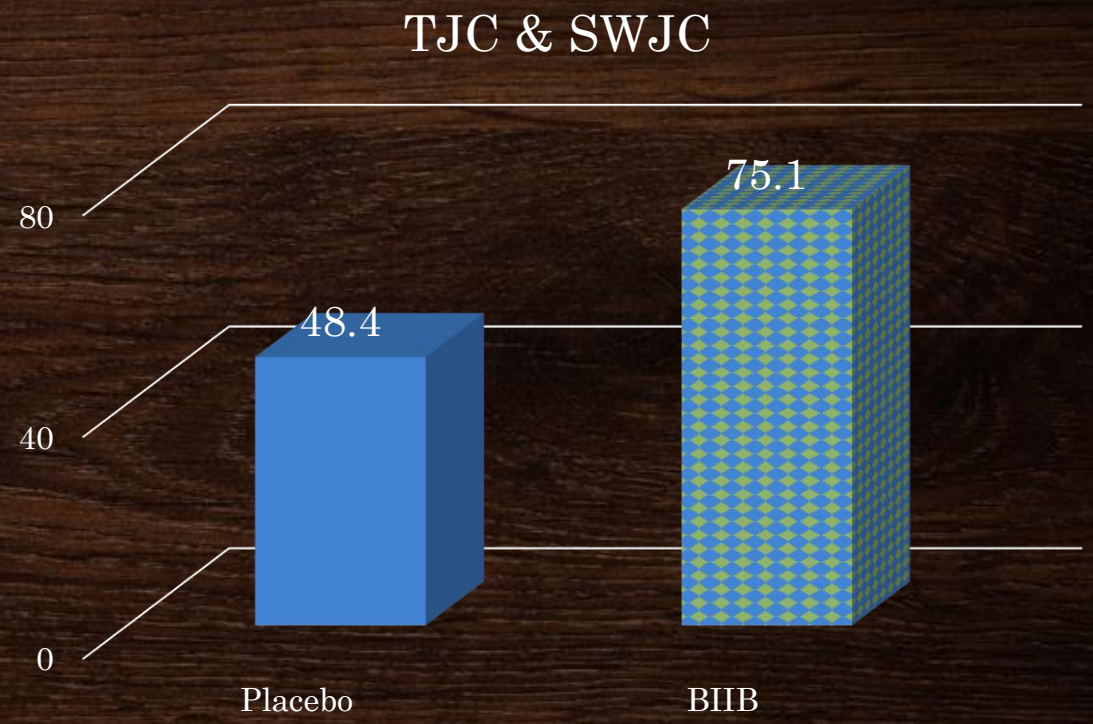


Conclusion: Anifrolumab appears to be associated with H. Zoster and immunosuppressives make it worse.

BIIB059 improved joint symptoms in SLE in a 24 wk, Phase 2 DB-RCT vs placebo

von Vollenhoven R, Furie R, et al. A&R 2021. 73 (suppl 10): abs 1747

- BIIB059 decreases interferon & other cytokines thru affecting plasmacytoid dendritic cells
- SLE by 1997 SLE criteria
- N=56 BIIB059 (450mg),56(?) Placebo
- >50% decrease of the sum of tender & swollen joints
- No idea if pts were on background SOC



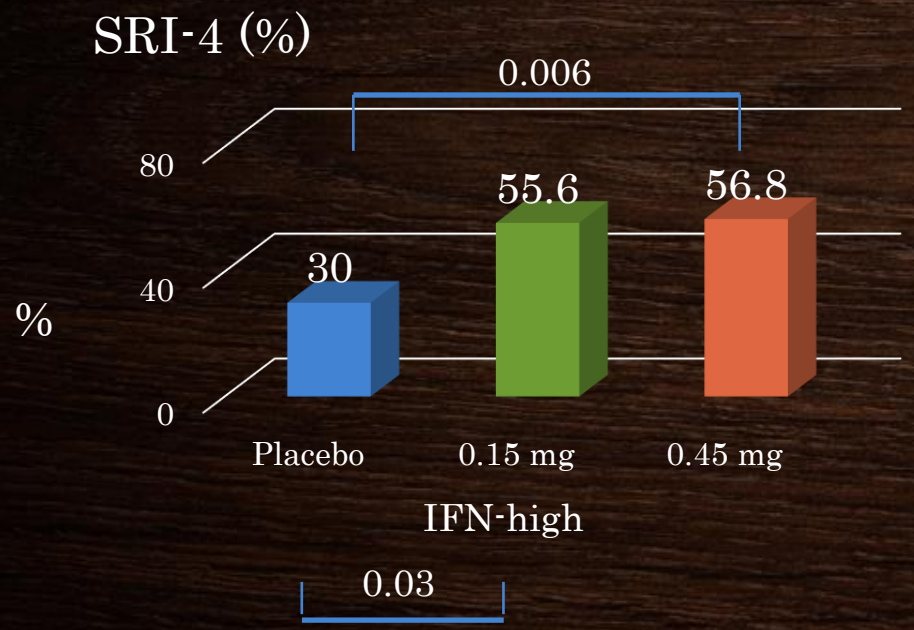
Least Square Mean >50% response
OR: 4.0 (1.6, 9.8) p=0.003

Conclusion: BIIB improves joints BUT do not know if on background SOC

Iberdomide decreases B-cells, Plasmacytoid Dendritic cells, INCR reg.T cells)

Lipsky P, Van vollenhoven R, et al. A&R 2020. 72 (suppl 10): abs 0851

- DB-placebo-controlled dose-ranging study
- Iberdomide 0.15, 0.3, 0.45 mg, placebo for 24 weeks



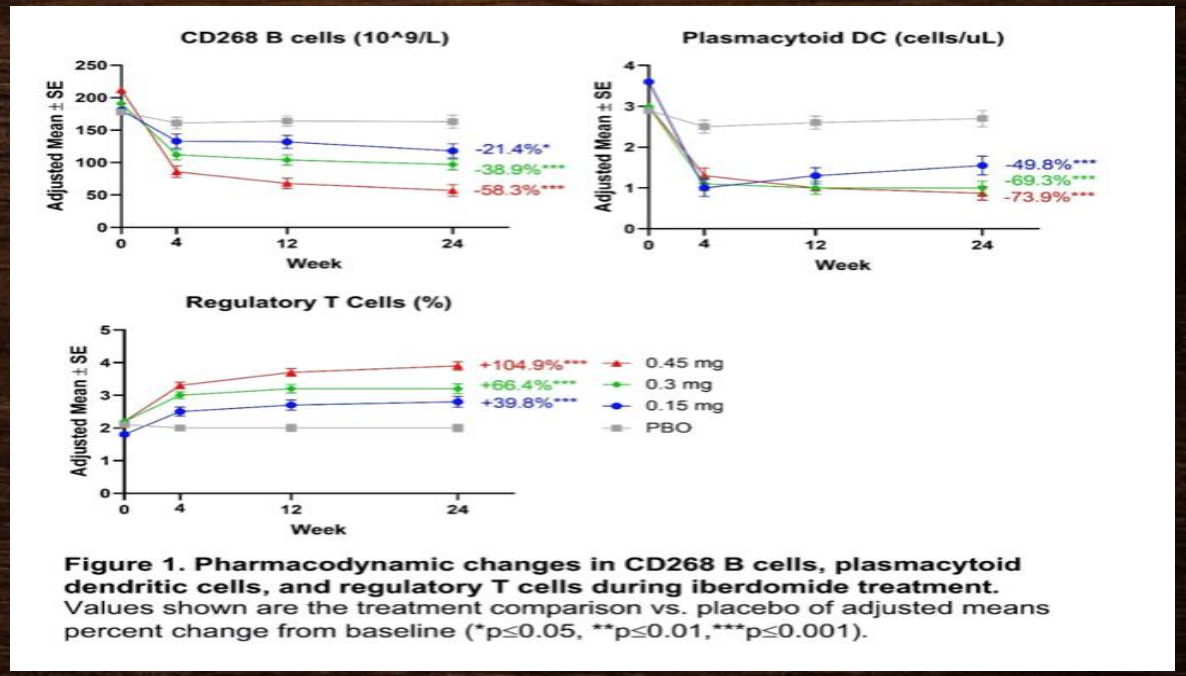


Figure 1. Pharmacodynamic changes in CD268 B cells, plasmacytoid dendritic cells, and regulatory T cells during iberdomide treatment. Values shown are the treatment comparison vs. placebo of adjusted means percent change from baseline (*p≤0.05, **p≤0.01,***p≤0.001).

Decreased, increased IL-2, decreased anti-dsDNA

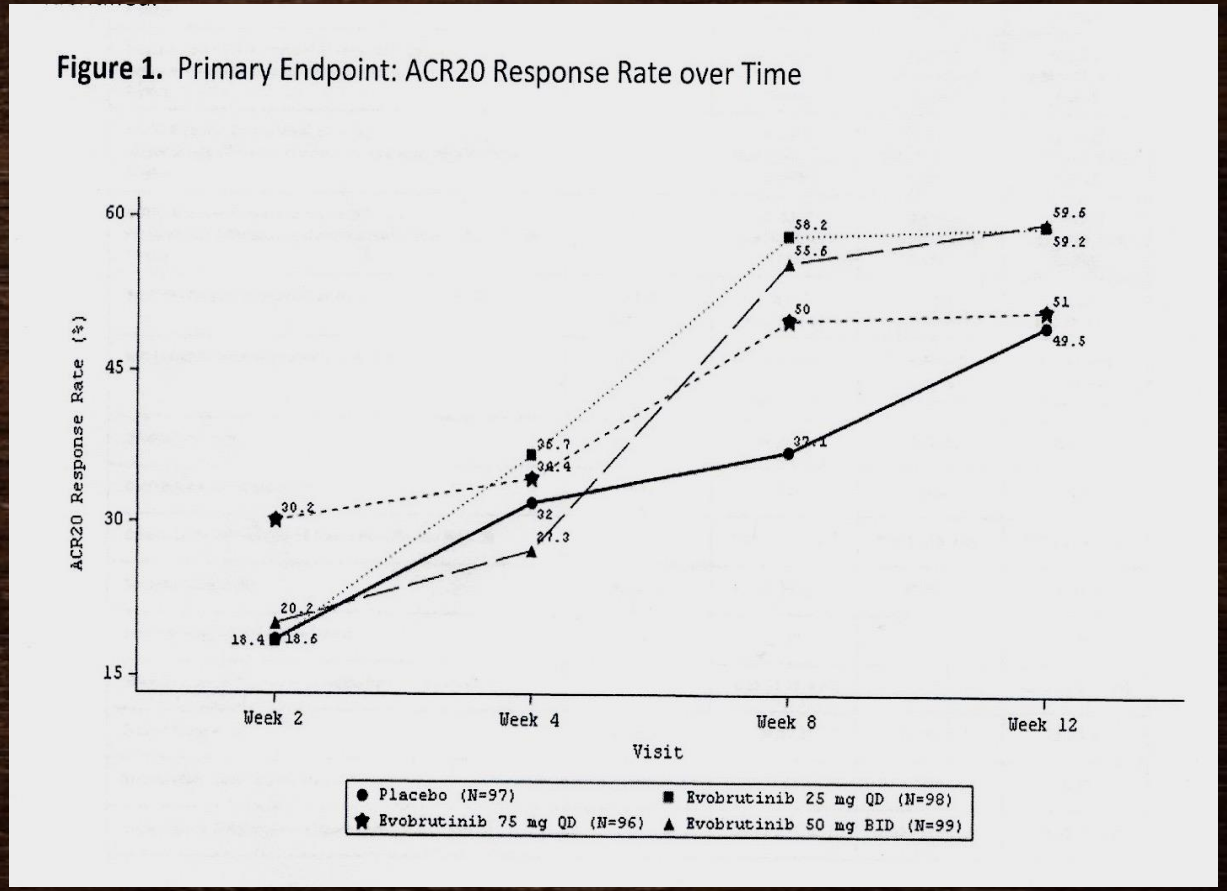
Conclusion: Iberdomide reduced IFN1 & B-cell/plasma and many others

Evobrutinib (btk inhibitor) in mtx-ir ra pts

peterfy c, buch m. a&r 2020. 72 (suppl 10): abs 2012

- N=390 RA pts
- NSAID + Pred ≤10mg qd allowed
- Evobrutinib 25, 75, 100qd vs placebo, =75/gp
- Primary outcome:
  - ACR20 at 12 wks
- Secondary outcomes:
  - ACR 50/70
  - DAS28-CRP
  - DAS28 CRP< 3.2+<2.6
  - RAMRIS
  - No data so assume no differences

(or they would have detailed them)



Conclusion: This BTK inhibitor did not show difference from placebo but placebo response was VERY high(49.5%)

Encouraging results after the irreversible BTK inhibitor (Orelabrutinib) in SLE: phase IB/2A DB-RCT

Zhu X, Liu S, Zhang X et al EULAR 2022 ARD 81(Suppl 1):LB004

- N = placebo (14), 50 mg q.d. (14), 80 mg q.d. (13), 100 mg q.d. (14)
- 12 week trial.
- Full receptor occupancy at 24 hours at ALL doses.
- AE's:
- placebo: 85.5
- 50 mg: 80.0
- 80 mg: 93.3
- 100 mg: 97.1
- SAE: 3 BT K (one was grade 3): placebo: 0.0. Deaths: 0.0

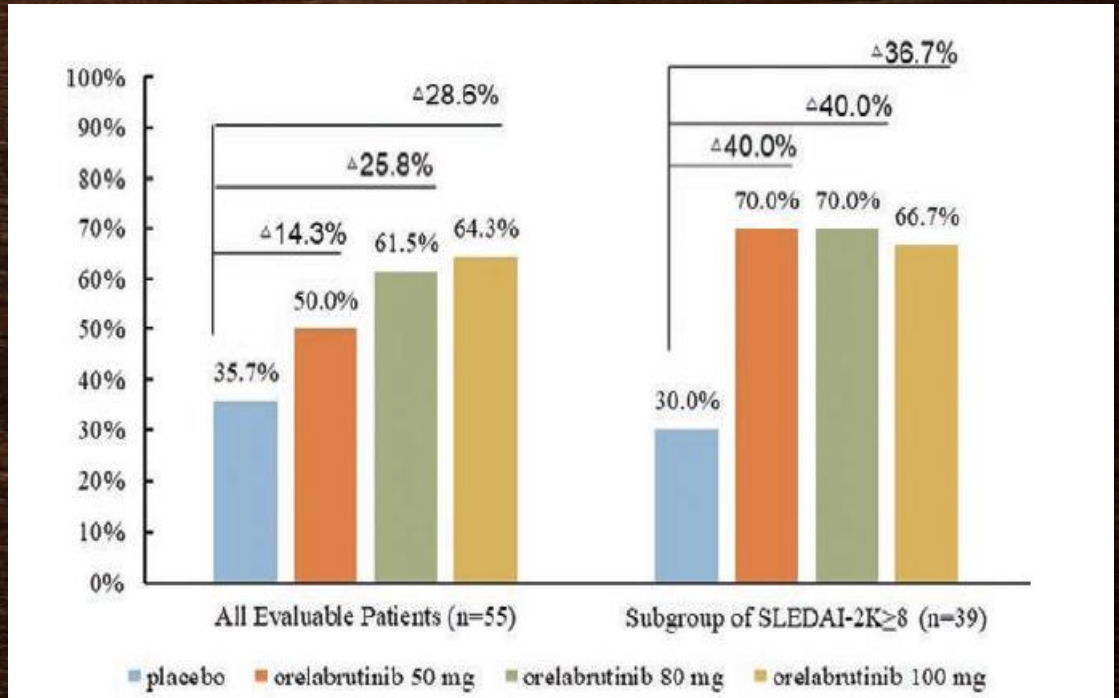


Figure 1. SRI-4 response rates at week 12.

Conclusion: encouraging phase 1B/2A, trial. Note, however: irreversible binding!

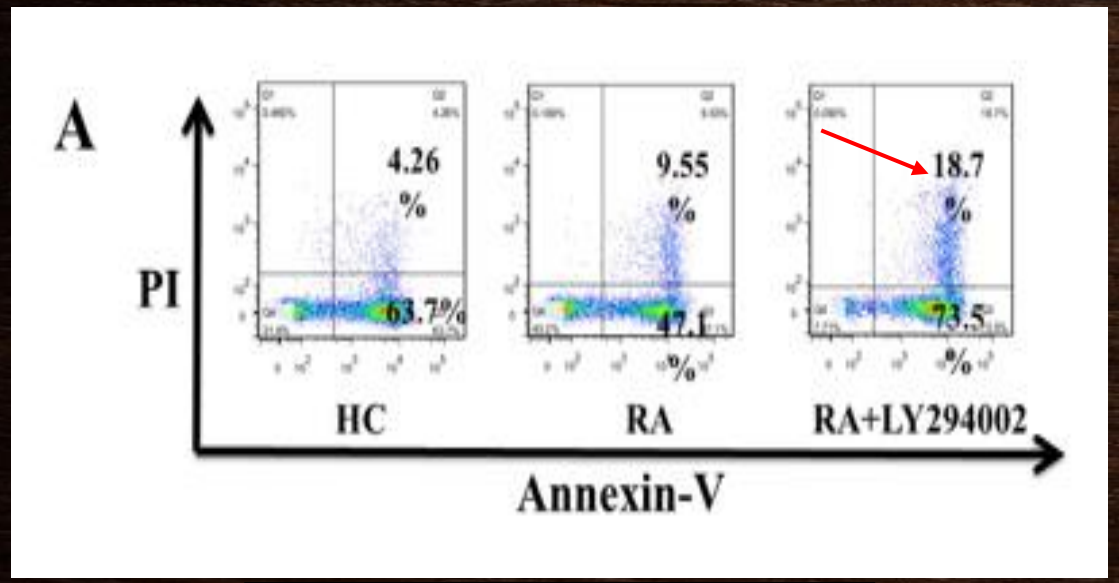
RA

Pathogenesis

Neutrophil apoptosis thru pi3k inhibitor (ly294002) improves cia mouse disease

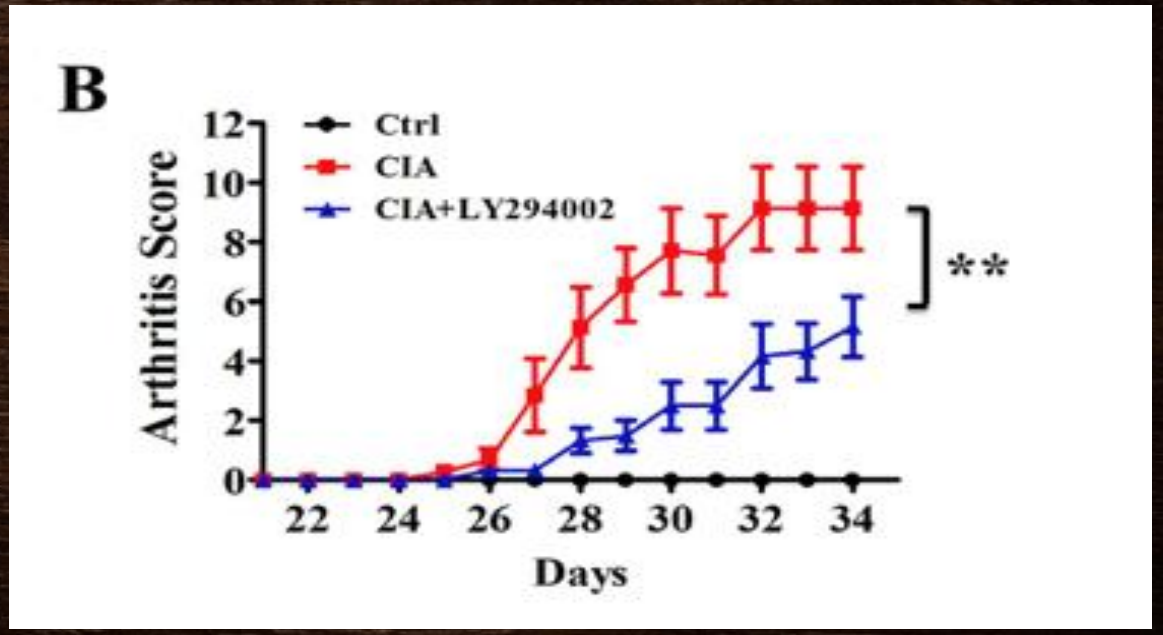
Huang x, li t, etal. A&R 2020. 72 (suppl 10): abs 0792

- PMN APOPTOSIS IS DELAYED IN RA
- PI3K INHIBITOR SPEEDS APOPTOSIS IN VITRO



Increased apoptotic PMNs

- THERAPEUTIC LY294OO2 IMPROVES CIA-TYPE RA



Conclusion: Shows what neutrophils may do in RA, and possible treatment.

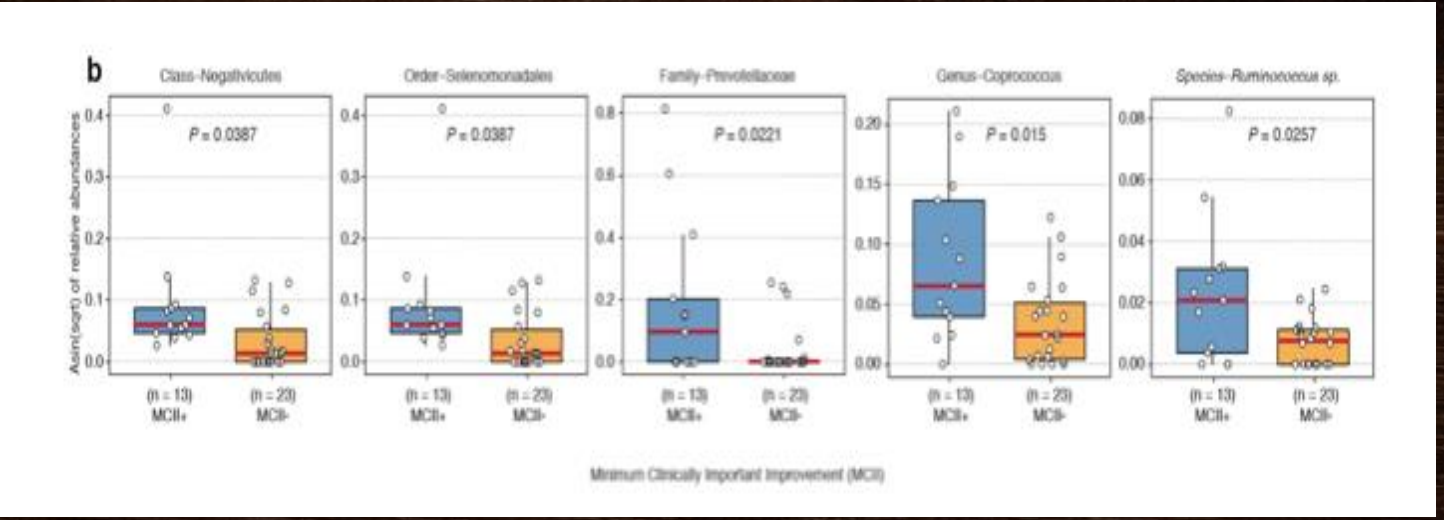
Clinical

Correlation of gut microbiome with improvement in the cdai in ra

gupta v, Cunningham k, et al. a&r 2020. 72 (suppl 10): abs 0795

- 36 RA pts
- 72 stool samples over time (how long?)
- Used minimally clinically important improvement (MCII) in CDAI
- What about worsening?

- MCII: ≥ 4 when baseline CDAI is <10; ≥ 6 when baseline CDAI is 10-22; ≥12 when baseline CDAI >22



Conclusion: Gut microbiome associates with improved CDAI (?What about worsening; what about linearity—not just a dichotomous analysis)

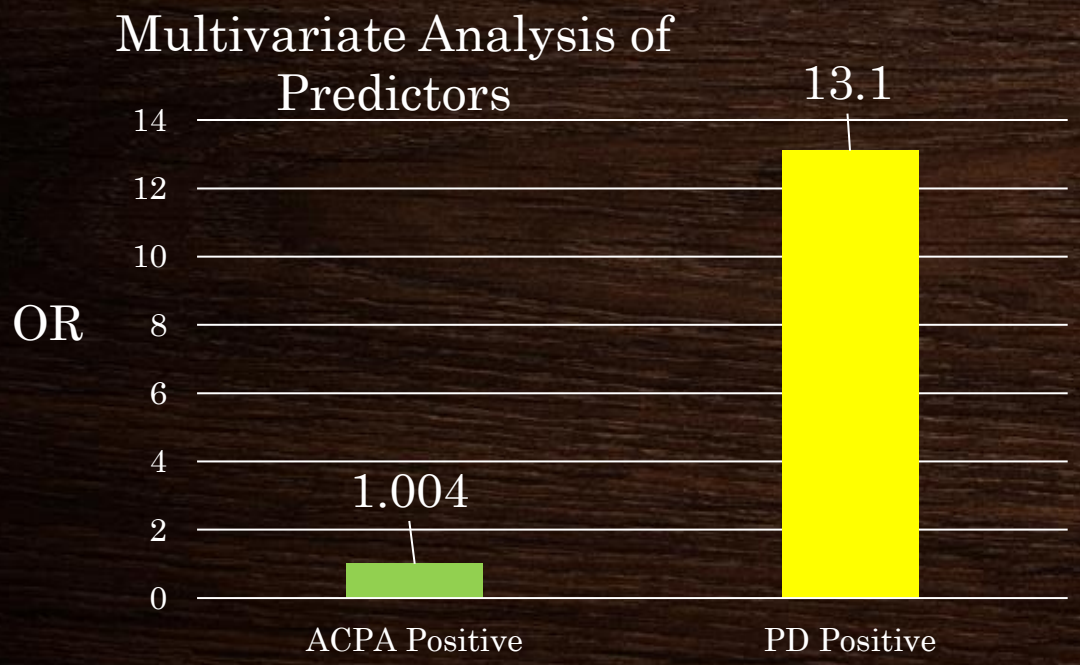
PREDICTION

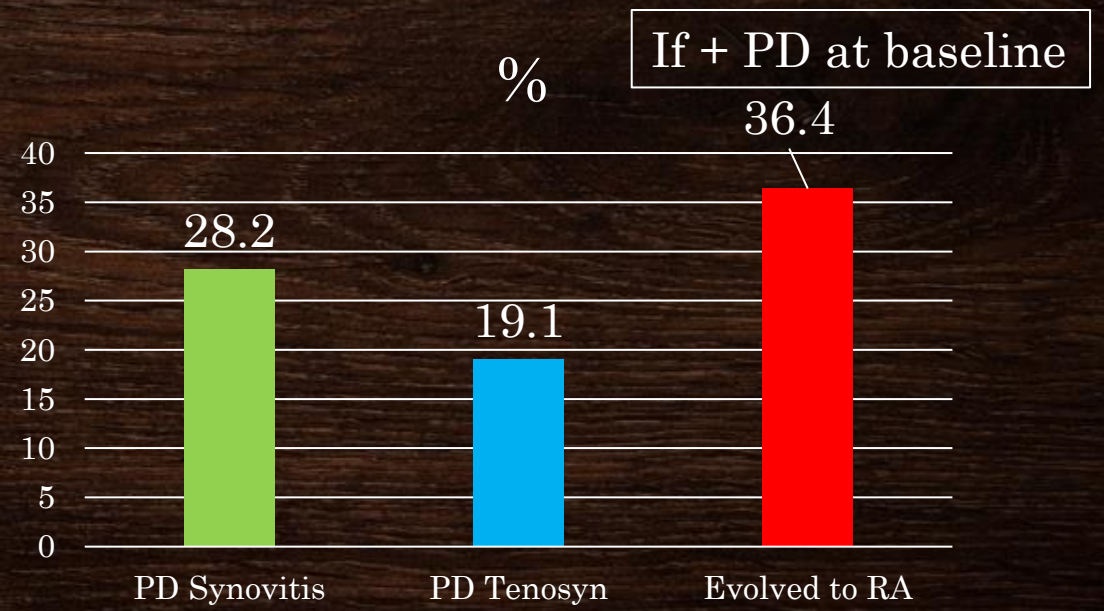
Ultrasound predicts RA in patients with arthralgia

Lopez K, Castrejon I, et al. A&R 2021. 73 (Suppl 10): abs 1199

- Retrospective
- N=110 clinically suspect arthralgias
- F/U for 12 months

- All US by the same rheumatologist
- PD ≥ grade 1 joints or tendons





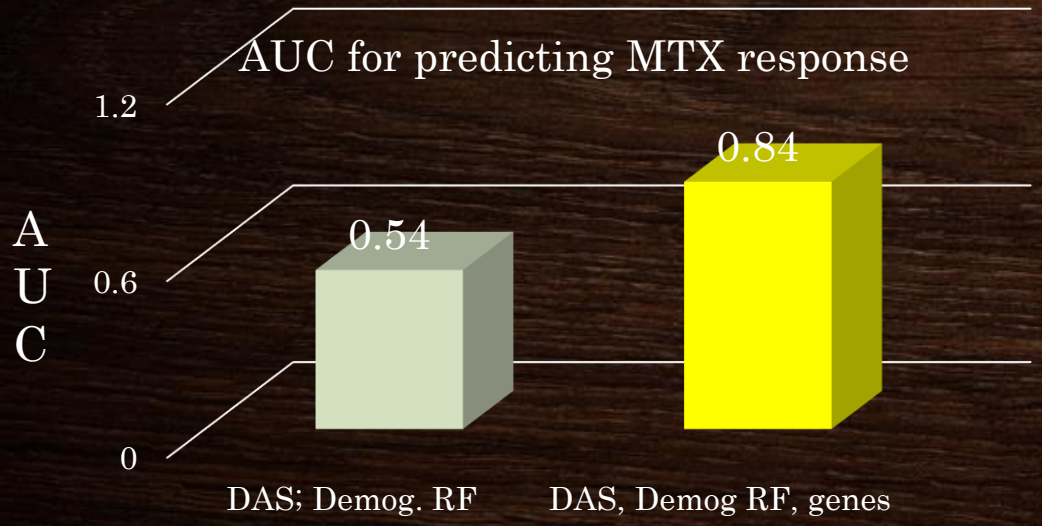
Conclusion: In a retrospective analysis over 1 yr, Positive Power Doppler and Positive ACPA predicted evolution to RA

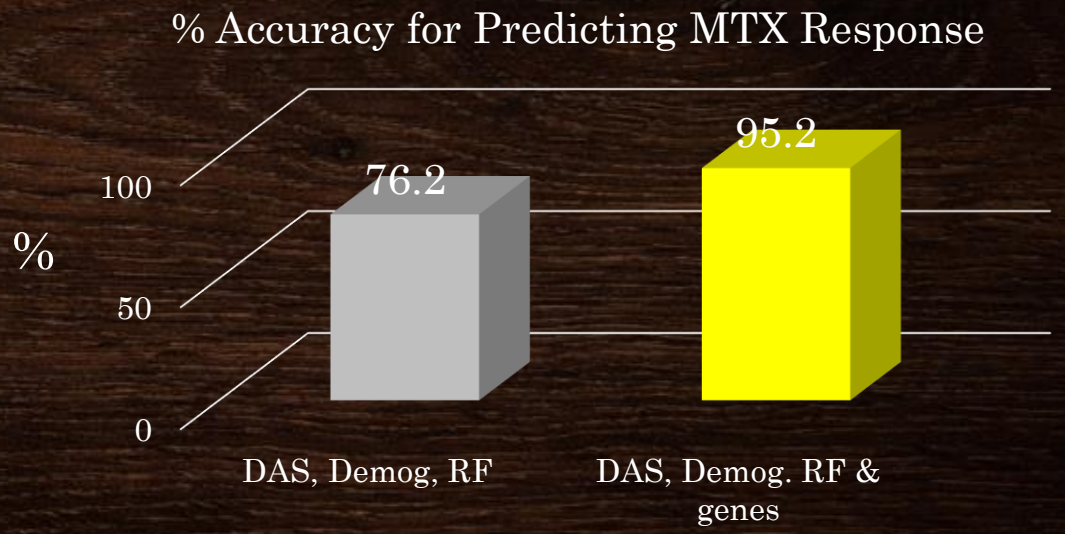
Individualized prediction of response to MTX in RA: added effect of using genomic data

Myasoldova e, Athreya a, et al. A&R 2020. 72 (suppl 10): abs 2003

- N=647 RA pts: 336 UK, 307 European
- DAS28: 5.65
- GWAS found 160 SNPs associated with RA& MTX metabolism

- EULAR criteria (good or moderate)
- Used machine learning for analysis
- SNPs that improved prediction CASC15, B3GNT2, PARK2, ATIC





Conclusion: Adding SNPs to baseline DAS, Demographics and RF seems to improve individual prediction of response to MTX by 20-30%

Treatment

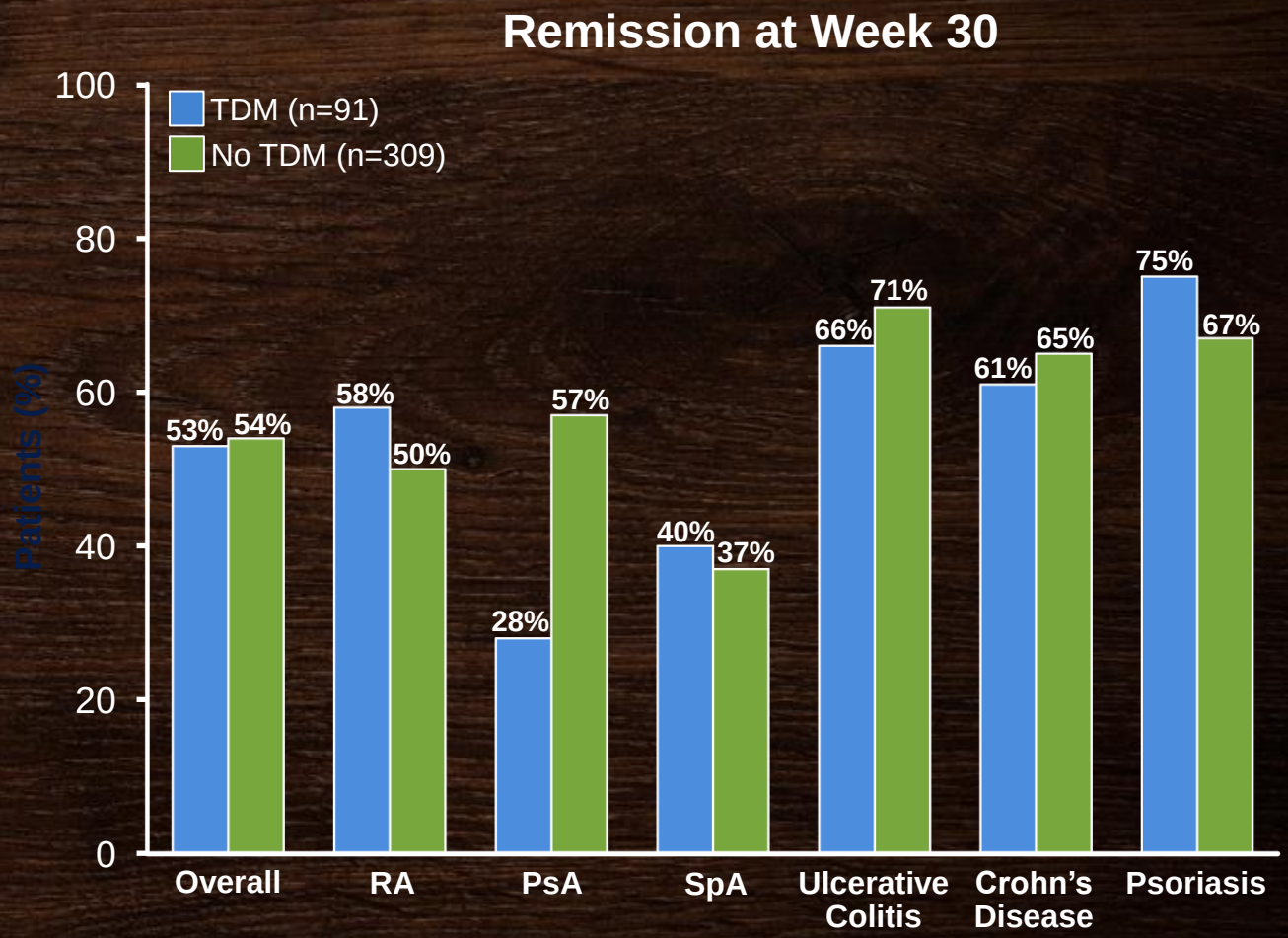
NOR-DRUM Study: Therapeutic Drug Monitoring(TDM) Versus Standard Treatment With Patients Initiating Infliximab

TDM strategy

- Increase the dose (increase by 2.0-2.5 mg/kg to maximum 10 mg/kg, decrease the dose interval by 2 weeks to a minimum of 4 weeks)
- Decrease the dose (increase the dose interval by 2 weeks to a maximum of 10 weeks, decrease dose by 2.0-2.5 mg/kg)

Achieving remission at week 30-**TDM did not lead to improvement in remission rates or other efficacy outcomes versus standard therapy**

- Safety- no differences in AEs **except- There were fewer infusion-related reactions in the TDM arm (5% versus 16%)**



NOR-DRUM: NORweigen DRUg Monitoring.
TDM: therapeutic drug monitoring.

Syversen SW, et al. *Ann Rheum Dis.* 2020;79(suppl 1):12. Abstract OP0017.

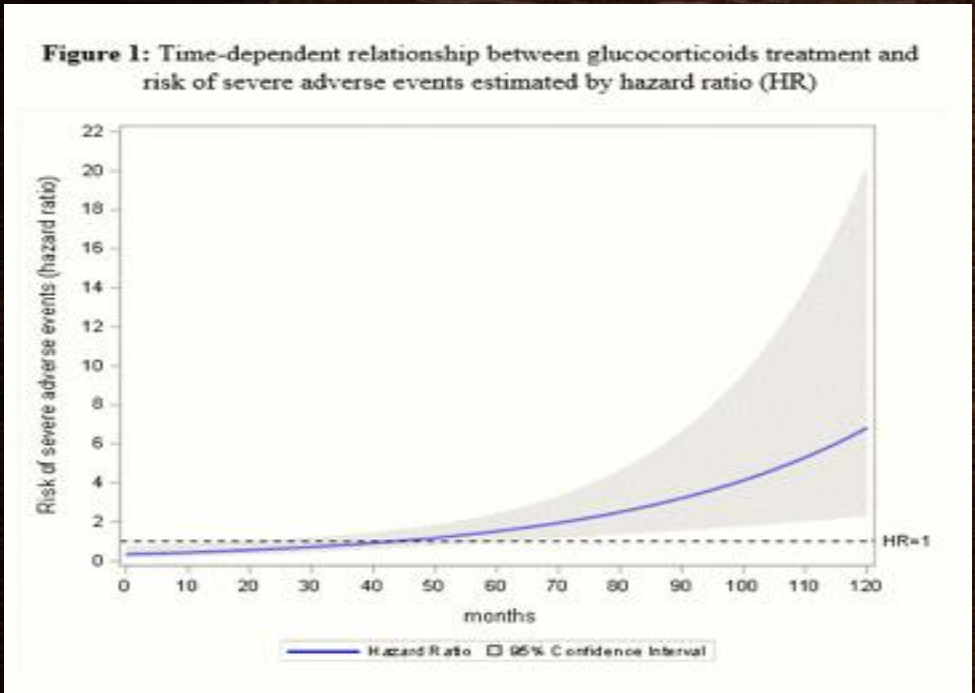
Marketed medications

10 year risk of severe outcomes using very low dose corticosteroids in RA

roubille c, coffy a, et al. a&r 2020. 72(suppl 10): abs 1998

- French cohort study (ESPOIR)
- N=608
- Mean CS: 2.8(2.8)mg/d

- Total dose: 8468 mg—70% during first 6 months
- F/U: 44.6 (40.1) months
- Used propensity scoring—What factors?

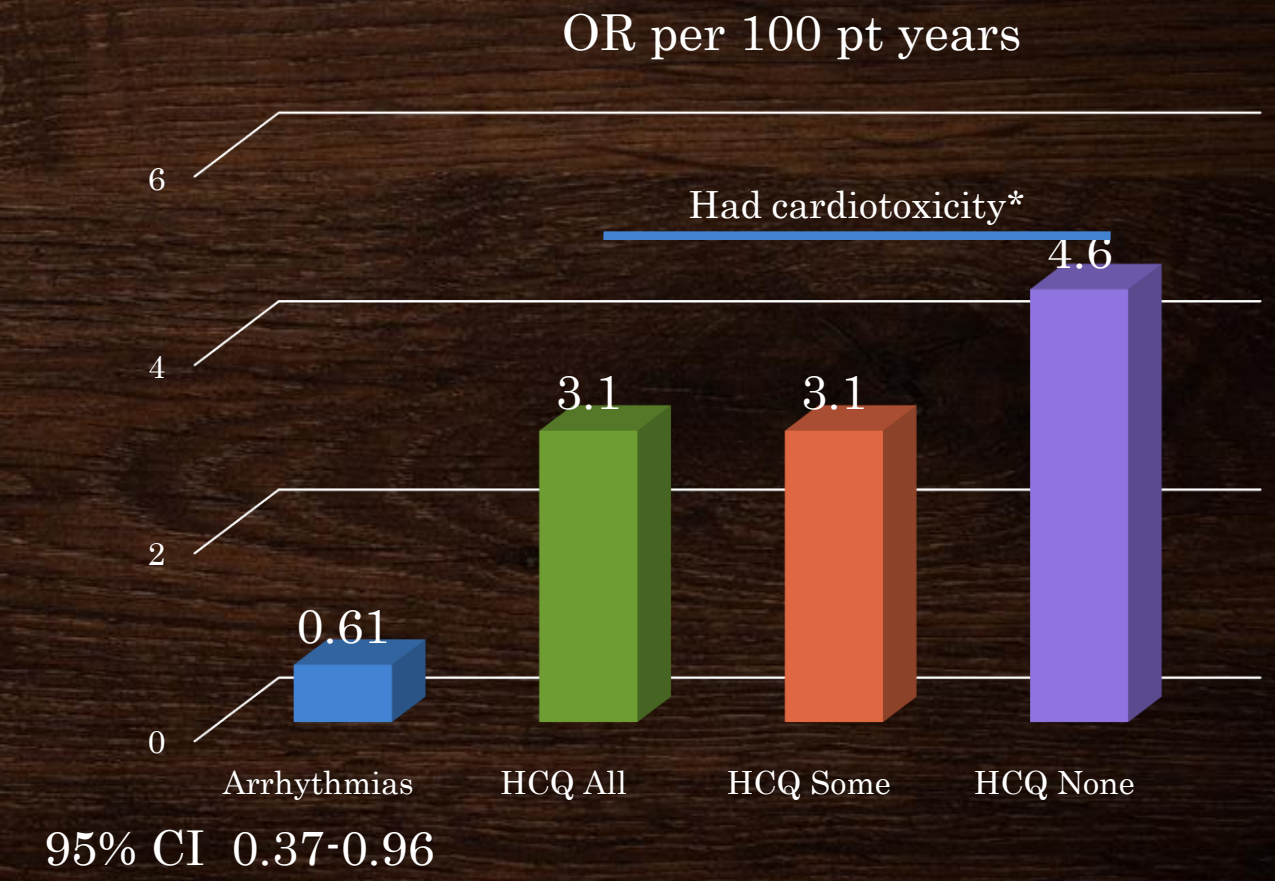


	p value
Any severe AE	0.035
Death	0.10
CV disease	0.18
Severe infection	0.009
Fractures	0.16

Hydrochloroquine (HCQ) is not cardiotoxic in RA

Restrepo jf, Escalante A, et al. A&R 2020. 72 (Suppl10): abs 1999.

- Patients came from "Public, private, military, VA", but do not know how recruited.
- N= 1328,
- 8336 patient years
- N= 114 used HCQ at all visits (338 visits)
- N= 891 used HCQ at no visits (3746 visits)
- N= 323used HCQ at some visits (1742 visits)
- Cardiotoxicity was MI, arrhythmia, cardiomyopathy



95% CI 0.37-0.96

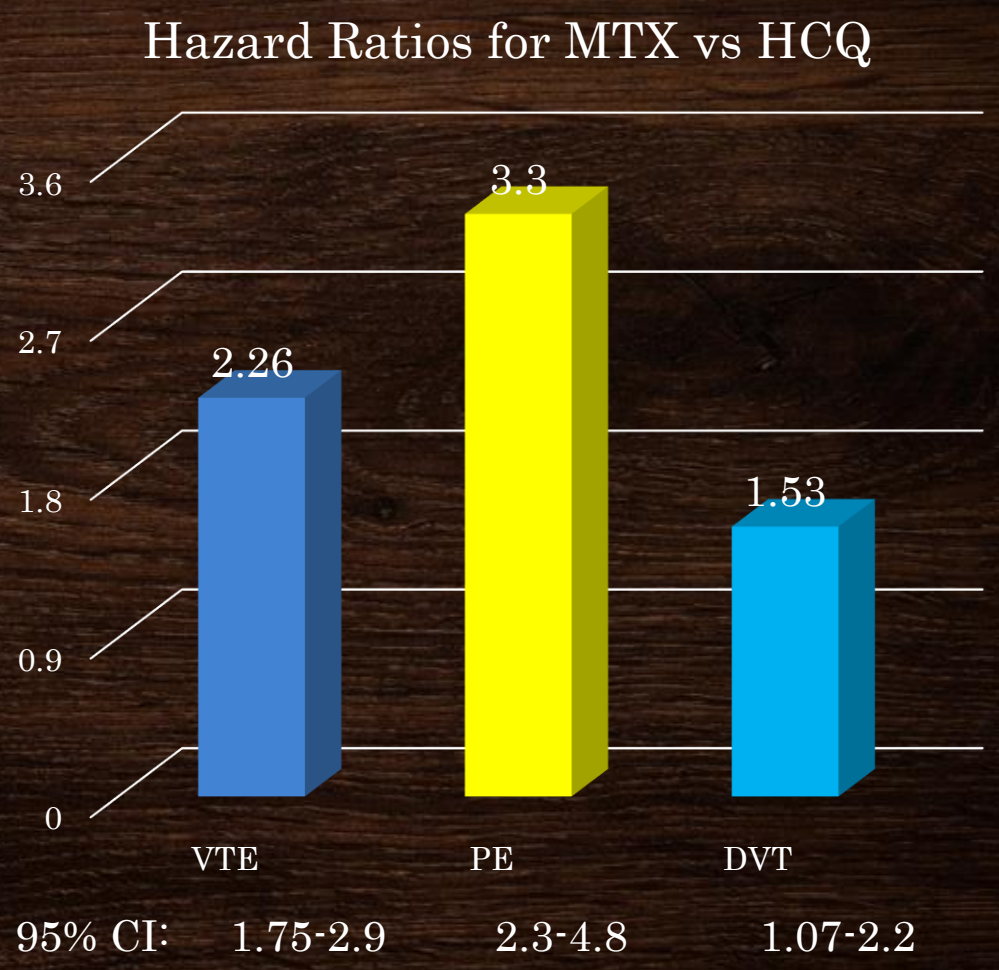
Conclusion: HCQ NOT associated with cardiotoxicity. Possible association with less toxicity.

HCQ decreases VTE in RA compared to MTX

He M, Pawar A, et al. A&R 2020. 72 (suppl 10): abs 2000

- Medicare claims database 2008-2017
- ≥ 65 yrs: mean age: 74 yrs
- Excluded prior VTE, cancer, anti-coag, CQ
- Outcome: VTE or PE or DVT (inpt or outpt)
- 26534 pts; propensity score matched for demographics, co-morbidities, meds, procedures and medical care visits
- While statistical differences among VTE & controls, none were clinically significant

  (eg, statins used: 49.1% vs 48.9%)
- 208 MTX & 83 HCQ had VTE during 190 days
- CAVEAT: No dosing, not clear if any used MTX & HCQ combo



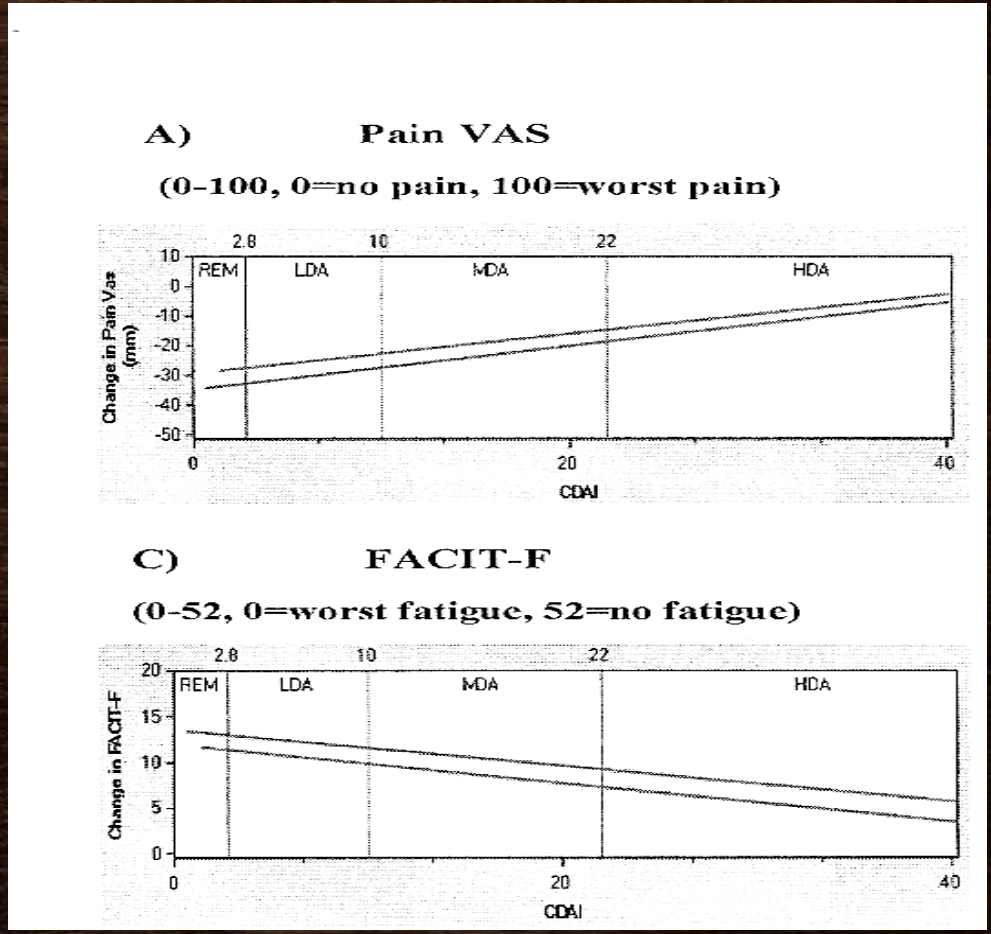
Conclusion: HCQ is associated with about 50% decreased rate of VTE,PE or DVT vs MTX

JAKi

Baricitinib 2 mg qd in RA from 2 trials does not separate from placebo

Bingham C, jia b, et al. A&R 2020. 72 (suppl 10). Abs 1228.

- Data from 2 phase 3 studies
- actual N not given but I would assume several hundred pts(?)
- bDMARD-IR & csDMARD-IR
- Baricitinib 2 mg



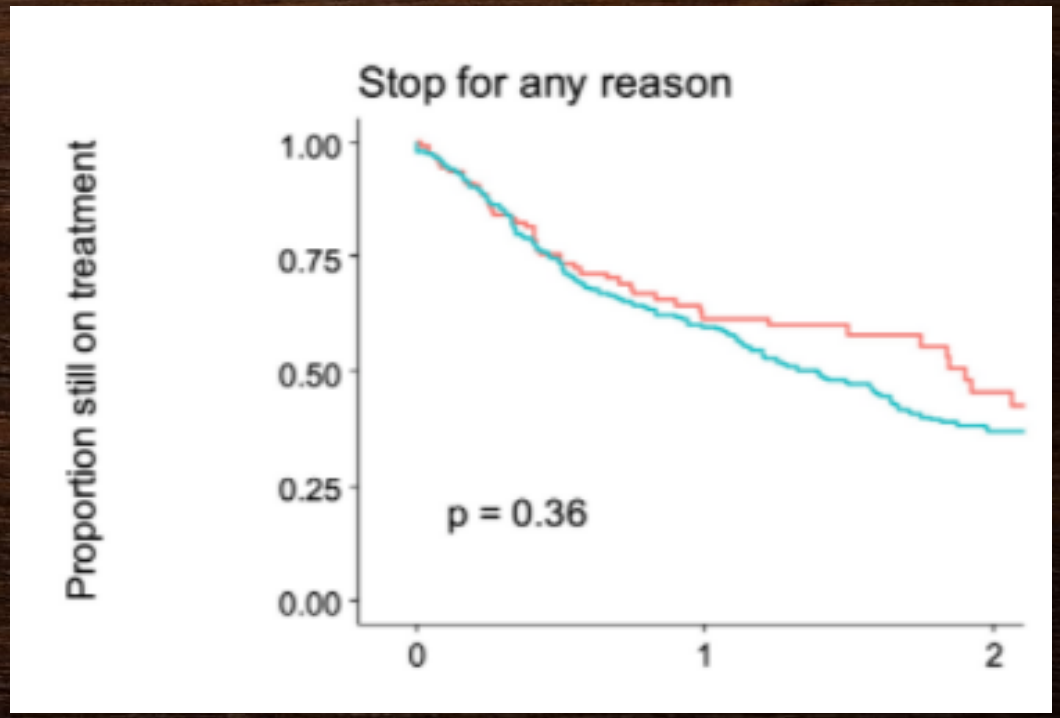
No Difference between switching from JAKi to another JAKi vs JAKi to bDMARD

Pombo-Suarez m, Sanchez-Piedra C, et al. A&R 2021. 73 (Suppl 10): abs 1442

- Nested cohortstudy within 14 national RA registries
- Drug retention rates or DAS28 response over 1 year
- N= 154 JAKi to JAKi

N=554 Jaki to bDMARD

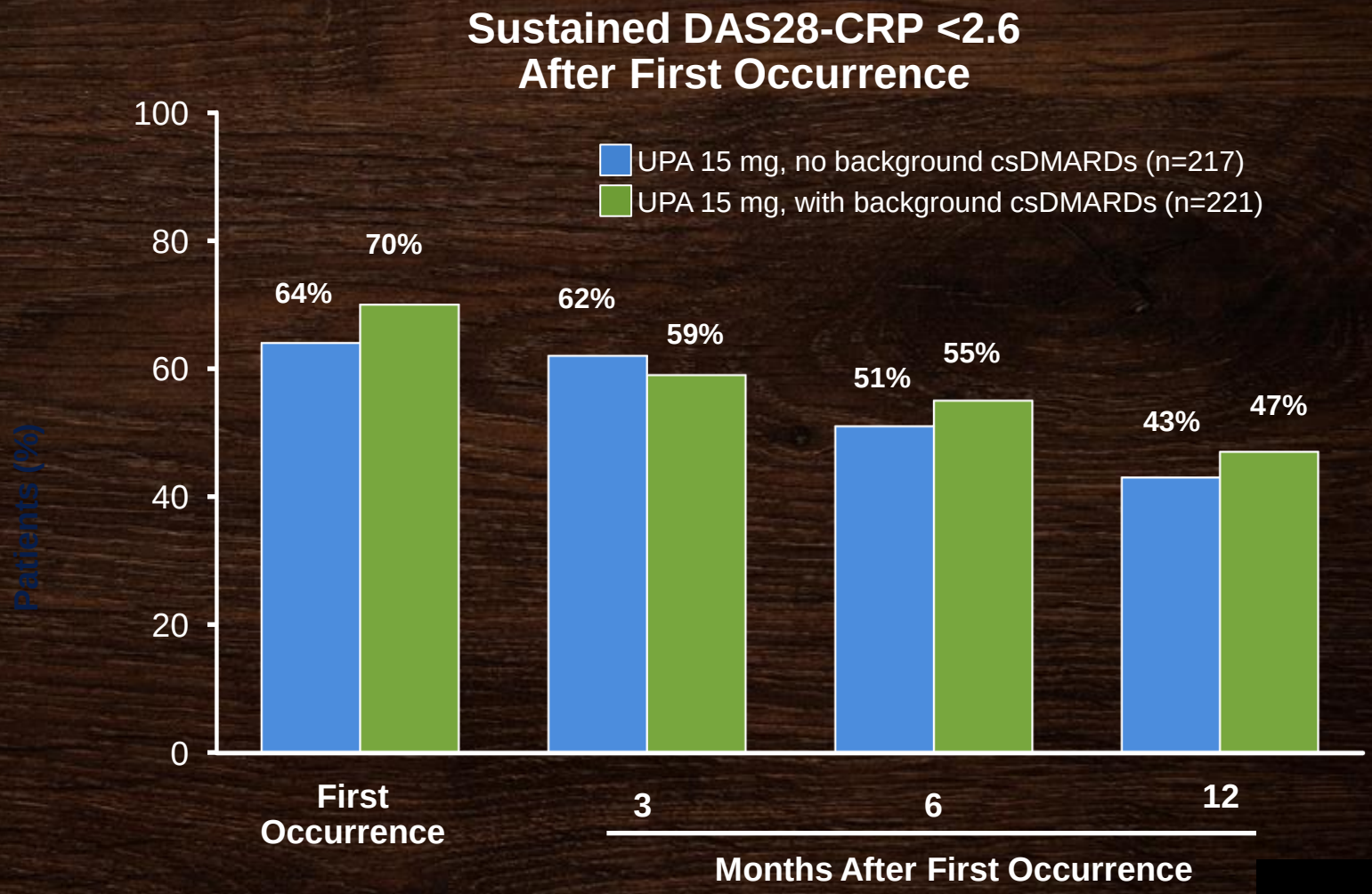
- No differences if stopped first drug for ineffectiveness, AE, other
- Note: subject to selection bias



Conclusion: JAKi to JAKi same as JAKi to bDMARD

UPADACITINIB--SELECT-MONOTHERAPY and Sustainability of DAS28-CRP Remission

- Similar rates of DAS28-CRP remission were achieved and sustained with upadacitinib 15 mg regardless of use of background csDMARDs
- **32.8% percent loss of DAS28-CRP "remission" over 12 months**
- Approximately 85% of patients who lost remission recaptured it



Analysis through up to 84 weeks.

Kavanaugh A, et al. *Ann Rheum Dis.* 2020;79(suppl 1):327-328. Abstract THU0207.

A Small Seque

bDMARD and tsDMARD plus MTX

DRUG	MTX ADDS TO EFFICACY
ABATACEPT	YES
TNF INHIB	YES
TOFACITINIB	NO
TOCILIZUMAB	NO
RITUXIMAB	?? PROBABLY BUT NO ACTUAL DATA

Burmester G. *Ann Rheum Dis*. 2017;76:1279-1284

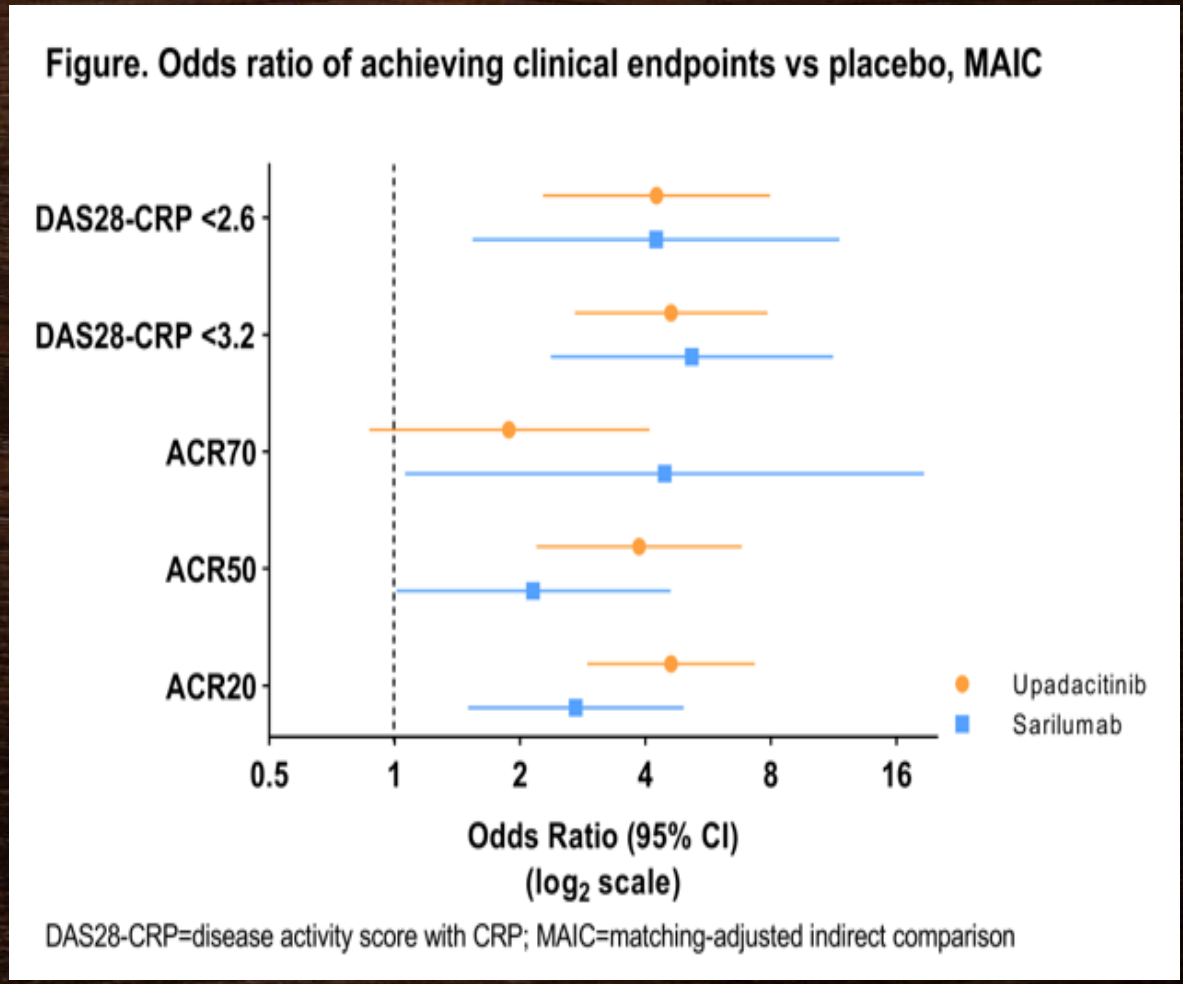
Takahashi,N,Kojima T et al J Rheum 2015. 42:786-793 doi 10.3899/jrheum.141288

Sarilumab vs Upadacitinib in RA

Huizinga t, choy e, et al. A&R. 2020 72 (suppl 10): abs 0827

- DB-RCTs for 24 weeks (Sari & Upa)
- Matching adjusted indirect comparison (MAIC) where patient level data from one trial is matched to aggregated data from the other trial
- Matching for age, TJC, SwJC, CRP
- N= 89 Sar/96 Upa after matching

Conclusion: Sarilumab equals Upadacitinib for efficacy in RA. AEs not compared



Abatacept Prevents the Development of RA—DB-RCT vs Placebo—6 months RX plus 12 months observation

Rech J, Kleyer A, et al. EULAR 2022. ARD. 81 (Suppl): POS 0531

- N=49 Aba 125mg SQ X 6 mos; 49 Placebo
- Inclusion: ACPA positive plus MRI "inflammation" (? BME)
- % Developing RA (by 2010 ACR/EULAR criteria (?))

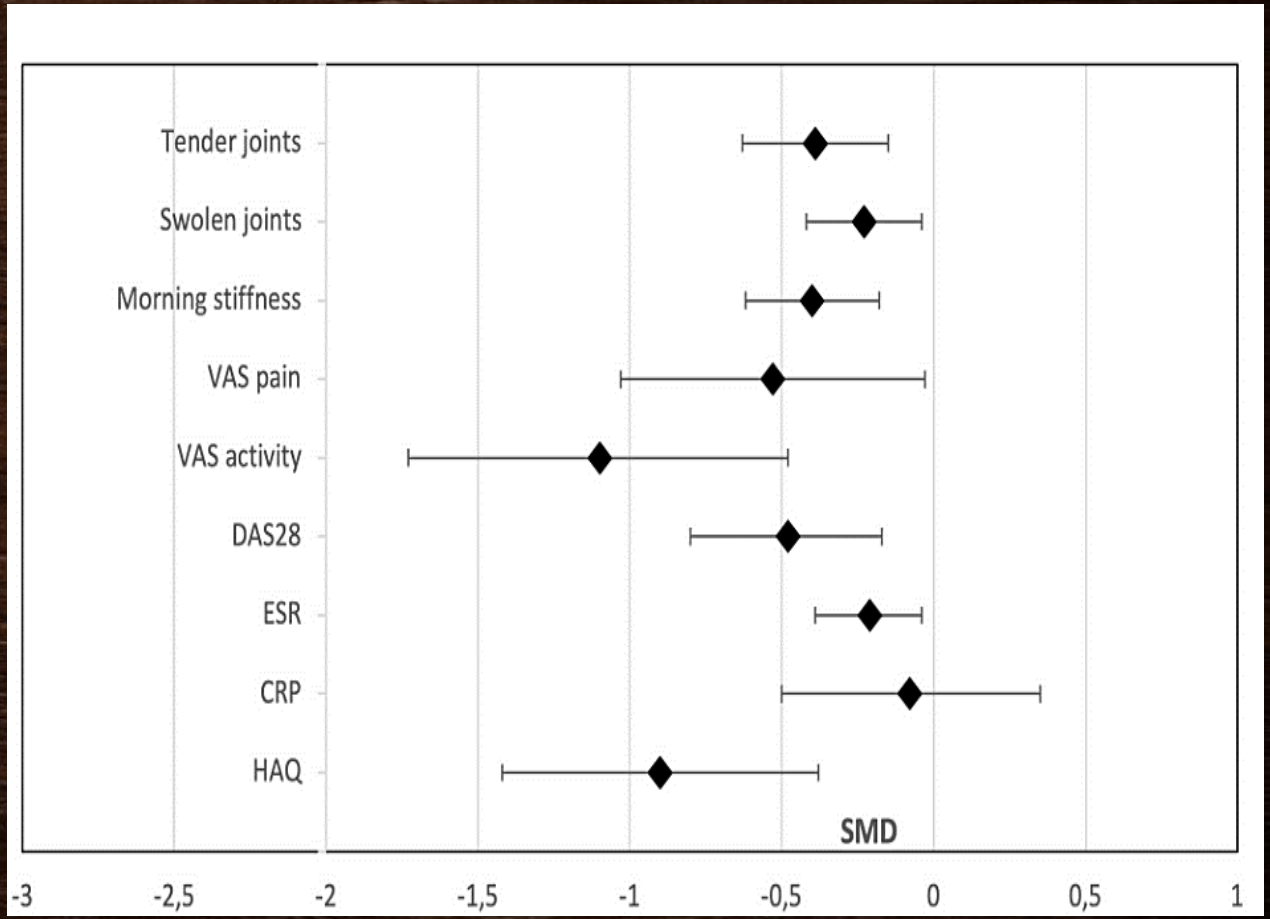
Conclusion: 6 months of ABA prevented development of RA over 12 subsequent months

Supplements

Effect of Polyunsaturated fatty acids on Rheumatic Disease Activity: SLR and Meta-analysis

Sigaux J, Mathieu S , et al. A&r 2021. 73 (Suppl 10): abs 1682

- 43 articles (31 RCTs)
- 732 rheumatic disease pts
- 0-3 or 0-6 fatty acid
- No difference between n-3 and n-6
- Low dose (< 2 gm/d) < high dose (> 2 gm/d)

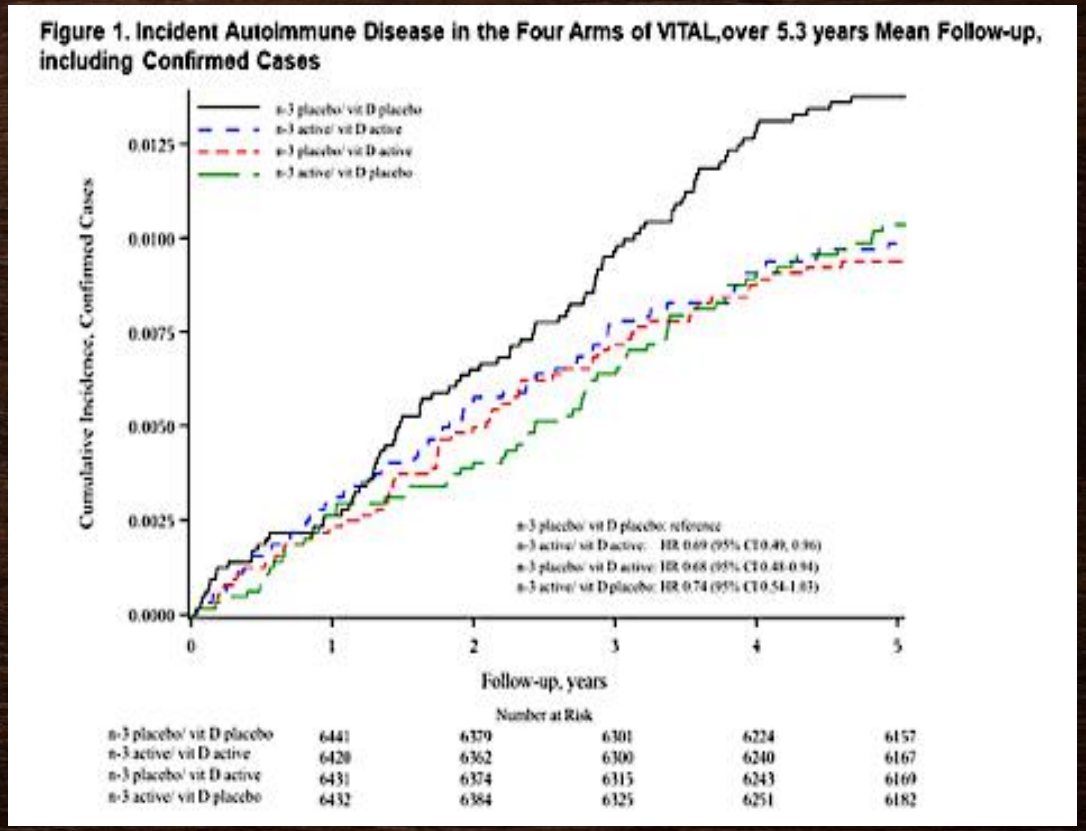


Conclusion: Polyunsaturated fatty acids improved multiple aspects of RA disease activity

Nationwide DB-RCT comparing Vit D (2000 IU/d) , n3 fatty acid (1000 mg/d),their Combo & placebo to decrease autoimmune disease incidence

Hahn j, cook n, et al. a&R 2021. 73A(suppl10): abs 957

- N=25,871 pts
- Dx confirmed by med. Record review
- ARMS:n-3 Active/VitD PlAC;n-3 Plac/VitD active; N-3 Acu=ive/-3 Activw;Plac/Plac
- Outcome: incidence of RA, PMR, thyroid disease, psoriasis
- f/u 5.3 yrs
- No breakdown by autoimmune disease

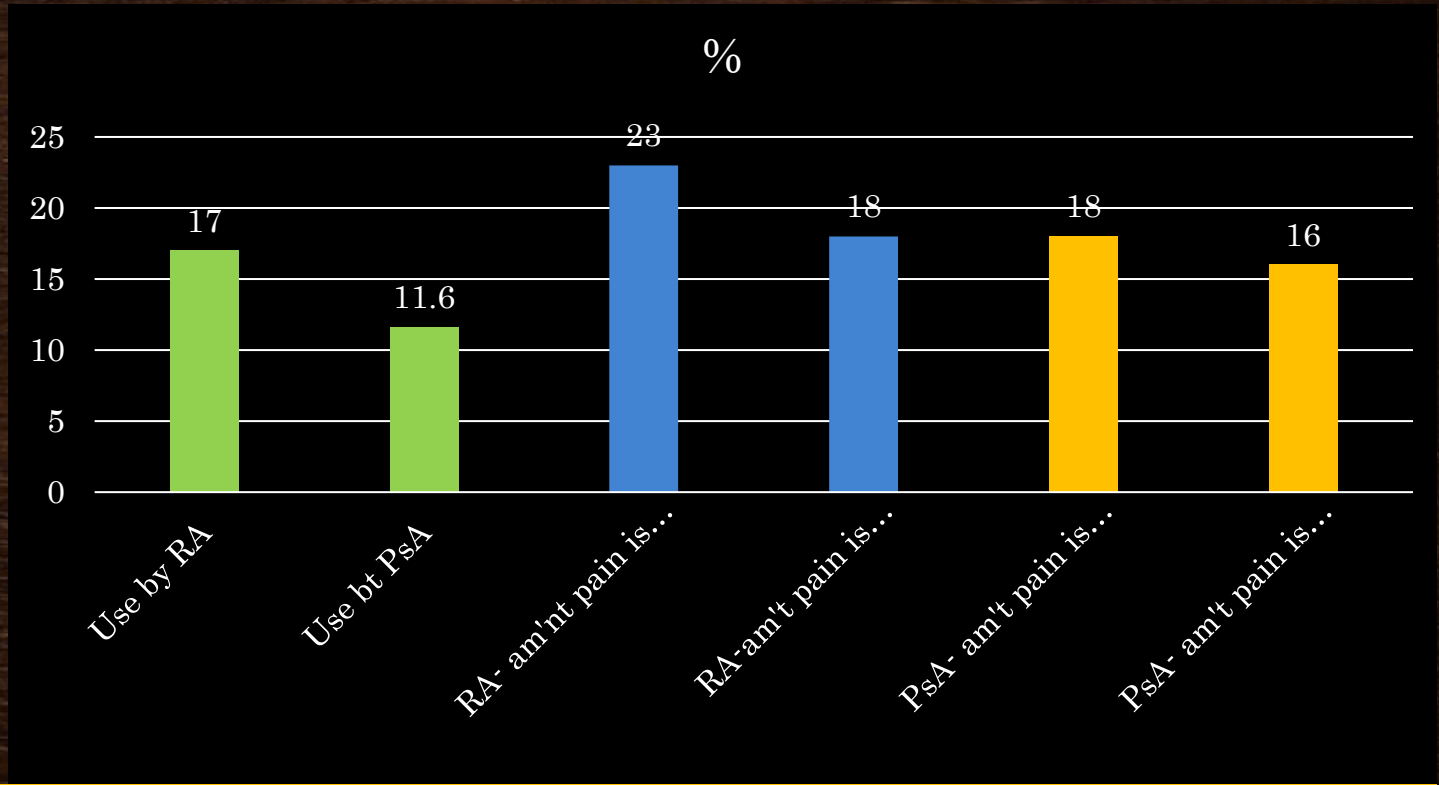


Conclusion: 5 yrs of Vitamin D3= N-3 Fatty Acid, = Combo All > PLAC combo no advantage

Uncontrolled survey of cannabis for pain relief in rheumatoid arthritis and psoriatic arthritis

Jehu T, Bhaskar N et al. EULAR 2022 ARD 8-(Suppl 1): POS1573-PARE

- N=Survey
- N= 236 R A. and 43 PSA patients
- Short term and long-term use (not defined)



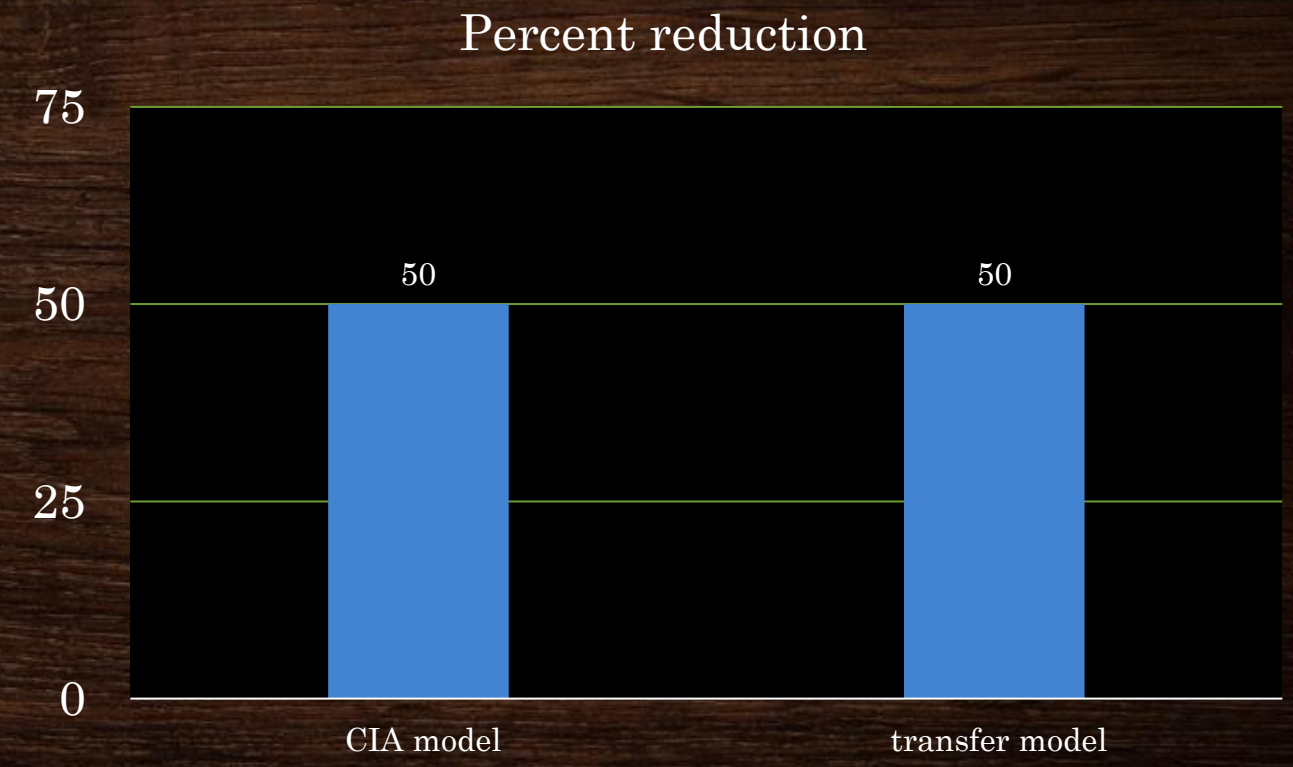
Conclusion: cannabis is reported to be mildly effective to reduce pain (16 – 23%) in rheumatoid arthritis and psoriatic arthritis.
Study is uncontrolled, cross-sectional and memory biased

New drugs

First in class nanoparticles, anti- CCP ameliorates CIA and serum transfer of CIA

Khatri S, HansenJ et al. ARD 2020. 79(suppl1): pg 208,abs LB0002

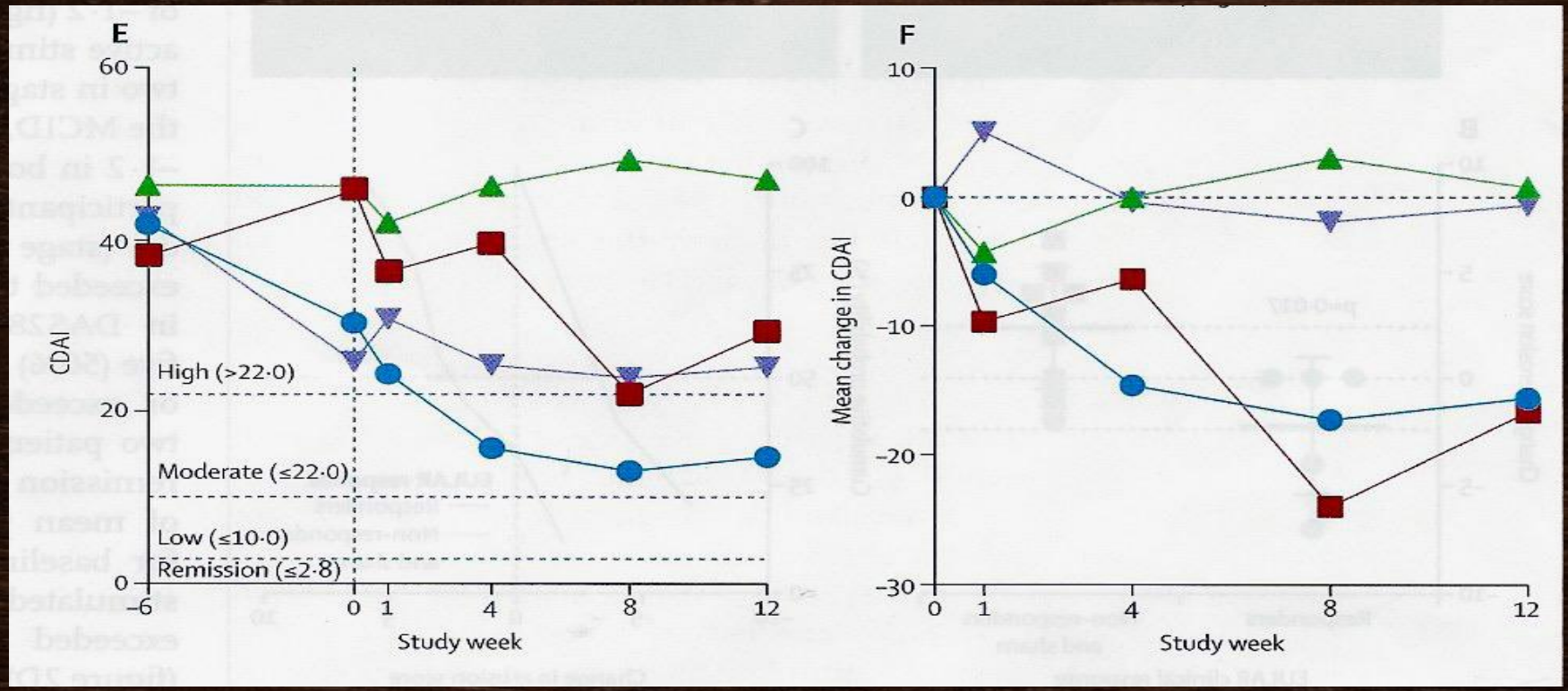
- Fibrinogen derived, 21 amino acid citrullinated peptide
- Incorporated into a nano particle
- No immunogenicity in peripheral blood monocytes
- Method: one nanomolar given every 48 hours in CIA mice



Conclusion: the principle of using anti-CCPs seems reasonable for inflammatory arthritis

Use of vagal nerve stimulation (1 min QD or QOD) in RA (N=4/gp)

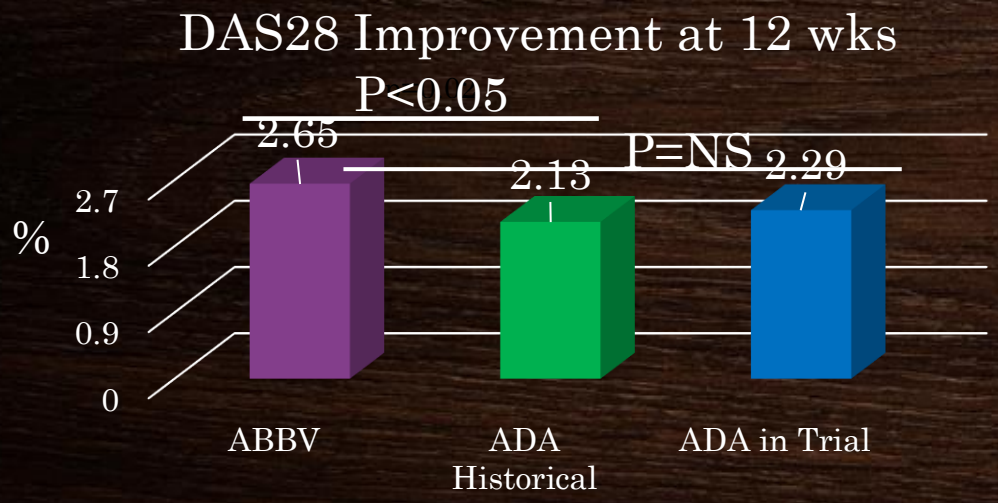
Genovese mc, Gaylis nb, et al. Lancet Rheumatology 2020. 2:e527-38.



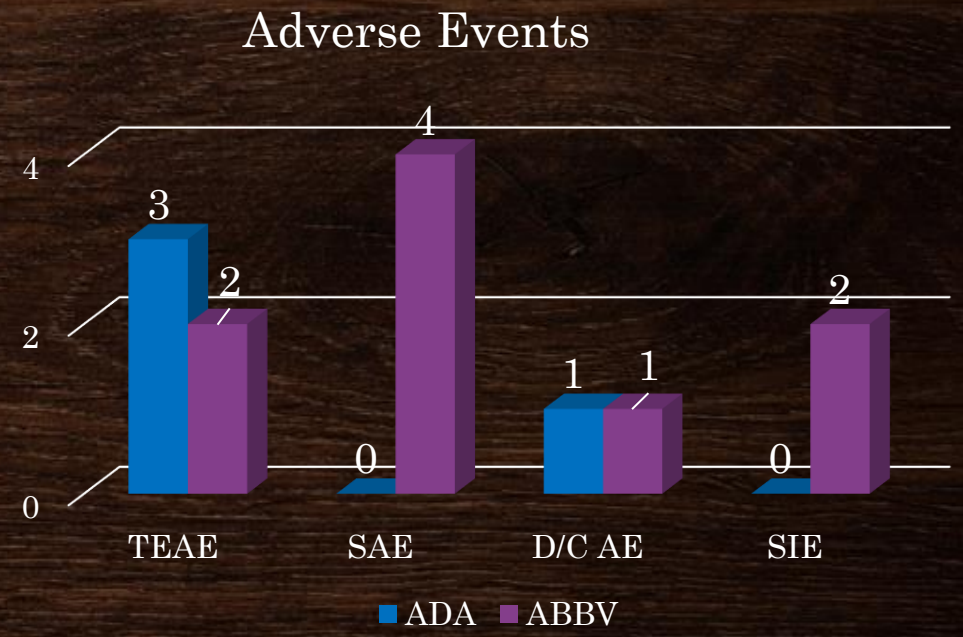
24 week phase 2a db-rct of adalimumab conjugated to glucocorticoid-receptor modulator ab (ABBV-3373)

Buttgereit f, Aelion j, et al. ARD 2021 Vol 80(suppl1):64 (abs OPO115)

- N=31 ABBV-3373 x12 wks then placebo x12 wks
- N=17 Adal 80 mg qwk x24 wks



- No steroid-type AE



SAE-ABBV:1 non-cardiac chest pain,1 pneumonia, 1 URI, 1 anaphylaxis (none after increased infusion time from 15 min to 30 min)

Conclusion: some early evidence of efficacy but some AEs,too

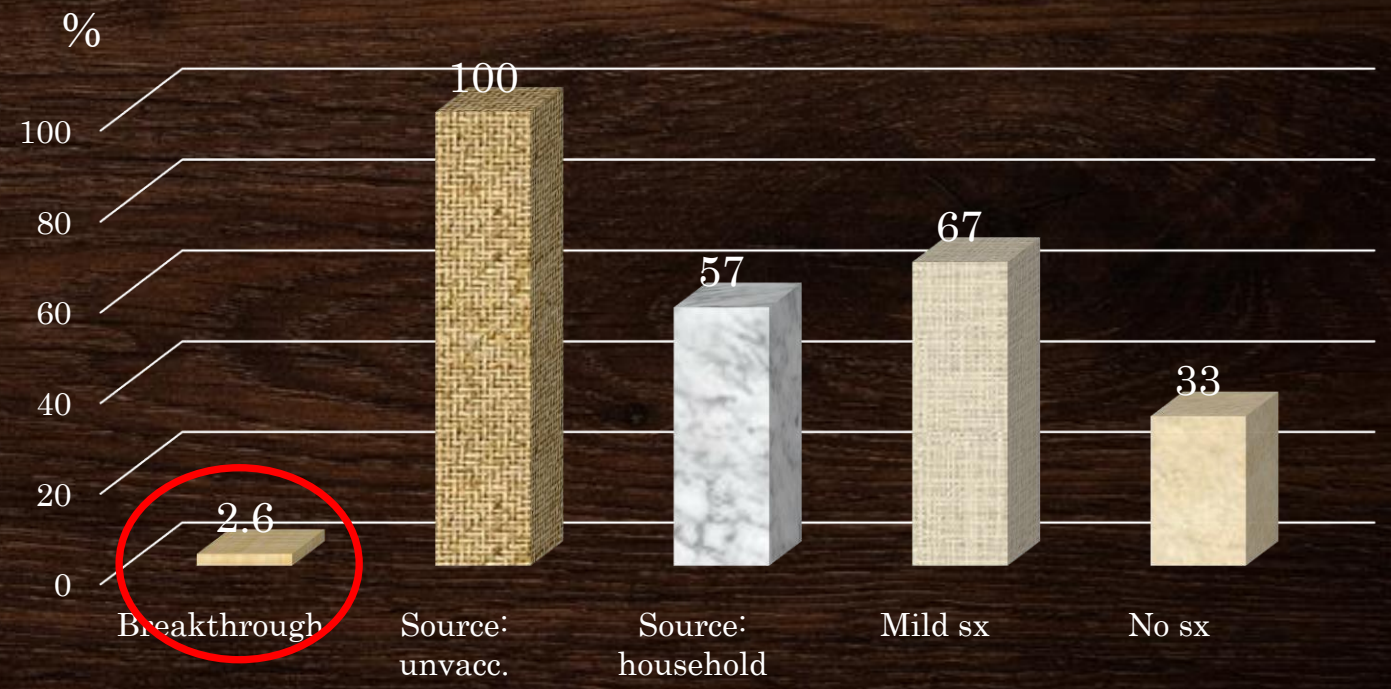
COVID19

COVID-19 after vaccination in Israel

BergwerM,Ggonen t, et al. NEJM. June 28, 2021.doi.10.1056/nejmoa21-9072

- Case-control study: controls from a previous cohort study
- 1 case: 4-5 controls
- Matched for sex, age, immunosuppression
- Compared spike IgG ab at 1 week after vaccination
- **(Note: this may be a false negative - RT-PCR positive-alpha variant (B1.1.7)**
- N= 1497 healthcare workers after Pfizer vaccination
- Breakthrough infection by RT-PCR positive (independent of sx) after vaccination

Median time to breakthrough: 39 days (range 11-102)



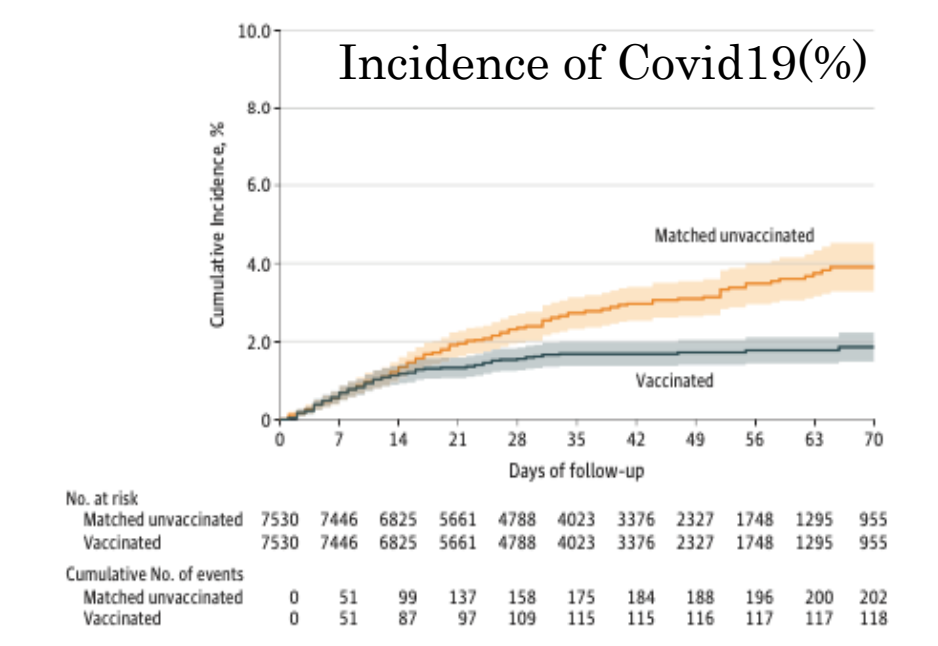
Conclusion: 2.6% breakthrough after Pfizer vaccination; most thru household contact (57%): all mild (67%) or no sx (33%).

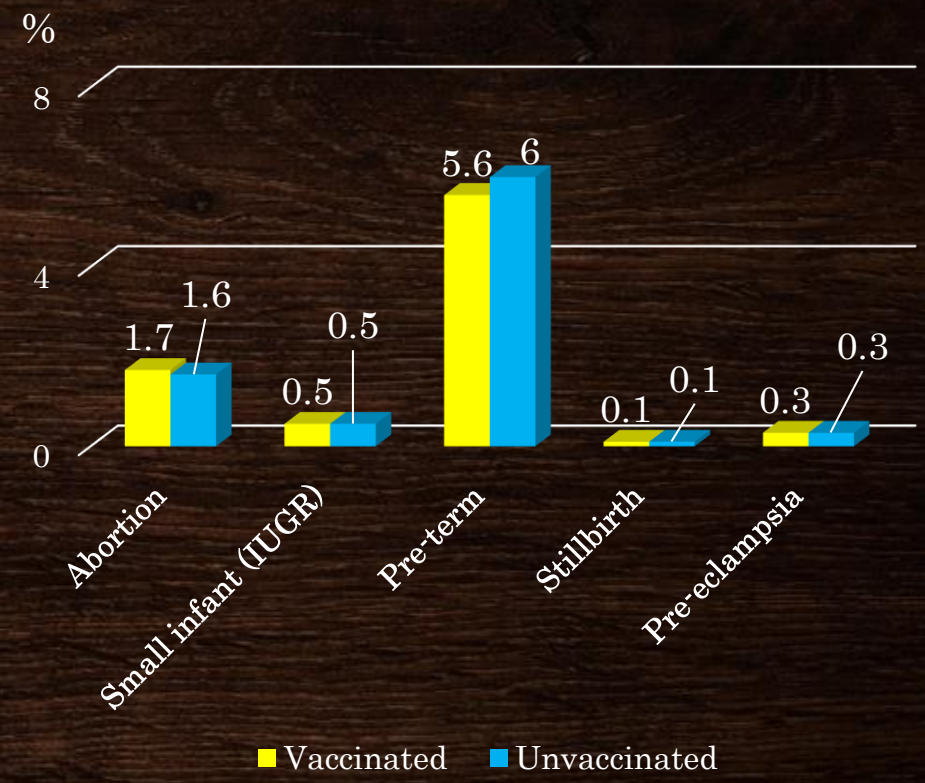
Can an mRNA SAR-COV-2 vaccine (Pfizer) be used in pregnant women?

Goldshtein I, Nevo D, et al. JAMA 2021. 326: 728-735. doi: 10.1001/jama.2021.11035.

- Retrospective controlled study
- Outcome: COVID-19 infection at 28d, pregnancy complications & births
- N= 7530 vaccinated; 7530 unvaccinated.

Matched by age (+/- 5 yrs), gestational age (+/- 5 yrs), residential area in Israel, sub-group (non-ultraorthodox, orthodox, Israeli Arab) parity, updated flu vaccine, chronic co-morbidities (eg. HBP, DM





Conclusion: vaccination decreased COVID-19 and caused no unexpected complications.

Long-covid symptoms > 7 months after diagnosis of SX Covid19

Nehme m, Braillard O, et al. Ann int med 2021; 174: 1252-1260
doi: 10.7326/M21-0878

- Swiss
- **N=410 of initial 703 (58%) responded in follow-up**
- Pt recall q2d X10d after 1st shot, at 30-45 days and 7-9 months
- Outcomes: a list of symptoms, a fatigue questionnaire, a dyspnea scale
- Stats: descriptive plus a regression including age, sex, number of baseline symptoms/person adjusted for missing data
- Co-morbidities:
  - CV: 11%
  - HBP: 30%
  - Resp: 23%
  - DM: 12%
  - Cancer 7%
  - Immunosupp: 4%

	%		%
Any SX	39	Muscle Pain	6
Fatigue	21	Joint Pain	3
Loss of smell/taste	17	Equilibrium	3
SOB	12	Neuropathy	2
Headache	10	Loss of Appetite	2
Cough	4	Rash	2
GI SX	2	Memory	6
Fever	0	Hair Loss	3

Conclusion: 39% had symptoms after >7 months

Side Effects

Death
100% mortality for all studies if the follow up is long enough

THANK YOU FOR YOUR ATTENTION