BRIGHAM AND WOMEN'S HOSPITAL

RA Therapy Update 2025

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2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

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- 50 year old woman with RA RF and CCP+, on mtx 17.5 mg/ week. Has been on mtx for 8 wks improvement CDAI at 20 was 35 before MTX. What should you now?
- A. Hold the course another 12 wks
- B Start prednisone 5 mg
- C Add sulfasalazine and hydroxychloroquine
- D Increase the MTX to 25 mg per week in split oral dosing

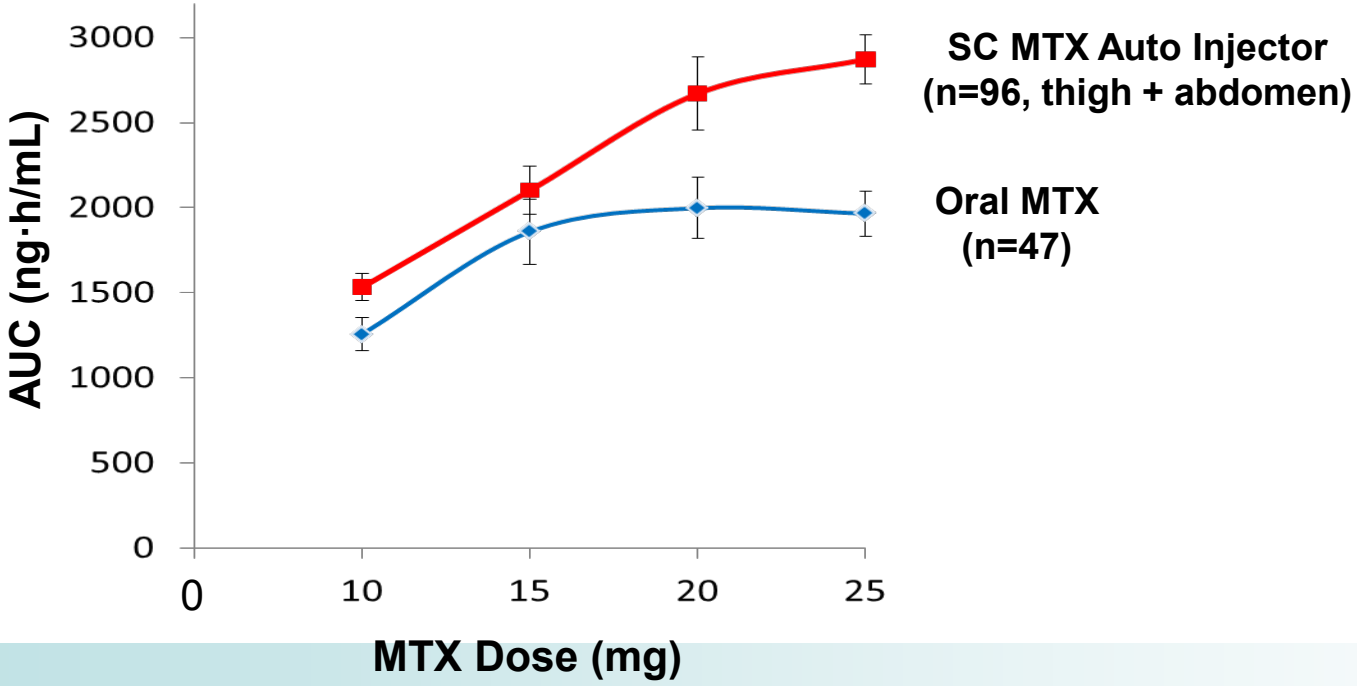
MTX Dosing

- Starting dose 10-20 mg/wk
- Onset of effect –4wks due to polyglutamation
- Increase dose for therapeutic effect
- Therapeutic dose 15-25mg/wk
- Little value in increasing above 25 mg/wk
- Due to variability in absorption at doses above 17.5- 20 mg/wk consider sq or split dose oral
- Time to maximum effect 12 weeks
- Dose reduction achievable over time

SQ vs Oral MTX: PK Study

Ann Rheum Dis 2014; 73:1549

- 12 wk, crossover open-label study
- 49 RA pts on MTX were given oral of sq MTX 10,15,20 or 25
- PK studies were performed, oral MTX plateued at 15 mg but sq did not
- No increase in AEs



MTX: Split Dose Oral

J Rheumatol 2006; 33: 481-485

- Pk study of 10 pts on stable MTX 25-35 mg week
- Pk study after a single oral dose or after two doses 8 hours apart.
- Split dose oral MTX achieved an increase in bioavailability of >28% compared to single dose. Oral bioavailability was 0.76 and split dose was 0.90 as compared to sq rx

ACR 2021 RA Guidelines

Arthritis Care Res 2021; 73:924

Table 3. Methotrexate administration*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)	Evidence table(s), in Supp. App. 2
Oral methotrexate is **conditionally** recommended over subcutaneous methotrexate for patients initiating methotrexate.	Moderate	PICO 9	p. 181
Initiation/titration of methotrexate to a weekly dose of at least 15 mg within 4 to 6 weeks is **conditionally** recommended over initiation/titration to a weekly dose of <15 mg.†	Moderate/ very low‡	PICO 10.C1–C3	p. 184–5
A split dose of oral methotrexate over 24 hours or subcutaneous injections, and/or an increased dose of folic/folinic acid, is **conditionally** recommended over switching to alternative DMARD(s) for patients not tolerating oral weekly methotrexate.	Very low	PICO 16 and PICO 15	p. 206–10
Switching to subcutaneous methotrexate is **conditionally** recommended over the addition of/switching to alternative DMARD(s) for patients taking oral methotrexate who are not at target.	Very low	PICO 18	p. 235

- 45 year old pt with RA started MTX and is now of MTX 17.5 mg per week, diclofenac 50 mg/day and acetaminophen 3000 mg/day. Has been on the drug for 8 wks and still has active disease. No clinical toxicity but AST is 55 (ULN 40) and ALT is 50 (ULN 42).
- What should you do?
- A. Stop MTX and start adalimumab 40 mg/wk
- B. Stop oral MTX and start MTX sq
- C. Increase MTX to 25 mg per week as split dose oral weekly
- D. Repeat labs in 4 wks

MTX Liver Disease

ACR 2018:959

- Retrospective study of pts on MTX between 2006-2016
- 5000 pts were identified with a rheumatic disease on MTX. Less than 3% with persistent transaminitis on MTX
- Only 1% underwent additional wu for suspected liver disease with either liver bx or elastography (Fibroscan)
- 48 pts were evaluated and of these 26% steatosis, 14% fibrosis,13% NASH cirrhosis, 34% normal and 5% suspected MTX cirrhosis (3 pts)
- Risk factors for NASH were increased BMI, DM and elevated triglycerides
- Authors conclusion: “Likelihood of developing liver damage on MTX is extremely low and careful consideration needs to be made before prematurely stopping mtx due to elevated liver function tests”

MTX and Liver Disease

J Am Acad Derm 2021; 84:1636

- Objective: compare liver disease risk in Danish pts with psoriasis 5686, psa 6520 and RA 28030 pts on MTX
- Population based cohort study between 1997-2015
- Liver disease definitions
  - Mild chronic hepatitis or cirrhosis without portal hypertension
  - Moderate severe- liver failure, encephalopathy, portal hypertension, hospitalizations
- Mild- 4.22 pso, 2.39 psa, 1.29 ra
- Moderate-severe- 0.98 pso, 0.51 psa, .46 ra
- Cirrhosis 1.89 pso, 0.84psa, 0.42 ra
- Conclusions- Independent of other risk factors psoriasis and psa increase risk of serious liver disease

- 50 year old woman has active RA, RF CCP+ with 6 months of disease activity. Has been on MTX 25 mg/wk (split dose) weekly for 8 wks. CDAI 22
- What should you do now??
- A stay the course for another 6 wks
- B switch to sq mtx 25 mg/wk
- C add sulfasalazine and hydroxychloroquine
- D continue MTX and add anti-tnf therapy

Addition of a bDMARD or tsDMARD is conditionally recommended over triple therapy (i.e., addition of sulfasalazine and hydroxychloroquine) for patients taking maximally tolerated doses of methotrexate who are not at target

The panel vigorously debated whether to recommend addition of a bDMARD or tsDMARD versus sulfasalazine and hydroxychloroquine (triple therapy) for patients with an inadequate response to methotrexate monotherapy in view of very low- certainty evidence favoring bDMARDs or tsDMARDs, randomized controlled trials demonstrating equivalent long- term outcomes across both treatment strategies, and significantly less societal cost associated with triple therapy. Addition of a bDMARD or tsDMARD was ultimately preferred because the patient panel strongly prioritized maximizing improvement as quickly as possible. In addition, both the patient and voting panels valued the greater persistence of methotrexate plus a bDMARD or tsDMARD compared to triple therapy (defined in Table 1) The recommendations from these studies are conditional because triple therapy may be preferred in lower resource settings as well as in patients with specific comorbidities for whom triple therapy may be associated with significantly less risk of adverse events. This choice is highly preference sensitive, and decisions on how best to escalate care should incorporate patients' preferences. There is no current recommendation for a bDMARD versus a tsDMARD when adjusting treatment; however, the voting panel acknowledged that safety data released in early 2021 may require a modification of this recommendation when peer- reviewed results are published.

Arthritis Care Res 2021; 73:924

REMISSION IN EARLY RA:COMET Lancet 372:375,2008

- 24 MONTH RCT-542 PTS
- ETN +MTX VS MTX IN RA PTS WITH LESS THAN 2 YRS OF DISEASE
- MTX TITRATED OVER 8 WKS TO 20 MG
- PRIMARY OUTCOME – DAS REMISSION
- PRIOR DMARDS- ONLY 22%
- AT WK 52

	DAS <2.6	ACR 50	NO XRAY
ETN +MTX	50%	71%	80%
MTX	28%	49%	59%

MTX and Biologics

- MTX increases the efficacy of selected biologics including anti-TNF, abatacept and rituximab
- In the case of infliximab and adalimumab MTX increases the drug levels of these MAB
- A dose dependent effect has been observed with MTX dosing and the development of adalimumab antibodies
- A cohort study of pts on chronic MTX and adalimumab reported an increase in HAMA with no MTX and low dose MTX (5-10mg/wk) vs MTX 12.5-20 and >22.5 mg/wk

ARD 71:1914,2012

MTX Dose and ADA Response

Ann Rheum Dis 2015; 74:1037

- RCT of 395 MTX and biologic naïve pts enrolled in 26 wk DB study of MTX at varying doses (2.5,5,10,20 mg/wk) plus OL adalimumab 40 mg q2wks

	MTX +ADA			
	2.5 mg	5mg	10	20
DAS<2.8	43%	44%	57%	60%
CDAI<2.8	12	22	29	28
ACR 50	46	51	54	62

- Less efficacy and lower serum drug levels seen at 2.5 and 5 mg dose of MTX

- 35 year old woman with RA of 18 mo duration, CCP and RF +.
- Has been on MTX 25 mg/wk split dose and etanercept 50 mg/wk.
- Has been in LDA/remission by CDAI for more than 6 months.
- She asks whether she can stop her meds
- What should you do??
- A. Stop etanercept
- B. Stop MTX
- C Continue both drugs at current doses
- D. Begin to taper the MTX

Anti-TNF Withdrawal Studies

- Adalimumab – withdrawal design
- Etanercept – dose reduction, withdrawal
- Certolizimab– dose reduction, withdrawal

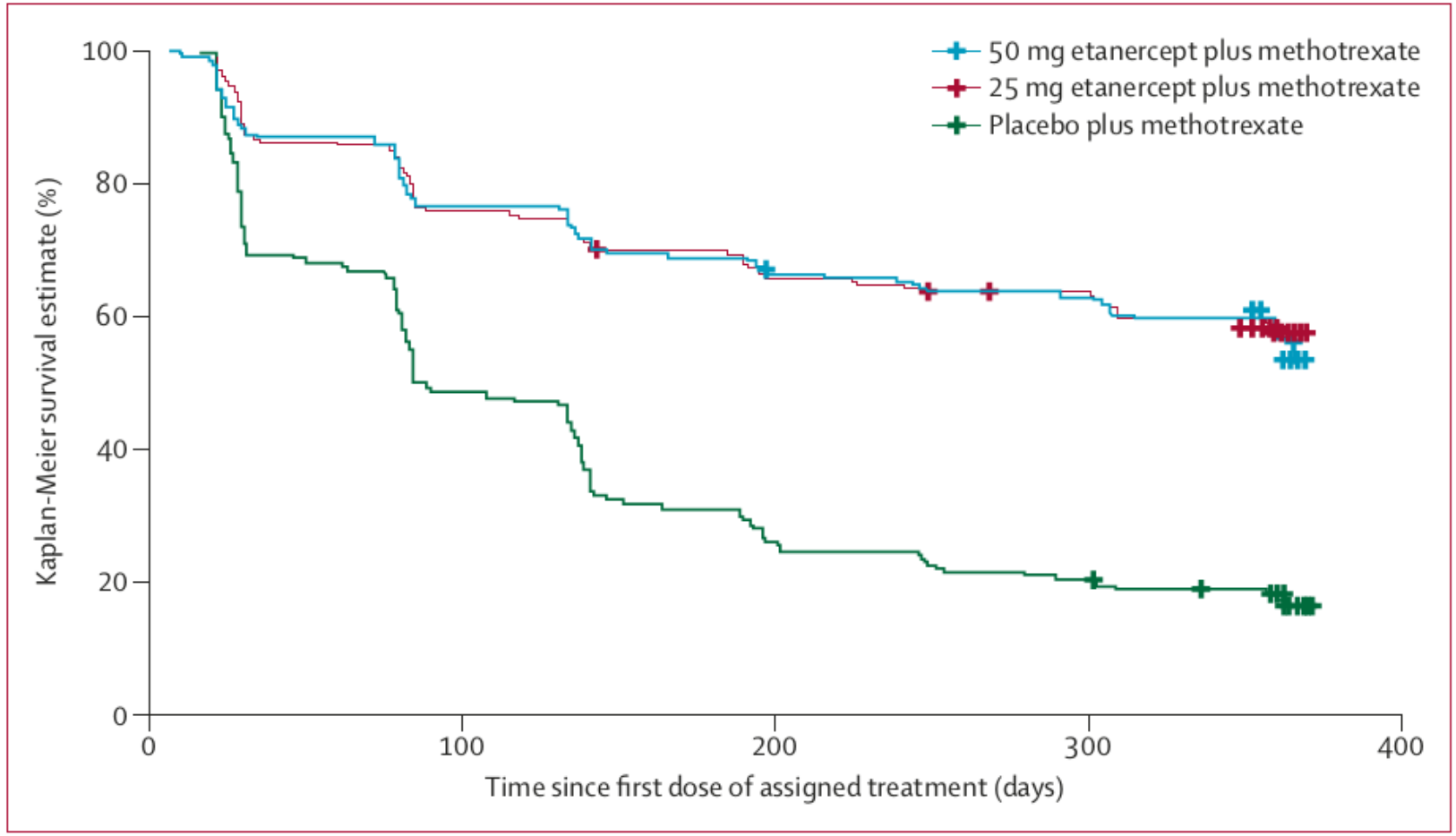
  Flare with withdrawals but dose reduction worked

- Abatacept and Tocilizumab –

  Flare with drug withdrawal

Etanercept: Dose Reduction/Discontinuation

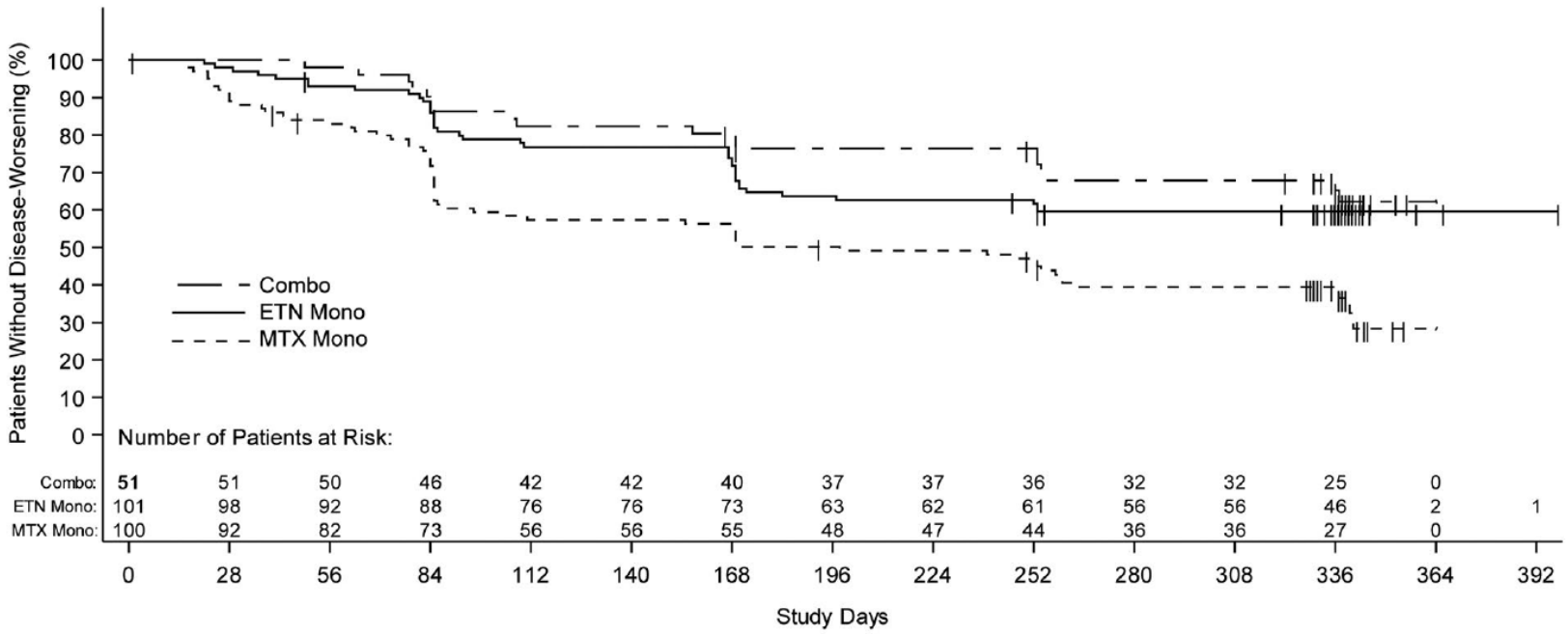
Lancet 2013 381:918-929



Withdrawal of Etanercept or MTX

Arthritis Rheum 2021;73:759

- 371 pt withdrawal study of either MTX or etanercept vs the comb in pts in SDAI remission after 24 wks open label MTX + ETN.
- At wk 24 pts entered a double blind study of stopping MTX, ETN or remaining on the combo over the next 48 wks.
- Endpt of worsening SDAI >11 at any time or SDAI>3.3 and <11 on 2 consecutive visits
- Endpts also included proportion of pts in SDAI remission at wk 24



	MTX Mono (N = 101)	ETN Mono (N = 101)	Combo (N = 51)
Days to Disease-Worsening, Median (95% CI)	198 (96, 263)	NE (253, NE) P<0.001*	NE (336, NE) P<0.001*

Figure 3. Kaplan-Meier curves of time to disease-worsening in the 3 treatment groups (in the primary analysis set). The censor bars represent

Tapering and Discontinuation: TARA study

Ann Rheum Dis 2020

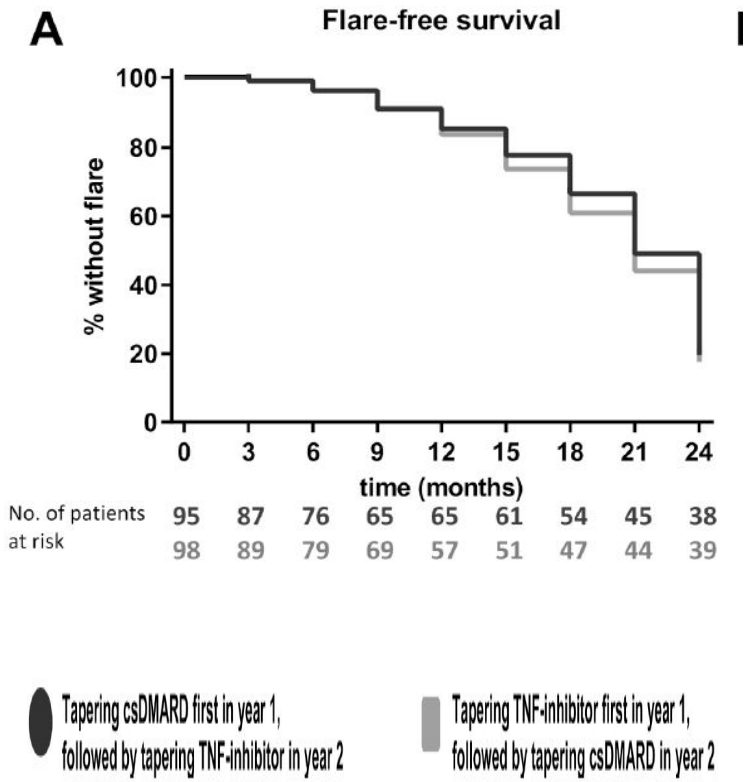
2 yr single blinded study of gradual tapering of csDMARDS and anti-TNF followed by discontinuation of therapies (DFR)

189 pts (71%CCP+ and only 1 pt on oral steroids) with well controlled disease with DAS<2.4 and <1 swollen jt for >3 months

Primary outcome no of disease flares

Cumulative flare rate after 24 mos was 61%, more pts in DFR with tapering csDMARDs first

Drug free remission was achieved in **15%** of pts



Tapering and stopping anti-tnf in remission ACR 2020 no 2010

Objective was to assess effect of tapering and stopping anti-TNF on risk of flare in pts in remission

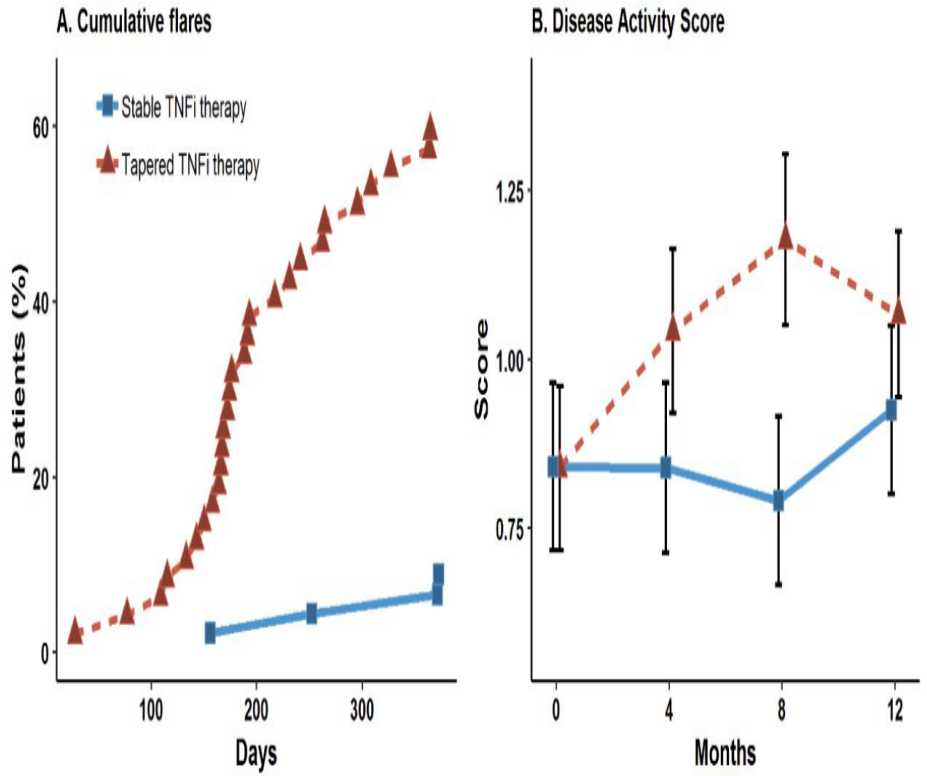
RA pts in remission for at least 12 mo on stable anti-TNF were randomly assigned to continue on stable anti-TNF or tapering (half dose anti-tnf for 4 months then stopping)

Primary endpt was disease flares over 12-44 months of study.

Disease flare defined as DAS>1.6, change in DAS>0.6 and 2 or more swollen jts

99 pts were randomized and 84 were in the per-protocol population

Flare in 5% of stable antiTNF compared to 63% of tapering anti-TNF



Tapering vs Full Dose Rx of Aba or Toci in RA

Arthritis Rheum 2024; 76:541

Open label non inferiority study of progressive treatment spacing (S) of Aba or Toci vs full dose therapy (M) in pts in remission

Primary end pt was DAS 44 during the 2 years fu

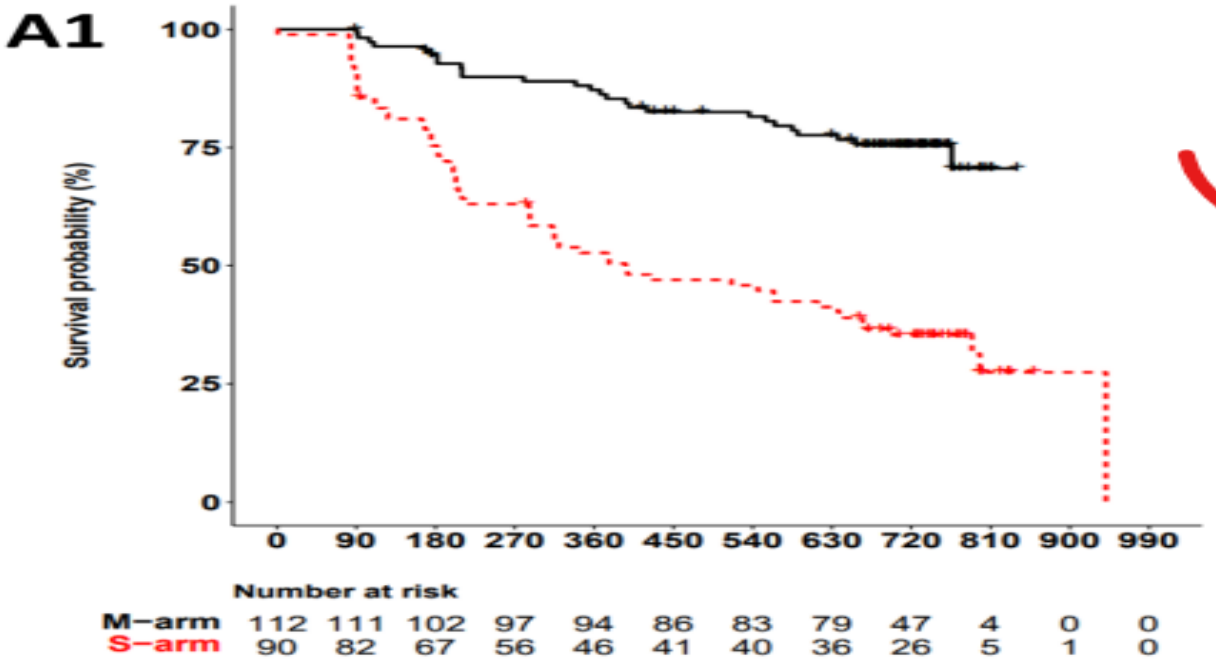
202 pts were enrolled in the study, 90 in the tapering discontinuation arm and 112 in the maintenance arm

At the end of fu 16 in the S arm could discontinue therapy, 47% tapered rx and 37% returned to full dose

Non inferiority was not established in primary outcome, flare incidence or structural progression

Conclusion- Trial failed to demonstrate

Non-Inferiority for Aba or Toci tapering strategy



Gradual discontinuation of methotrexate is conditionally recommended over gradual discontinuation of the bDMARD or tsDMARD for patients taking methotrexate plus a bDMARD or tsDMARD who wish to discontinue a DMARD

In the absence of direct evidence, gradually discontinuing methotrexate is preferred because a bDMARD or tsDMARD is typically added following an inadequate response to methotrexate. Thus, the continued use of the bDMARD or tsDMARD is more likely to maintain disease control than the continued use of methotrexate. The recommendation is conditional because gradual discontinuation of the bDMARD or tsDMARD may be favored depending on comorbidities, risk for infection, cost concerns, as well as patient and clinician preferences. The voting panel cautioned that many patients treated with certain monoclonal antibodies may require ongoing treatment with methotrexate to prevent the formation of antidrug antibodies.

Arthritis Care Res 2021; 73:924

- 55 year old woman with RA on MTX 25 mg sq and has been on infliximab 5 mg/kg every 8 wks for 12 wks (started on 3 mg/kg induction dosing). RA has improved with CDAI decreasing from 25 to 15. What should you do now??
- A. Stay the course for another 12 wks
- B. Stop infliximab and start adalimumab
- C. Increase infliximab to 8 mg/kg every 4 wks
- D. Obtain trough infliximab level with antibody level

Anti-drug antibodies and response to therapy in RA

JAMA Network Open 2023;6:e 2323098

Objective: Association of anti-drug antibodies with response to therapy

Trial Design: Open prospective study of RA pts initiating a new bDMARD.

Primary outcome: Anti-Drug antibody positivity and Eular Response at month 12

Results: 254 recruited, 230 analyzed. At 12 months

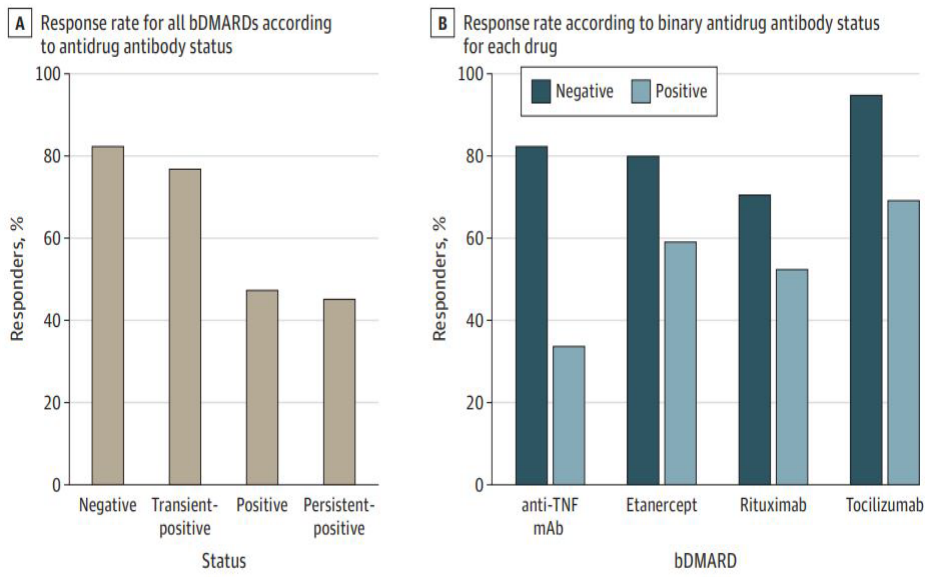
Anti drug ab positivity in 38% on anti-tnf MAB, 6% with etanercept, 50% with rituximab, and 20% with tocilizumab

Inverse association with anti drug ab and response

MTX at baseline inversely associated with anti drug ab

This is another study that recommends monitoring anti-drug ab esp in non responders

Figure 1. Response to Treatment and Antidrug Antibody Status at Month 12



- 66 year old male with RA with nodule formation, hx of hypertension and elevated lipids. stopped smoking 5 yrs ago.
- Has been on MTX 25 mg/wk and adalimumab 40 mg q2wks for 24 wks. Remains with active disease CDAI 20
- What should you recommend
- A. Stop ada and start etanercept 50/wk
- B. Stop ada and start anti-6 therapy
- C. Stop ada and start a JAK inhibitor
- D. Add prednisone 5 mg/day

Switching to a bDMARD or tsDMARD of a different class is conditionally recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target

The recommendation is based on very low- certainty evidence supporting greater improvement in disease activity and drug survival among patients switching classes. The recommendation is conditional because patient and physician preferences are likely to vary based on prior experiences with specific DMARDs.

Arthritis Care Res 2021; 73:924

TCZ vs ETA in RA: CV Outcome

Arthritis Rheum 2020; 72:31

- Phase 4 non-inferiority study of open label etanercept (ETA) vs tocilizumab (TCZ) 8 mg/kg monthly in RA pts with CVD risk factors, extra-articular disease or prior CV event
- Primary outcome was MACE, addressing whether a HR of >1.8 could be excluded in pts receiving TCZ as compared to ETA
- 3080 enrolled, mean fu 3.2 yrs
- MACE events 83 TCZ, 78 ETA HR 1.05
- “This study ruled out risk of MACE of 1.43 in pts rx with TCZ”

Tofacitinib: CV/ Ca Outcome Study

NEJM 2022; 386:316

4362 pts enrolled in an FDA mandated open label endpt driven study of CV and cancer events of Tofa 5, 10 mg bid vs anti-tnf (etanercept or adalimumab).

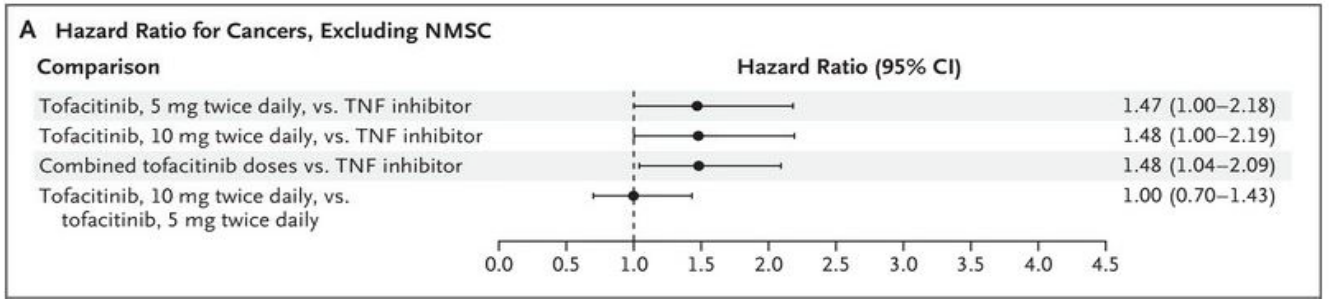
Entry criteria pts >50 yrs of age and 1 CV risk factor and all were on MTX.

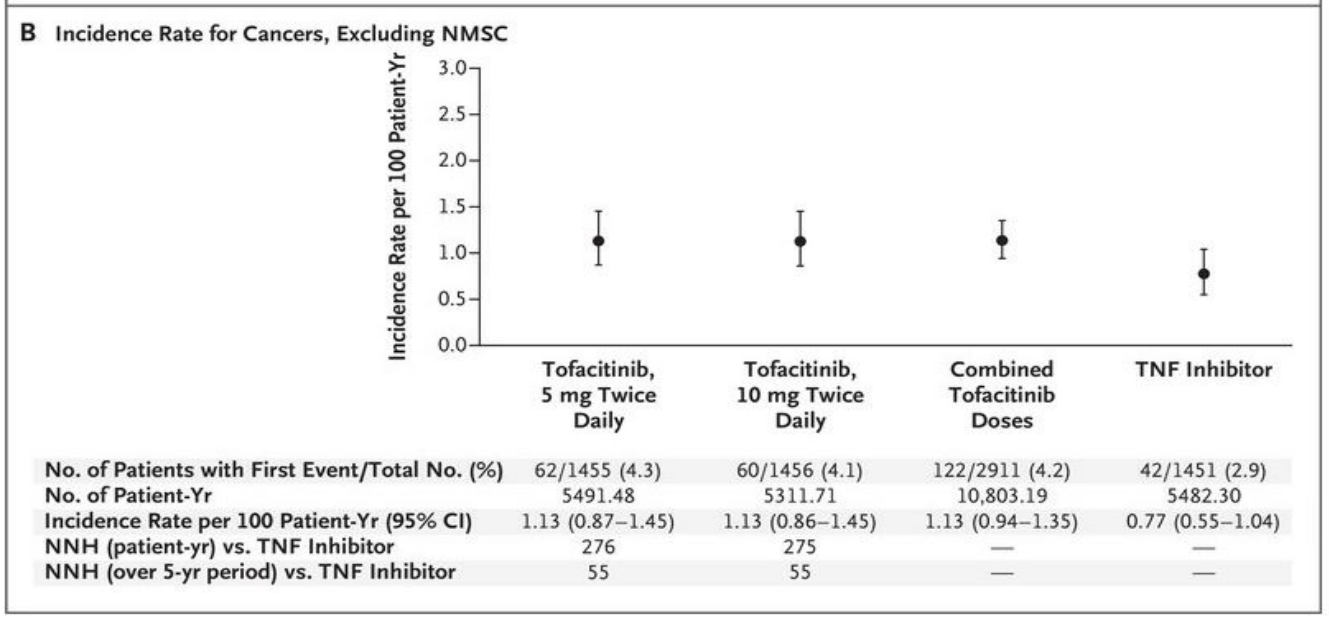
Non-inferiority study-upper bounds of CI<1.8

Non inferiority not met with Tofa as compared to anti-TNF with MACE and Malignancy

Independent Risk factors were >65yrs, current smokers, male, asa use

Figure 2. Hazard Ratios and Incidence Rates for Adjudicated Cancers, Excluding NMSC (Safety Analysis Population, Total-Time Analysis).





	Tofacitinib, 5 mg Twice Daily	Tofacitinib, 10 mg Twice Daily	Combined Tofacitinib Doses	TNF Inhibitor
No. of Patients with First Event/Total No. (%)	62/1455 (4.3)	60/1456 (4.1)	122/2911 (4.2)	42/1451 (2.9)
No. of Patient-Yr	5491.48	5311.71	10,803.19	5482.30
Incidence Rate per 100 Patient-Yr (95% CI)	1.13 (0.87–1.45)	1.13 (0.86–1.45)	1.13 (0.94–1.35)	0.77 (0.55–1.04)
NNH (patient-yr) vs. TNF Inhibitor	276	275	—	—
NNH (over 5-yr period) vs. TNF Inhibitor	55	55	—	—

- 50 year old female with RA on MTX 25 mg per week (split dose)
- Remains with active RA, CDAI 15 (CDAI was 30 prior MTX)
- Hx of lung cancer 4 yrs ago treated with surgery
- What are the best options for her
- A. Add an anti- tnf therapy
- B. Start a Jak inhibitor
- C. Start an IL-6 inhibitor
- D Switch to SQ MTX

Anti-TNF and Cancer Recurrence

Ann Intern Med Aug 2018

- Population Based Cohort study of nationwide registries in Sweden
- Pts with RA who started anti-TNF between 2001-2015 after being dx with cancer and matched RA pts with hx of the same cancer who never received biologics
- Primary outcome was first recurrence of cancer
- 467 pts who started anti-tnf – mean time after cancer dx was 7.9 yrs. 42 had cancer recurrence (9%). In the 2164 matched pts 155 had recurrence of cancer (7.2%). HR 1.06
- This study suggests no increased risk of cancer recurrence in pts receiving anti-tnf rx

Biologics and Cancer Recurrence

Arthritis Care Res 2023; 75:260

- Metanalysis of 24 observational studies including 12 studies of RA pts receiving bDMARDs with a hx of cancer
- 8 studies included pts on anti-TNF and included at least 1494 pts on anti-tnf and 4454 controls. Risk of recurrence was not sign increased RR1.11 (p=0.45)
- RR for skin cancer was 1.32 ($p<0.04$) and RR for breast cancer was 1.21 (p=0.31)
- Risk of recurrent or new cancer was not increased with initiation of bDMARD (anti tnf or rituximab) except skin cancer

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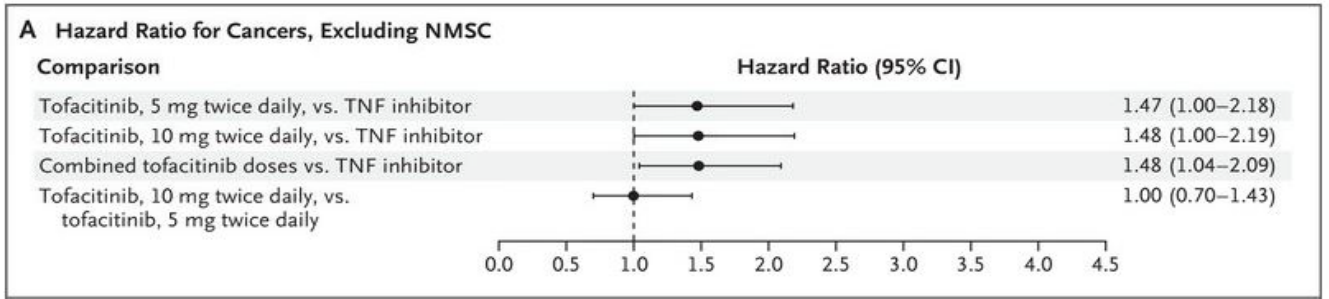

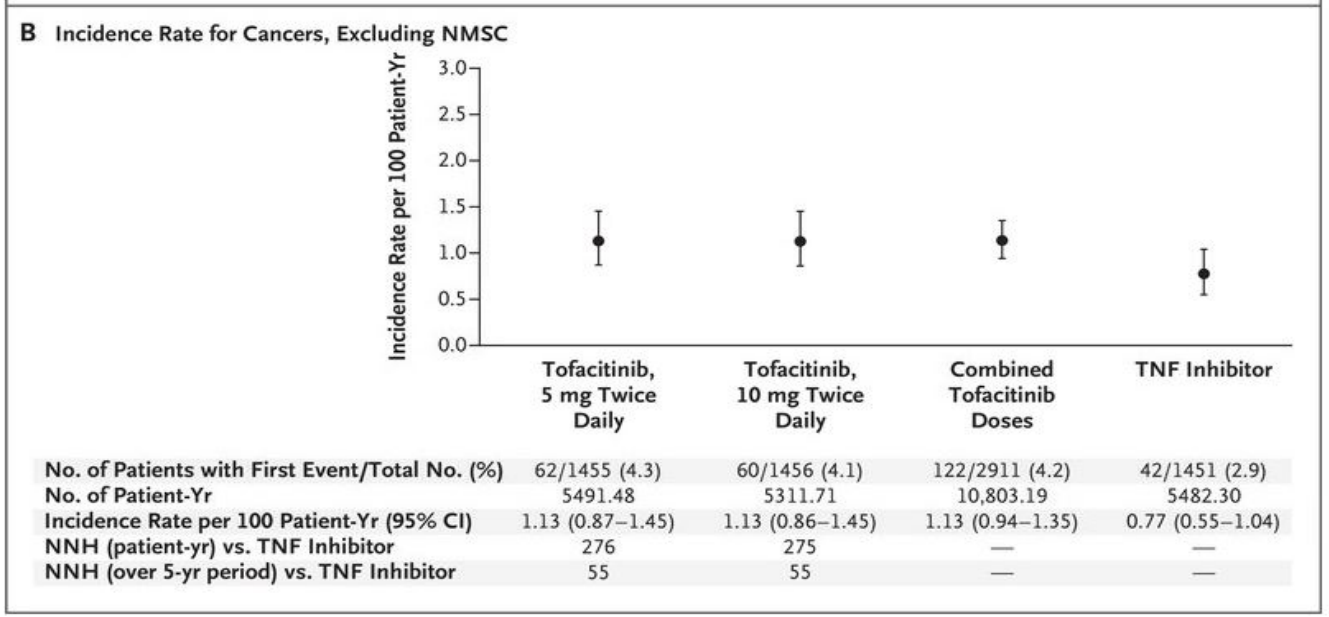

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NNH (patient-yr) vs. TNF Inhibitor	276	275	—	—
NNH (over 5-yr period) vs. TNF Inhibitor	55	55	—	—

- 60 year old woman with 15 yrs of RA. Remains with pain and stiffness and discomfort. Rates her disease 6/10. CDAI 20. HAQ 1.5. On mtx 25 mg sq, prednisone 7.5 mg/d, folic acid. Previously received HCQ, leflunomide, adalimumab, infliximab, abatacept, toci, rituximab and 2 JAK inhibitors'
- What should you do??
- A. start triple therapy
- B. start etanercept and abatacept
- C. increase prednisone to 10 mg/day
- D. Order MRI with gad of the mcp joints

Difficult to Treat RA
ARD 2021; 80:31

Box 1 EULAR definition of difficult-to-treat RA

1. Treatment according to European League Against Rheumatism recommendation and failure of ≥2 b/tsDMARDs (with different mechanisms of action)* after failing csDMARD therapy (unless contraindicated).†
2. Signs suggestive of active/progressive disease, defined as ≥1 of:
   a. At least moderate disease activity (according to validated composite measures including joint counts, for example, DAS28-ESR>3.2 or CDAI>10).
   b. Signs (including acute phase reactants and imaging) and/or symptoms suggestive of active disease (joint related or other).
   c. Inability to taper glucocorticoid treatment (below 7.5 mg/day prednisone or equivalent).
   d. Rapid radiographic progression (with or without signs of active disease).‡
   e. Well-controlled disease according to above standards, but still having RA symptoms that are causing a reduction in quality of life.
3. The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient.

Poly-refractory RA

Arthritis Rheum 2024; 76:510

- Cross sectional study of 1591 RA pt on b/tsDMARDs evaluated D2T-RA criteria. Evaluated for persistent inflammatory refractory RA (PIPPA) and noninflammatory refractory RA (NIRRA)
- 53% received only 1 class of drug so excluded. 47% had received 2b/tsDMARDs with different mechanism of action. 50% of these pts were in remission or LDA. 16% excluded due to missing clinical data. 17% of the 1469 had failed 2 drugs and had DAS crp>2.6
- Of the 247 pts who were poly-refractory 107 pts had ultrasound and 43% did not have synovitis on ultrasound. The NIRRA pts had higher rates of obesity and fibromyalgia
- 2.7% of pts in the cohort met definition of poly-refractory RA
- **A significant percentage of pts with poly-refractory RA did not have active synovitis on ultrasound!!! Obesity and fibromyalgia was increased in this group**

- 30 year old woman requests a visit to discuss treatment options
- Hx of intermittent joint pain. Very strong hx of RA with grandmother and mother having disease
- Rheumatic ROS negative
- She does not smoke
- Exam is entirely normal
- Labs include normal CRP and ESR, RF and anti-CCP are positive

- What would you do??
- A. Suggest starting hydroxychloroquine
- B. Start methotrexate 12.5 mg per week
- C. Administer one dose of Rituximab
- D. Start abatacept
- E. No therapy started, schedule fu appt

MTX+ single dose steroid vs Placebo- arthralgias and MRI subclinical inflammation

Lancet 2022;400: 283

1 yr RCT of MTX (25 mg/wk) and single dose GC (120 mg) vs placebo in 236 pts with arthralgias and subclinical evidence joint inflammation by MRI

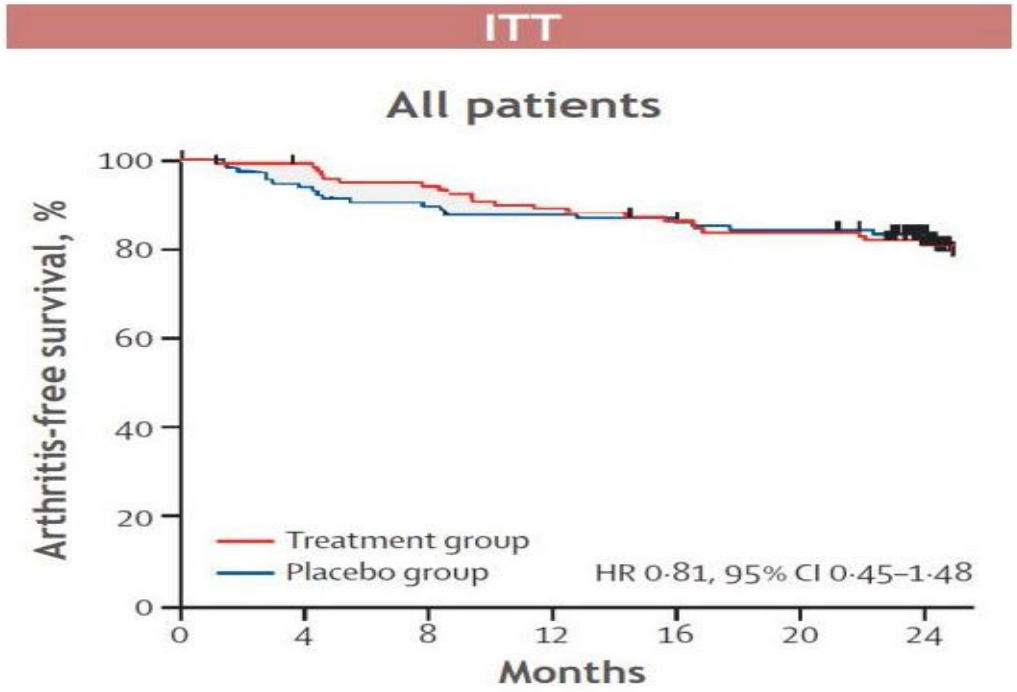
Exclusion: Hx of clinical arthritis

Past or current DMARD, steroid use

Primary outcome Clinical arthritis >2 wks and ACR/Eular 2010 criteria for RA

Primary outcome not met

At 2 yrs development of RA was same between treated group (19%) and placebo (18%)



Rituximab in pre-RA

Ann Rheum Dis 2019;78:179

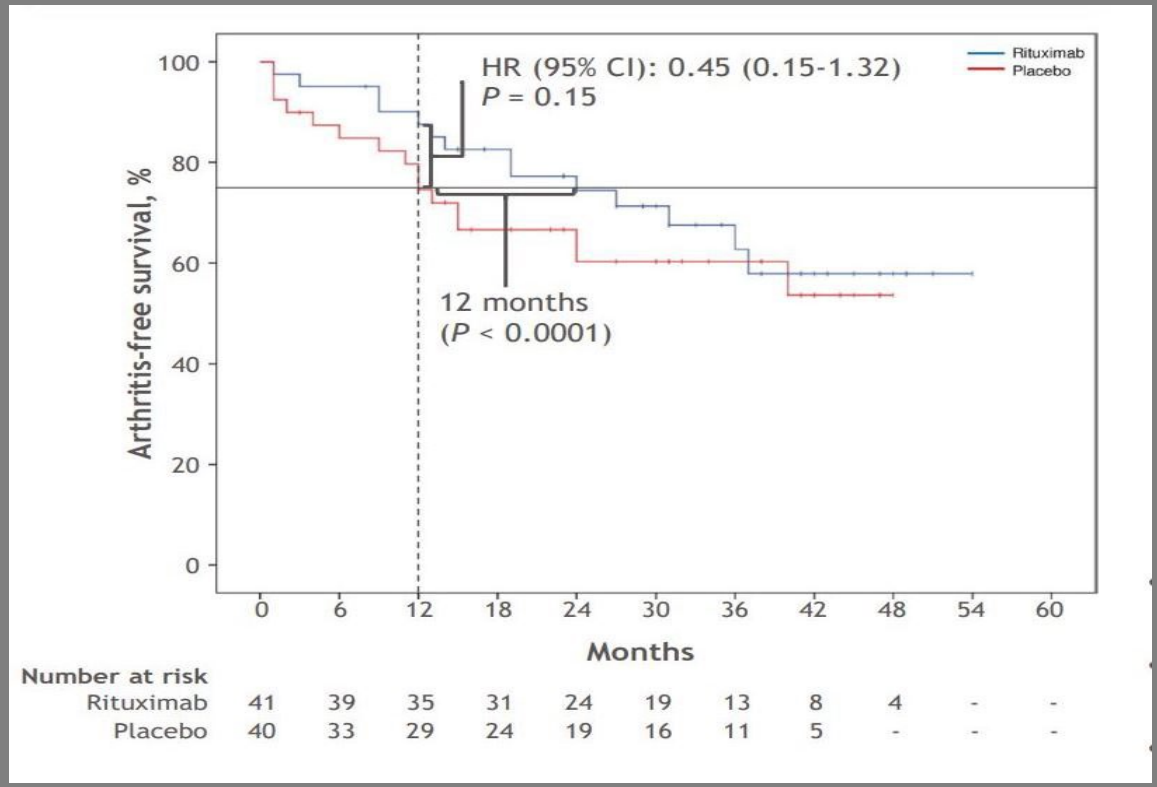
Placebo controlled study of single dose rituximab 1000 mg vs placebo

81 pts with Positive RF and CCP and either CRP>0.6 or evidence of subclinical synovitis by ultrasound or MRI

Exclusion- presence of clnical synovitis and prior DMARDs

Endpoint time for development of clinical synovitis at year 1

Primary endpoint not met



STOP RA: HCQ v Placebo

ACR 2022 #1604

Objective Determine if hydroxychloroquine treatment for 1 year reduced risk of developing RA at the end of 3 years in individuals with elevated anti CCP ab without inflammatory arthritis (IA) at baseline.

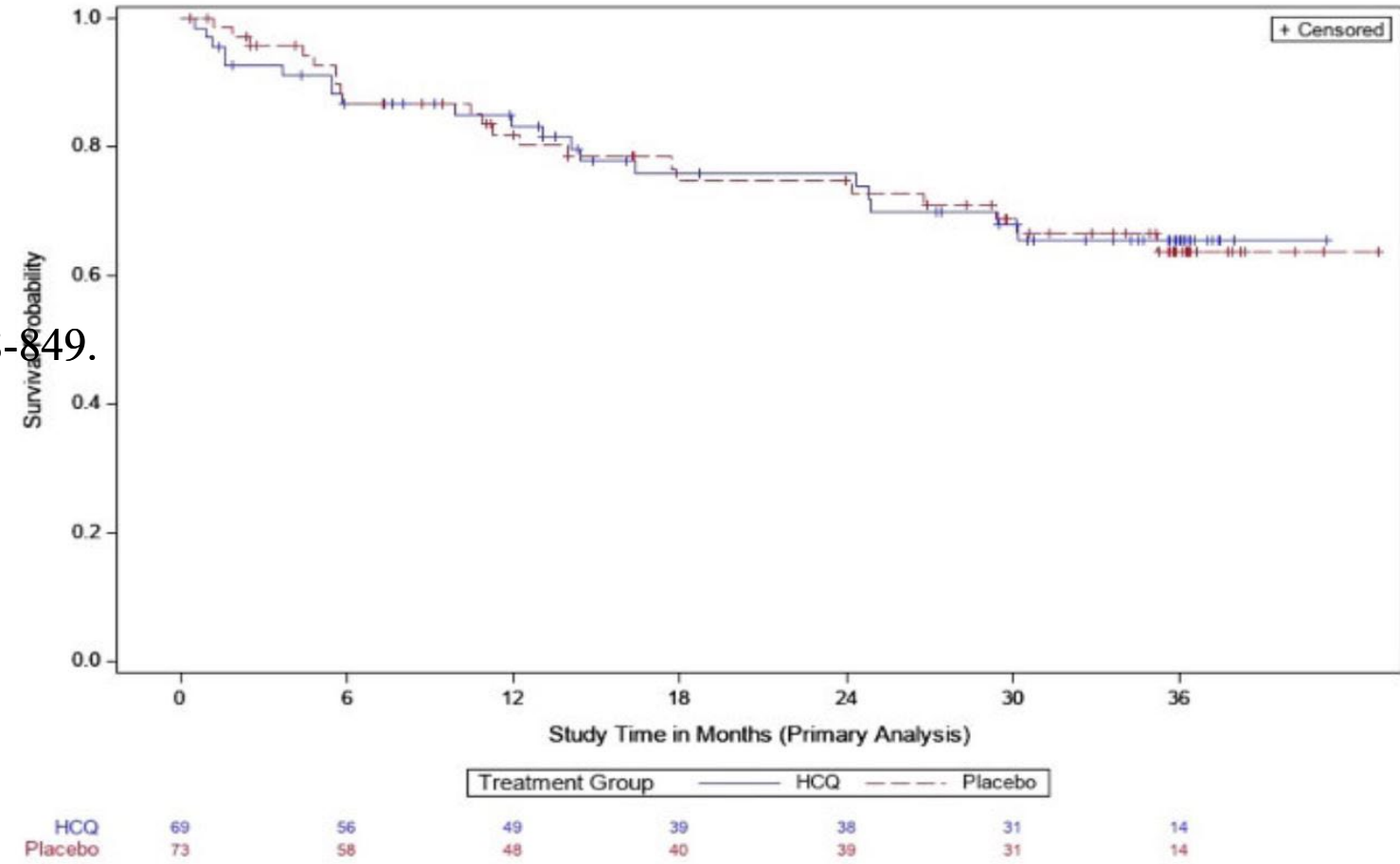
Methods 1 yr RCT of HCQ vs Placebo in adults with positive anti-CCP3 >40 U/ml and <10 joints

2024;403(10429):838-849.

Results; 144 randomized, 142 started therapy

Interim analysis 41 subjects developed RA, 34% in Hcq group and 36% placebo. Study met futility criteria so study was stopped

Conclusions; **Hcq was not superior to placebo in preventing or delaying IA and classified RA at 3 yrs in subjects with positive anti CCP3 antibodies**



Abatacept in Arthralgias+MRI Patients

ACR 2022 No 0455

RCT of Abatacept vs Placebo in pts with joint pain >6wks, autoab + (RF or ACPA) and MRI inflammation (synovitis, tenosynovitis or osteitis)

Exclusion- Joint swelling, prednisone, Dmard use

Aba 125 mg sq weekly or placebo for 24 wks

Primary outcome at month 6: Improvement in >1 Inflammation parameter by MRI (RAMRIS)

SUMMARY OF EFFICACY

	Abatacept SC (n = 49)	Placebo (n = 49)	Total (N = 98)	*P* value
PRIMARY ENDPOINT				
Improvement in MRI inflammation score, n (%)	20 (61.2)	15 (30.6)	45 (45.9)	0.0043
SECONDARY ENDPOINTS				
Progression to arthritis, n (%)				
6 months	4 (8.2)	17 (34.7)	21 (21.4)	0.0025
18 months	17 (34.7)	28 (57.1)	45 (45.9)	0.0421

- Abatacept is superior to placebo in improving subclinical inflammation in "at-risk" subjects (ACPA+, MRI+, arthralgia+) at 6 months
- Abatacept is superior to placebo in inhibiting the progression to arthritis at 6 months
- Follow-up results at 18 months reveal that a time-limited intervention of abatacept has a sustained effect on inhibition of progression to arthritis
- Use of abatacept in "at-risk" subjects is safe and no new safety issues emerged

Abatacept in Pre-RA: A Placebo controlled study

Lancet 2024;403:838-849.

Double blind 52 weekly study of weekly abatacept 125 mg sq weekly or placebo and then followed for another 52 weeks

Arthralgia and positive ACPA/RF or ACPA (>3xULN)

Excluded prior synovitis, prior steroids or DMARDs

Primary endpt was time of development of either clinical synovitis >3 jts or RA by 2010 criteria. Jt swelling confirmed by ultrasound

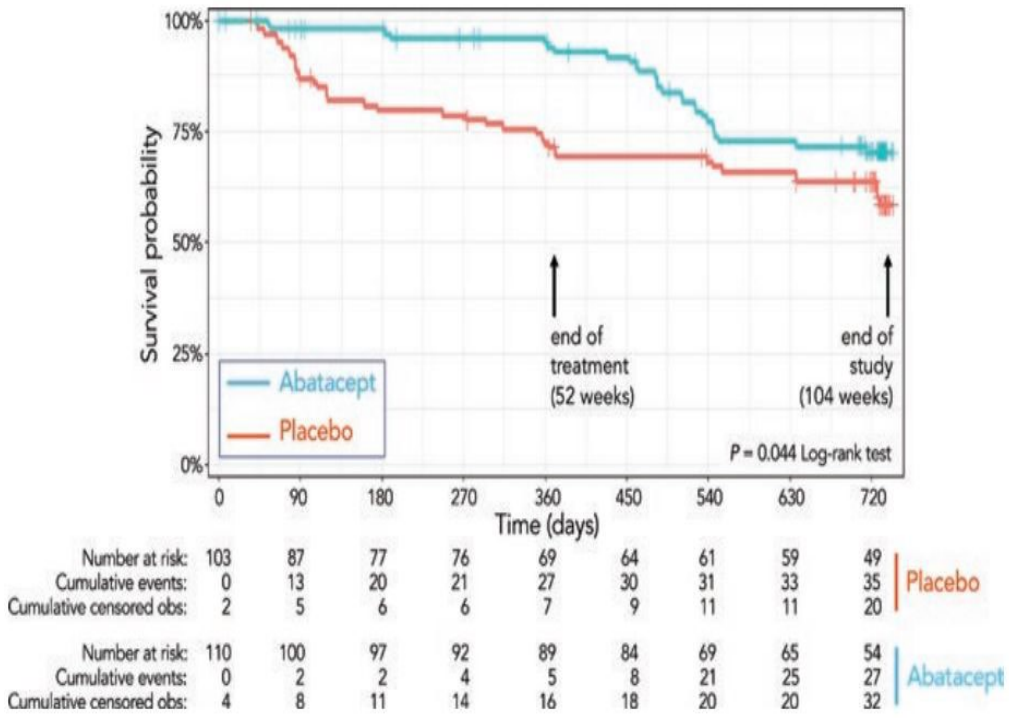
Between 2104-2019 -280 evaluated and 213 randomized in Uk and Netherlands

Mean age 49, 77% women Ultrasound suggested modest level of subclinical synovitis (73% with power doppler score of 0)

At week 52 29% in placebo and 6% in aba group met the end point.

At week 104 37% in placebo and 25% in the aba group that met the end pt

This study showed that individuals with auto-ab profile were most likely to remain arthritis free following aba therapy



- 55 year old woman has very active RA with CDAI of 25
- Has received methotrexate 25 mg/wk, 3 anti-TNF, Abatacept, Toci, 2 Jak inhibitors
- What can you offer her??
- A Combination therapy
- B Vagal nerve stimulation
- C PD 1 agonist
- D Cart T
- E T cell engagers

Combination Therapies

MTX+HCQ
MTX+IM Gold
MTX+Auranofin
MTX+Azathioprine
MTX+SSA

Additive effects
MTX+Leflunomide
MTX+AZA+HCQ
MTX+SSA+HCQ
MTX+CSA

Etanercept +IL1 ra
Etanercept + Abatacept
Etanercept +Rituximab
anti-TNF+ anti-cadherin 11
antiTNF+anti IL-17

antiTNF+BTK inhibitor

Vagal Nerve Stimulation in Biologic Experience RA pts
ACR L10, 2024

242 RA pts with active RA who were biologically experienced were randomized to receive vagal nerve stimulation or non active stimulation

Primary outcome was ACR 20 at 12 wks

Demographics- RA duration 12 yrs, 53% seropositive

39% >3 prior b/tsDMARDs

ACR 20 35.2% vs control 24.2% p=0.029

ACR 20 for 1 prior bdDMARD 44.2 vs 19% p=.0054

Serious AEs 1.7%

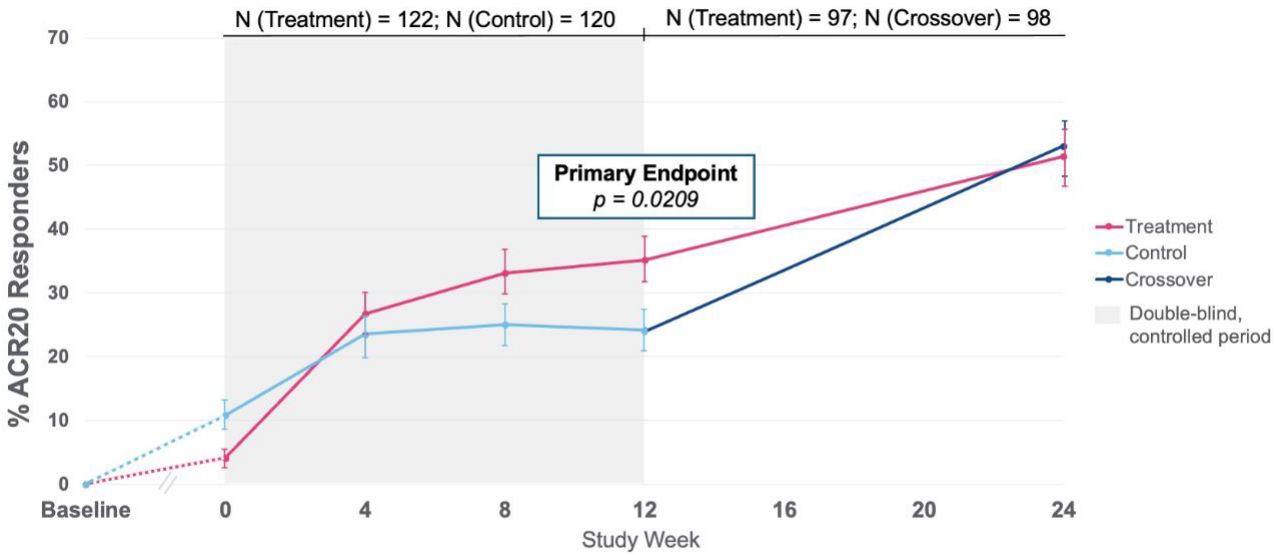
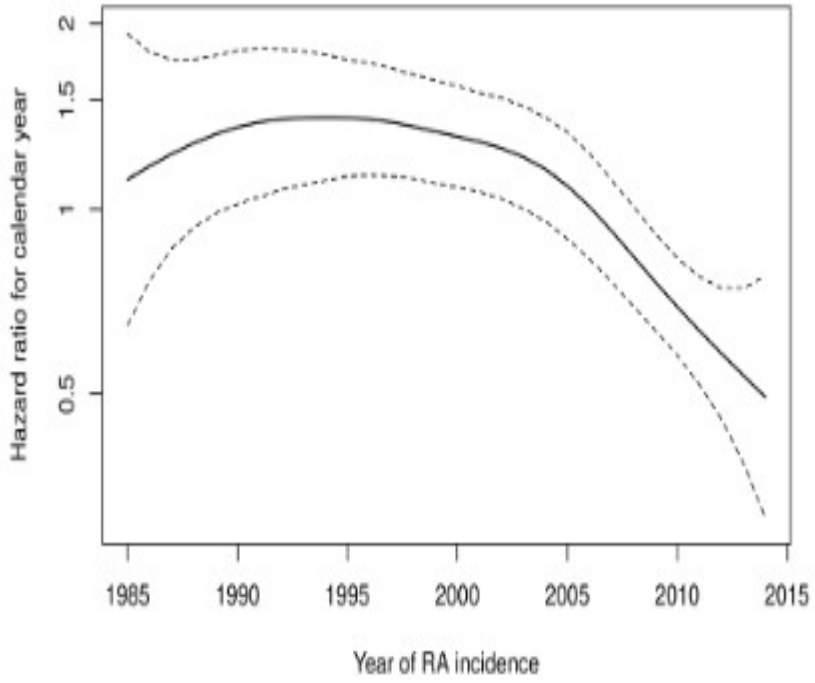


Figure 1: Primary endpoint of ACR20 response at Week 12 (p-value=0.0209, 95% CI 0.6 to 23.1 based on the Cochran-Mantel-Haenszel test accounting for stratification). Patients from Treatment and Control groups were imputed as non-responders if missing or rescued with steroid or b/tsDMARDs at any timepoint and excluded from analysis at all other timepoints.

Decline in Extra-Articular RA over 2 Decades

Arthritis Care Res 2024; 76:454

- Retrospective observational study from Mayo Clinic of an inception cohort of RA pts who lived in Olmstead County
- Pts with RA living in Olmstead County 907 pts (1985-1999) and 611 pts (2000-2014)
- Extra-articular RA declined 45% vs 32% primarily due to reduction in RA nodules
- Mortality was increased in pts with extra-articular RA



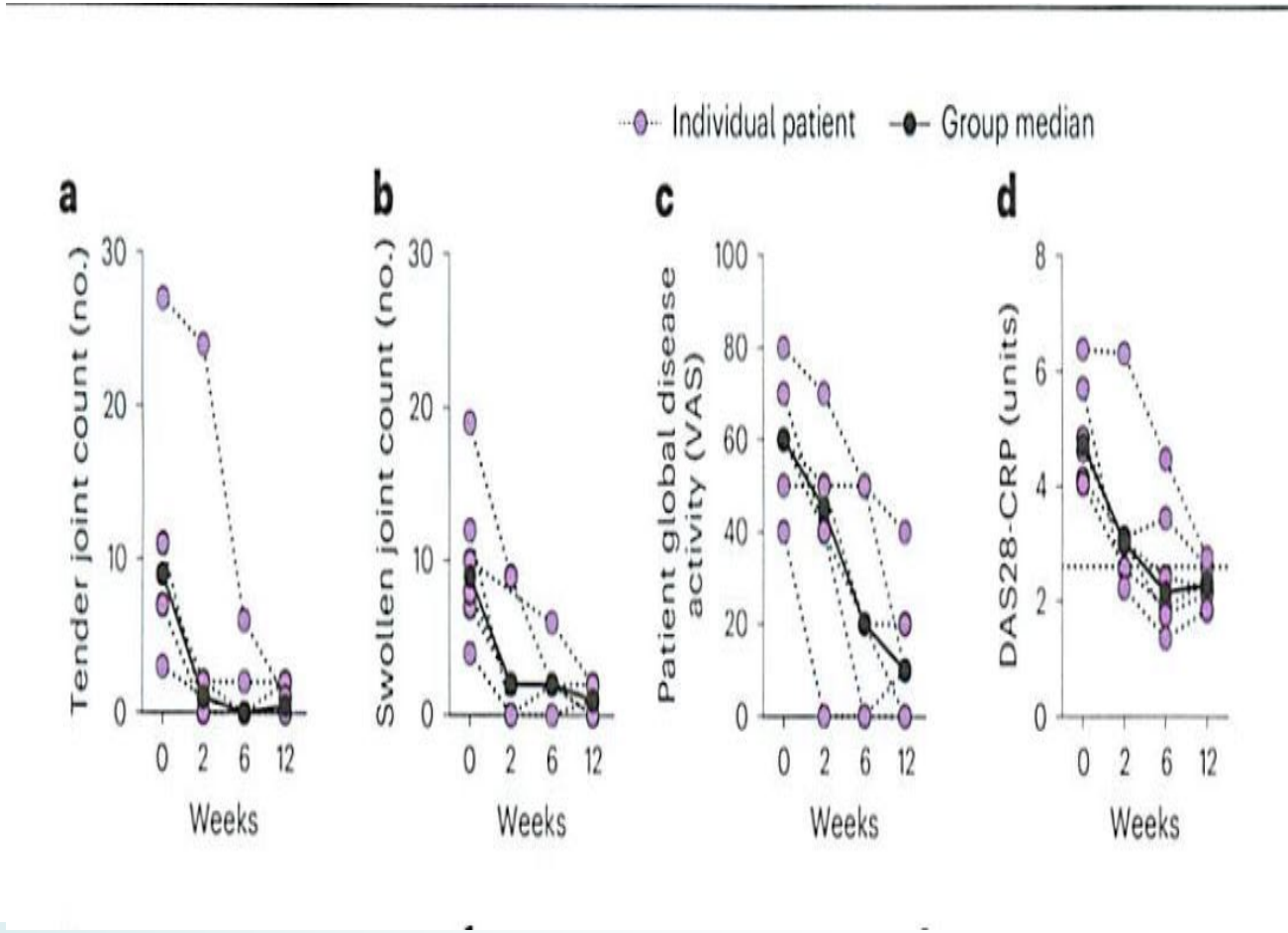
nature medicine

Article

https://doi.org/10.1038/s41591-024-02964

Bispecific T cell engager therapy for refractory rheumatoid arthritis

- BiTEs- Bispecific T cell engagers– kill B cells by engaging T cells
- Initially studied in hematologic malignancy
- Now being studied in pts with systemic rheum diseases including SLE and RA
- Case series of 6 pts with RA who received Blinatumomab which targets CD19 B cells via engaging CD3T cells
- Disease duration 6 yrs, multi-DMARD experienced pts including MTX, Leflunomide, TNF Inhibitors, I-6 and Jak inhibitors with DAS 5.1
- Treatment was for 5 days and reinfused 1 wk later for 5 days
- Infusions were reasonably well tolerated-mild increase in temp, increase in CRP and increase in IL-6
- Marked depletion in peripheral B cells and reduction in CD4 and CD8 Tcells, reduction in RF and CCP



RA:2025

- MTX remains the cornerstone of therapy–maximize the dose and go to sq or split dose as dose is escalated. Add another drug if not in low disease activity at max dose of MTX
- Biologics or JAK inhibitors induce a significant response in MTX partial responders in combo with MTX or as monotherapy. MTX reduces antibodies to biologics
- JAK inhibitors are better than MTX, work quickly and are at the minimum equal to ADA as monotherapy or in combo with MTX. DVT/PE/ MACE risk and mechanism unknown
- Consider reduction of MTX in combo pts in LDA after 6 months of desired clinical state.
- Complete discontinuation of therapy generally not effective!
- Confirm that the difficult to treat pt as active synovitis!!!
- Combination therapy needs to be explored – to date the experience has mixed
- Several novel therapies under study including vagas nerve stimulation, CART , BiTEs

- Thank you!!
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