Rheumatology Year in Review 2021-2022

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Disclosure Facts

ACCME Credit hours	1
Sponsor (Support)	MRS
Conflicts Stock/own	0
Investigator	none
Consultant	Abbvie, Amgen, Novartis, BMS
Coverage RA	Abatacept
TNF inhibitors	Glucocorticoids
IL-6 inhibitors	Rituximab
JAK inhibitors	Drug Safety

This talk represents my views of the above, sometimes with the aid of evidence based medicine. Corporate relationships and conflicts should NOT influence lecture content. Send your critique of the fair balance of this presentation/content to me at jackcush@rheumnow.com

Drug Approvals

FDA Approvals

- MTX + Pegloticase
- Tofacitinib in AS, atopic dermatitis
- Upadacitinib in PsA & AS, atopic dermatitis
- Baricitinib in COVID-19, Alopecia areata
- Secukinumab in jPsA & ERA
- Canakinumab in Adult Stills Dz
- IVIG inflammatory myositis
- Risakizumab in PsA and Crohns colitis

Problems

- Tanezumab denied
- Bimekizumab delayed

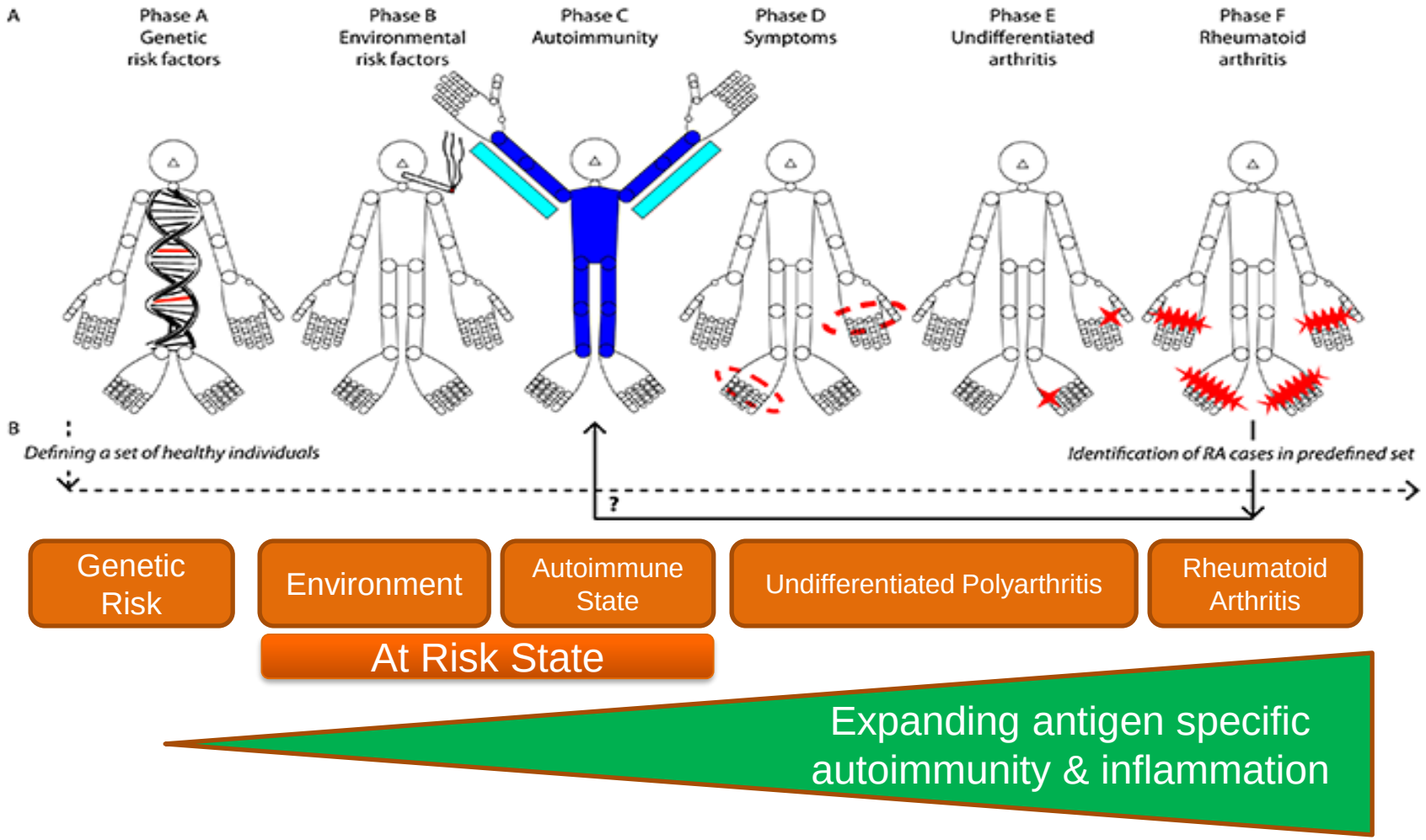
What to do with Pre-Clinical RA?

DEFINITION

- 1st Degree relatives, seropositive for ACPA + Arthralgias >12 wks
- No Synovitis by exam
- Elevated ESR or CRP
- Not meeting ACR RA Criteria

- What to Do:
  - Treat symptoms (not lab)?
  - Use DMARD as preventative Rx?

Rheumatoid Arthritis: Pre-clinical → clinical

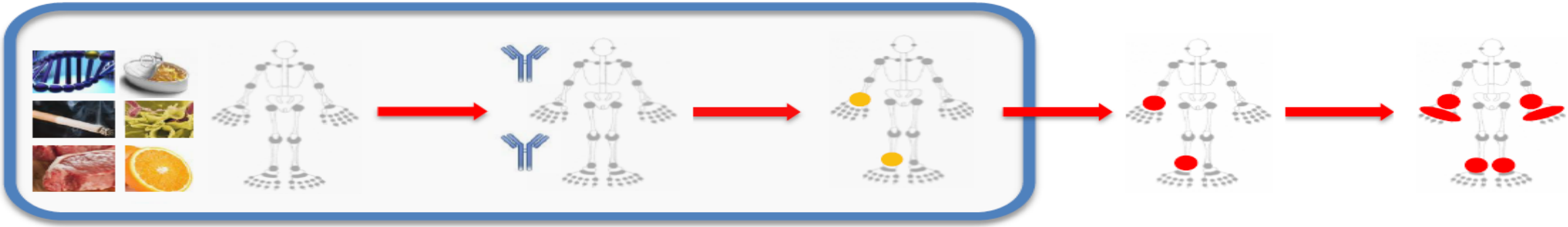


Holers MM. Rheum Dis Clin North Am.2014 Nov;40(4):605-620

SEROPOSITIVITY EFFECT ON PROGRESSION TO RA

Author, Year	Cohort	Cases (n)	Progression to arthritis (%)	follow-up, months	Predictive value
de Bois et al, 1996[32]	Arthralgia (secondary care)	52†	**21%**	12	RA; PPV 50%, NPV 100%.
Bos et al, 2010[22]	ACPA+ or RF+ arthralgia (secondary care)	147	**20%**	28	PPV for arthritis in 2 years: ACPA-RF+ 6%; ACPA+RF+ 40%.
van de Stadt et al, 2011[28]	ACPA+ +/-RF+ arthralgia (secondary care)	244	**28%**	36	
Shi et al, 2013[33]	ACPA+ +/-RF+ arthralgia (secondary care)	340	**38%**	36	PPV for Arthritis: ACPA+ anti-CarP− 40%, ACPA+anti-CarP+ 58%.
Van de Stadt et al, 2013[23]	ACPA+ +/- RF+ arthralgia (secondary care)	374	**35%**	32	
de Hair et al, 2014[29]	ACPA+ +/-RF+ @risk (secondary &public fairs)	55	**27%**	24	.
Rakieh et al, 2015[27]	ACPA+ MSK+ (PCP, secondary care)	100	**50%**	20	
Rombouts et al, 2015[31]	ACPA+ arthralgia (secondary care)	183	**57%**	35	
Janssen et al, 2016[30]	ACPA+ +/- RF+ arthralgia (secondary care)	34	**41%**	40	
van Steenbergen et al, 2016[24]	Clinically suspect arthralgia (secondary care)	150	**20%**	17	PPV for arthritis development within 1 year: ACPA 63%.
Nam et al, 2016[25]	MSK Sx (primary care)	2028	**47%**	12 -14	PPV of ACPA+ was 42%
Ten Brinck et al, 2017[26]	Clinically suspect arthralgia (secondary care)	241	**44%**	103	PPV for arthritis ACPA-RF+ 38%, ACPA+RF− 50%, ACPA+RF+ 67%.

What Will I do? – Hope & Wait for more Pre-Clinical RA Studies



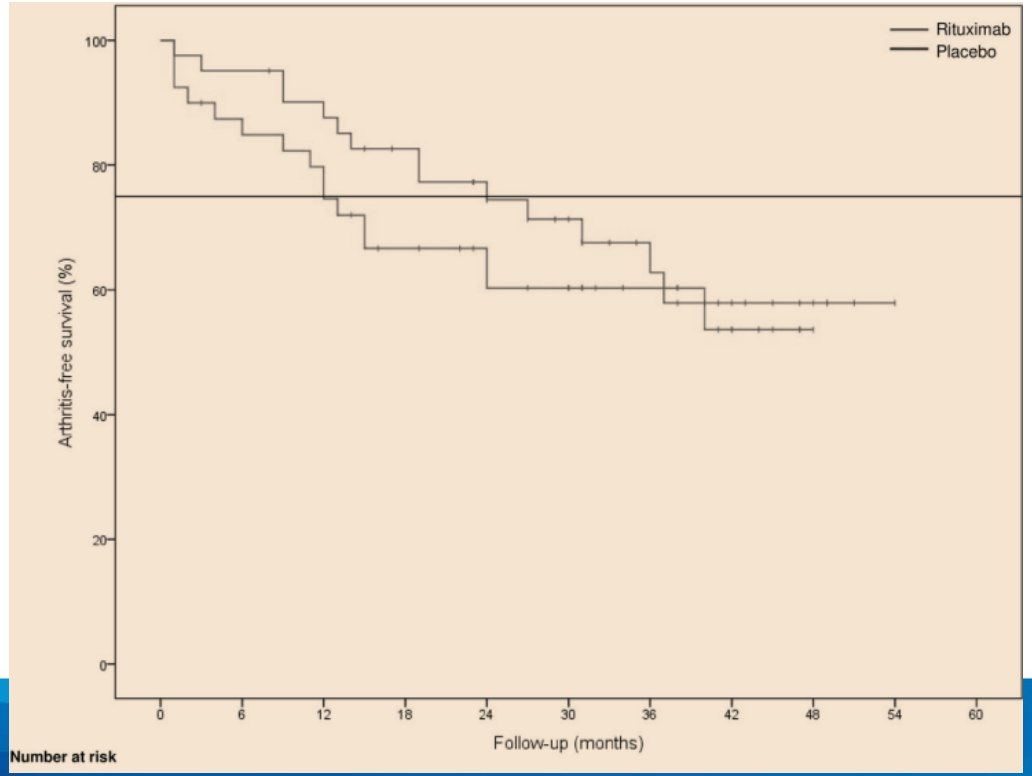
Study	Patients	Intervention	Control	Primary outcome	Trial reference
StopRA	ACPA FDRs Subjects at health fairs	HCQ 200-400mg/day for 1 year	Placebo	Clinical synovitis or RA	https://clinicaltrials.gov/ct2/show/NCT02603146
APIPPRA	ACPA >3xULN or ACPA plus RF inflammatory arthralgia	Abatacept s.c. 125 mg weekly for 1 year	Placebo	Clinical synovitis or RA	http://www.isrctn.com/ISRCTN46017566
ARIAA	ACPA arthralgia synovitis on MRI	Abatacept s.c. 125 mg weekly for 6 months	Placebo	Improvement of synovitis on MRI	https://clinicaltrials.gov/ct2/show/NCT02778906
STAPRA	ACPA >3xULN or ACPA plus RF inflammatory arthralgia	Atorvastatin p.o. 40 mg daily for 3 years	Placebo	Clinical synovitis	http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5265
TREAT EARLIER	Clinically suspect arthralgia Synovitis on MRI	Methotrexate p.o. weekly for 1 year	Placebo	Clinical synovitis	http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4853

PRAIRI study - RTX in Pre-clinical RA

- Intervention: placebo vs *single RTX infusion* (1000 mg)
- N=81 “at-risk” RF+/CCP+ patients with arthralgia and CRP >0.6 mg/L or subclinical synovitis (by US/MRI)
- F/U was 27 mos; 37%→arthritis
- SAE:⇧RTX (13/41 vs 3/40: p=0.014)

	PBO	RTX
Developed arthritis	40%	34%
Median (IQR) time to arthritis (months)	11.5 (2–15)	16.5 (9–28)
P<0.001		

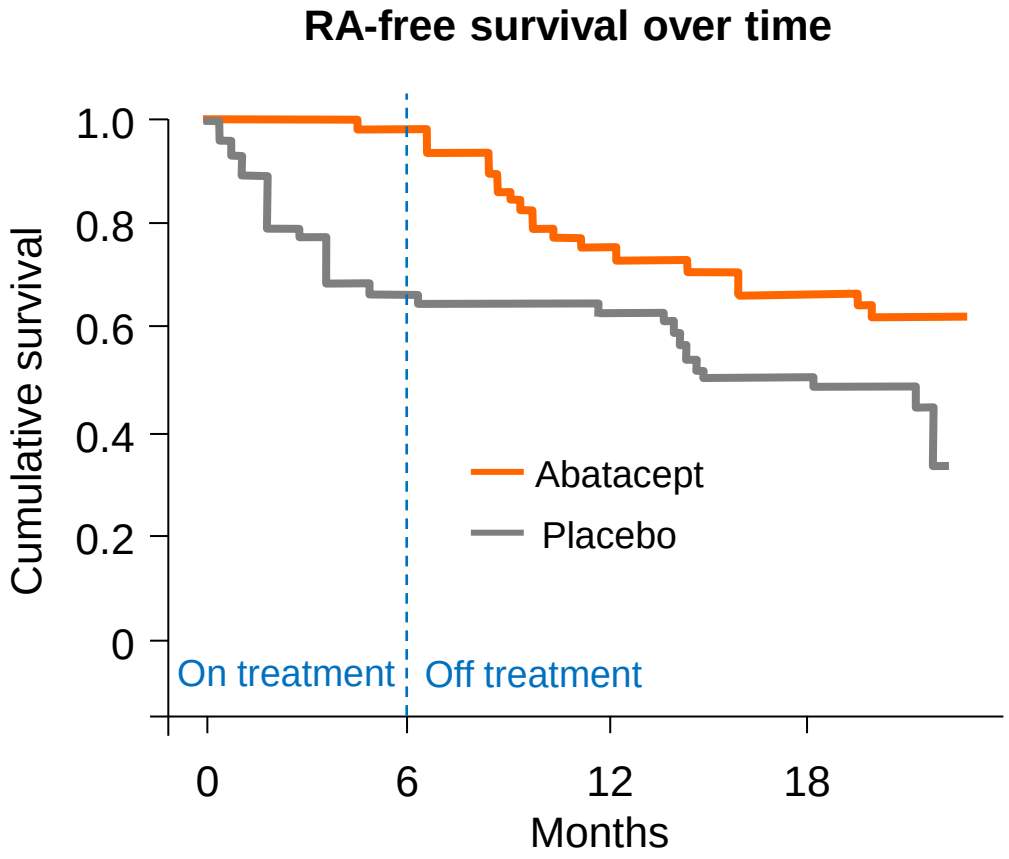
- One RTX dose delays RA onset



Gerlag DM, et al. Ann Rheum Dis. 2019 Feb;78(2):179-185.

ARIAA: Delayed RA onset with abatacept in at risk RA patients

- 18-month results from placebo-controlled DBRCT
  - ABA 125 mg SC qw ×6 months vs PBO in “RA at-risk” patients
    - ACPA+, arthralgia ≥6 weeks, MRI evidence of inflammation
  - 100 randomized; 98 evaluated
  - 1º endpoint 6 mos; Followed for 12 months off medication
- MRI improvement at 6 months
  - ABA 30 (61.2%); PBO 15 (30.6%); P=0.0043
- Progression to RA at 18 months
  - 6 mos: ABA (8%) vs PBO (31%); P=0.0025
  - 18 mos: ABA 17 (34.7%) vs PBO 28 (57.1%); P=0.0421
  - NNT = 8
- No significant safety signals noted
- Duration of arthralgia: ABA 883 vs PBO 387 days

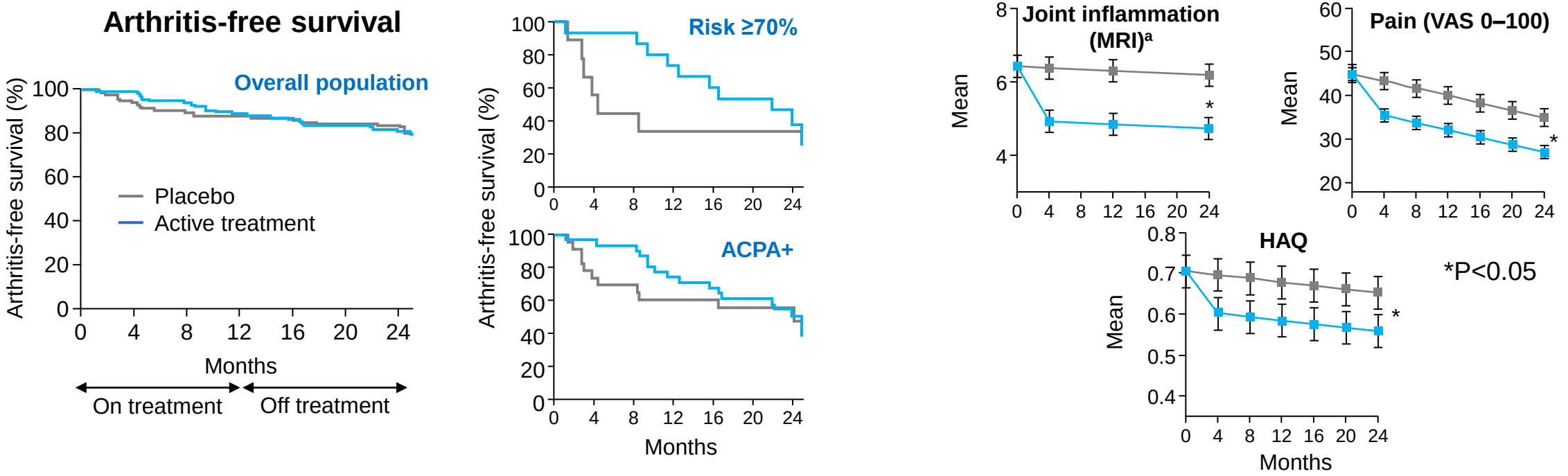


Treatment of “RA at-risk” patients with abatacept may delay onset of RA

Rech J, et al. EULAR 2022, Copenhagen, POS0531; Rech J, et al. ACR 2021, #455

TREAT EARLIER: MTX in arthralgia patients at risk of RA to reduce the development of persistent arthritis

- DBRCT of 236 Dutch patients with MRI-proven subclinical joint inflammation
  - Randomized to corticosteroid IM then MTX PO up to 25 mg/week for 1 y (n=119) or PBO (n=117); 1-y follow-up off treatment
  - Primary outcome: development of arthritis (2010 criteria or involving ≥2 joints) that persisted ≥2 weeks



Treatment of "RA at-risk" patients with MTX did not prevent RA, but modified disease course

[a]Sum of tenosynovitis, synovitis, osteitis, scored with RA-MRI Scoring (RAMRIS)

Krijbolder D, et al. EULAR 2022, Copenhagen, OP0070

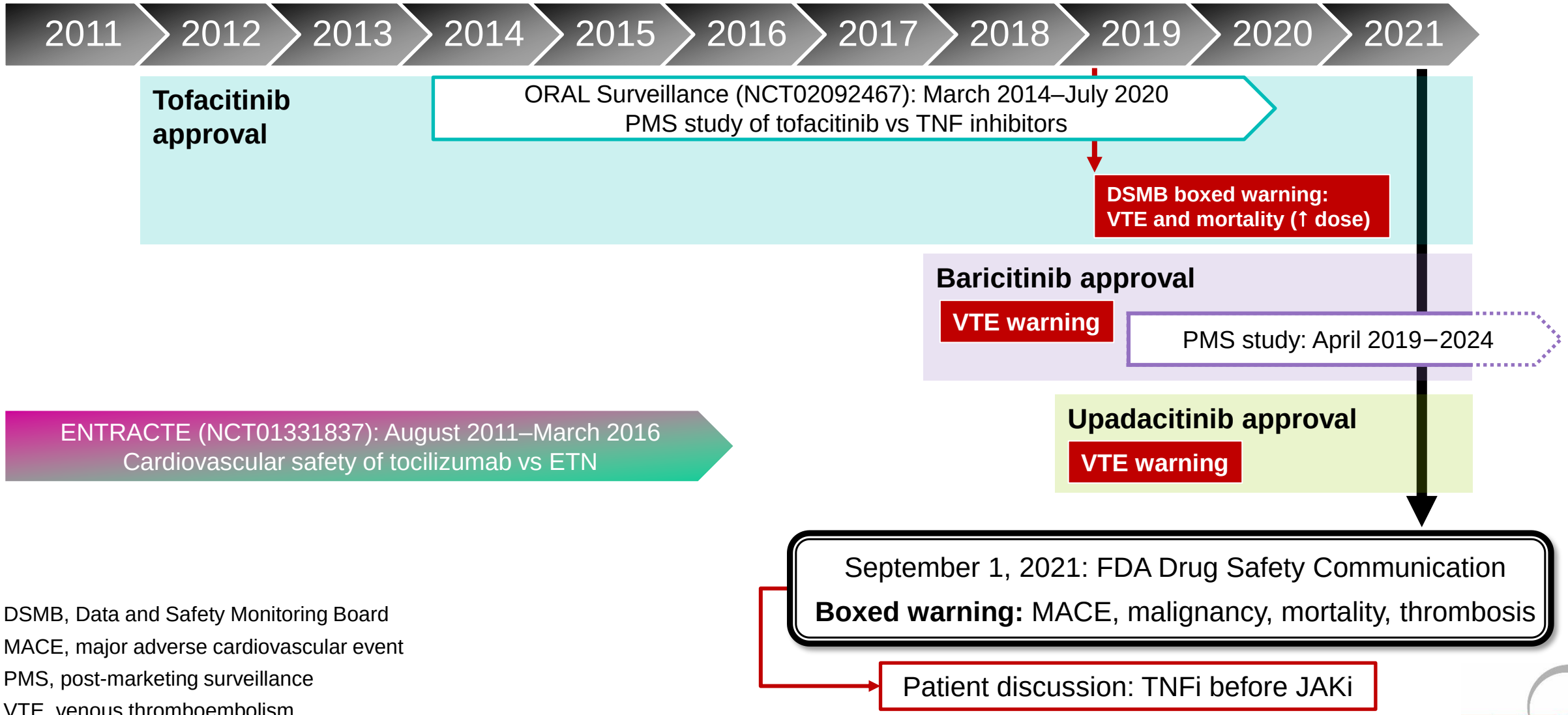
What are you going to do?

Worry?

- 1st FDRs; ACPA+, Arthralgias >12 wks
- Tenosynovitis
- Elevated CRP/ESR

(older, female, smoker?)

Jakinibs: Regulatory history and milestones



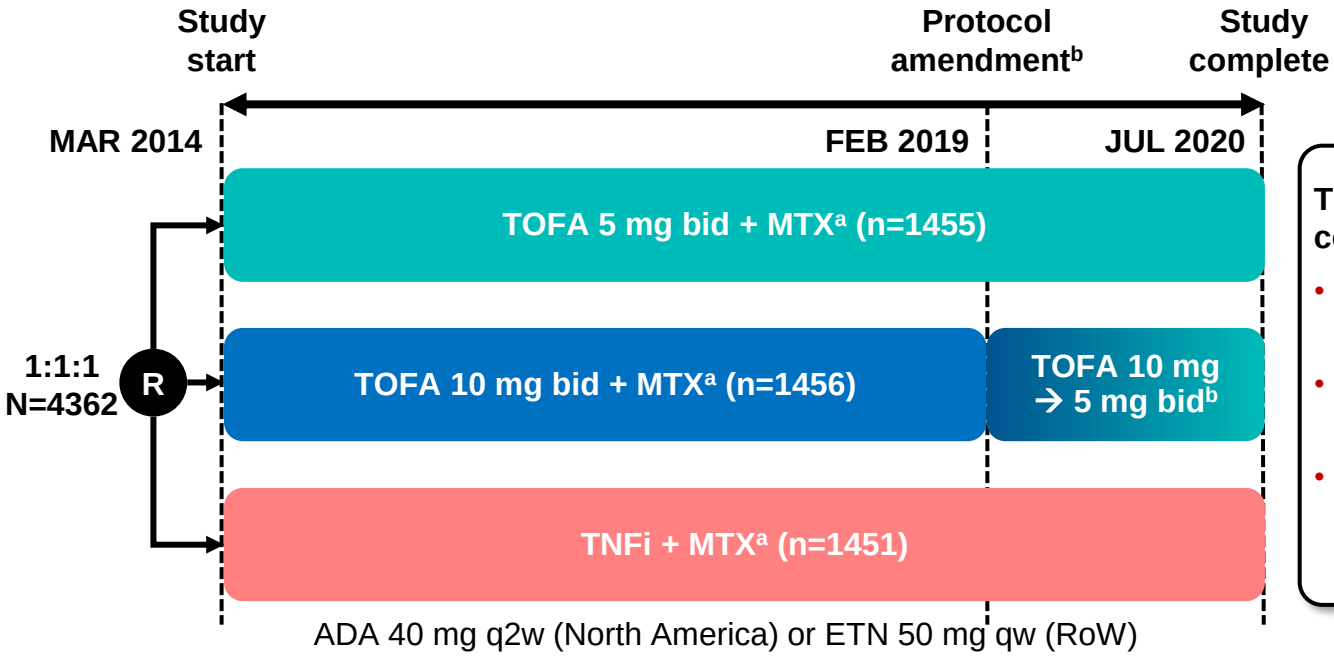
DSMB, Data and Safety Monitoring Board
MACE, major adverse cardiovascular event
PMS, post-marketing surveillance
VTE, venous thromboembolism
Rajpal A, et al. ACR 2021, FDA Safety Update

ORAL Surveillance: Tofacitinib vs TNF inhibitors in RA patients aged ≥50 y with ≥1 additional CV risk factor and an inadequate response to MTX

- Prospective, randomized open-label, Phase 3b/4 noninferiority trial – safety endpoint

Eligible patients

- **Moderate to severe RA**
- **MTX inadequate responder**
- **Age ≥50 years**
- **≥1 additional CV risk factor**
  Current cigarette smoker, HTN, HDL-C <40 mg/dL, diabetes mellitus, family history of premature CHD, extra-articular disease associated with RA, history of coronary artery disease
- **No current/prior malignancy**
  Except adequately treated NMSC or cervical carcinoma in situ



The study was completed once:

- ≥1500 patients were followed for ≥3 y
- ≥103 MACE were reported[c]
- ≥138 malignancies excluding NMSC were reported[c]

Primary comparison: combined TOFA doses vs TNFi
Noninferior if upper limit of 2-sided 95% CI: for HR was **<1.8**

Secondary comparison: TOFA 10 vs 5 mg bid
Non-inferior if upper limit of 2-sided 95% CI: for HR was **<2.0**

[a]Patients were maintained on pre-study stable dose of MTX (15–25 mg/week) unless modification of treatment was clinically indicated
[b]In Feb 2019, TOFA 10 mg bid dose was reduced to 5 mg bid after the FDA Data Safety Monitoring Board noted an increased frequency of pulmonary embolism in patients receiving TOFA 10 mg bid vs TNFi, and an increase in overall mortality with TOFA 10 vs 5 mg bid and TNFi
[c]103 MACE and 138 malignancies excluding NMSC were required to achieve 80% and 90% power, respectively

CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; NMSC, non-melanoma skin cancer

Ytterberg SR, et al. ACR 2021, #831; Charles-Schoeman C, et al. Ibid, #958

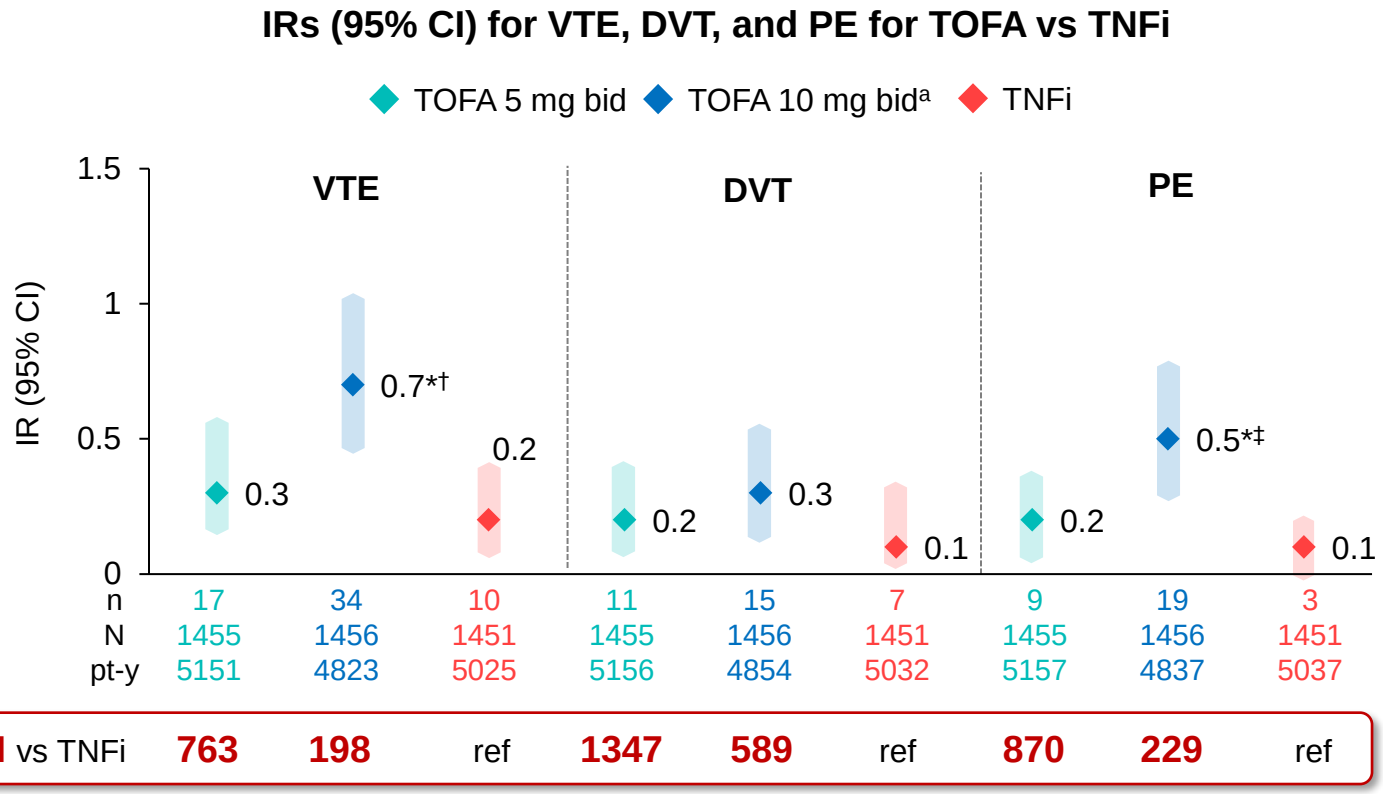
ORAL Surveillance:
Patient demographics and baseline characteristics

	TOFA 5 mg bid (n=1455)	TOFA 10 mg bid[a] (n=1456)	TNFi (n=1451)
Age (years), median (range)	60.0 (50.0–86.0)	61.0 (50.0–85.0)	60.0 (50.0–88.0)
≥65 years, n (%)	413 (28.4)	478 (32.8)	462 (31.8)
Female, n (%)	1169 (80.3)	1124 (77.2)	1117 (77.0)
Race, n (%) White Black Asian Other	 1128 (77.5) 63 (4.3) 65 (4.5) 199 (13.7)	 1126 (77.3) 65 (4.5) 56 (3.8) 209 (14.4)	 1099 (75.7) 83 (5.7) 55 (3.8) 214 (14.7)
Duration of RA (years), mean ±SD	10.4 ±8.8	10.2 ±9.0	10.6 ±9.3
Smoking status, n (%) Never Smoker Ex smoker	 735 (50.5) 411 (28.2) 309 (21.2)	 752 (51.6) 402 (27.6) 302 (20.7)	 772 (53.2) 353 (24.3) 326 (22.5)
History of hypertension, n (%)	955 (65.6)	954 (65.5)	969 (66.8)
History of diabetes mellitus, n (%)	243 (16.7)	261 (17.9)	255 (17.6)
History of extra-articular disease[b], n (%)	532 (36.6)	521 (35.8)	552 (38.0)
History of CHD, n (%)	161 (11.1)	172 (11.8)	164 (11.3)
Family history of coronary heart disease, n (%) First-degree male relative aged <55 y First-degree female relative aged <65 y	 154 (10.6) 115 (7.9)	 132 (9.1) 107 (7.3)	 151 (10.4) 100 (6.9)
HDL-C <40 mg/dL, n (%)	172 (11.8)	195 (13.4)	173 (11.9)
Aspirin use[c], n (%)	212 (14.6)	231 (15.9)	224 (15.4)
SDAI, mean ± SD	41.5 ± 12.5[d]	41.5 ± 12.6[e]	41.4 ± 12.5[f]

[a]TOFA 10 mg bid group included patients who switched from 10 to 5 mg bid as a result of a protocol modification in 2019; [b]Includes nodules, Sjögren's syndrome, anemia of chronic disease, pulmonary manifestations, and other; [c]Based on Day 1 of treatment with TOFA or TNFi in ORAL Surveillance; [d]n=1410; [e]n=1404; [f]n=1386

Ytterberg SR, et al. ACR 2021, #831; Charles-Schoeman C, et al. Ibid, #958

ORAL Surveillance:
Risk of VTE, DVT, and PE with tofacitinib vs TNF inhibitors



Overall risk factors for PE

Baseline covariate	HR (95% CI)
History of VTE	7.06 (2.46, 20.25)
Use of oral contraceptives/HRT	3.56 (1.05, 12.10)
Corticosteroid use[b]	3.01 (1.40, 6.46)
BMI ≥30 kg/m^2	2.97 (1.40, 6.32)
Antidepressant use[c]	2.94 (1.44, 6.02)
History of hypertension	2.57 (0.98, 6.76)
Male[d]	2.18 (1.06, 4.48)
Age ≥65 years	2.00 (1.03, 3.88)
Proton pump inhibitor use	0.32 (0.15, 0.71)

[b]Proxy for elevated BL disease activity; HRs for BL GC use similar for all TOFA doses combined and TNFi; [c]BL antidepressant use was an indicator of underlying depression, subgroup analysis did not identify the difference in HRs across groups; [d]Impact of sex on PE risk considered inconclusive

Incidence of VTE, DVT, and PE was higher for tofacitinib 10 mg vs 5 mg and TNF inhibitors

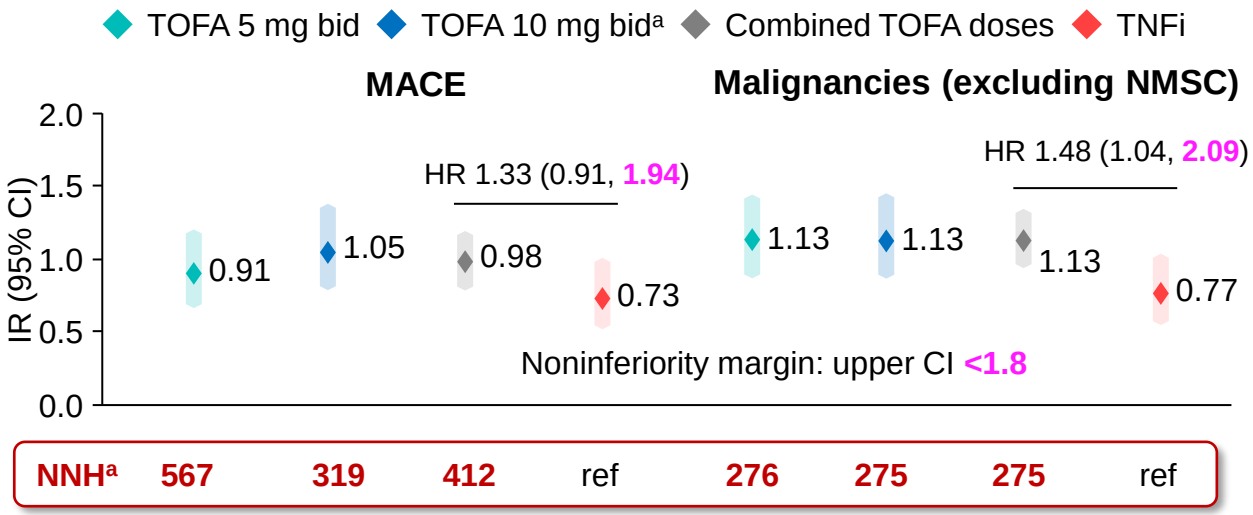
[a]Includes patients who switched from 10 to 5 mg bid as a result of 2019 protocol modification. *Nominal P<0.001 for TOFA 10 mg bid vs TNFi; Nominal †P≤0.05 and ‡P<0.01 for TOFA 10 vs 5 mg bid. NNH defined as the reciprocal of the IR difference between TOFA and TNFi and interpreted as pt-y of exposure to TOFA required to have 1 additional AE relative to TNFi

Charles-Schoeman C, et al. ACR 2021, #1941

ORAL Surveillance: Post hoc analyses of MACE by baseline cardiovascular risk

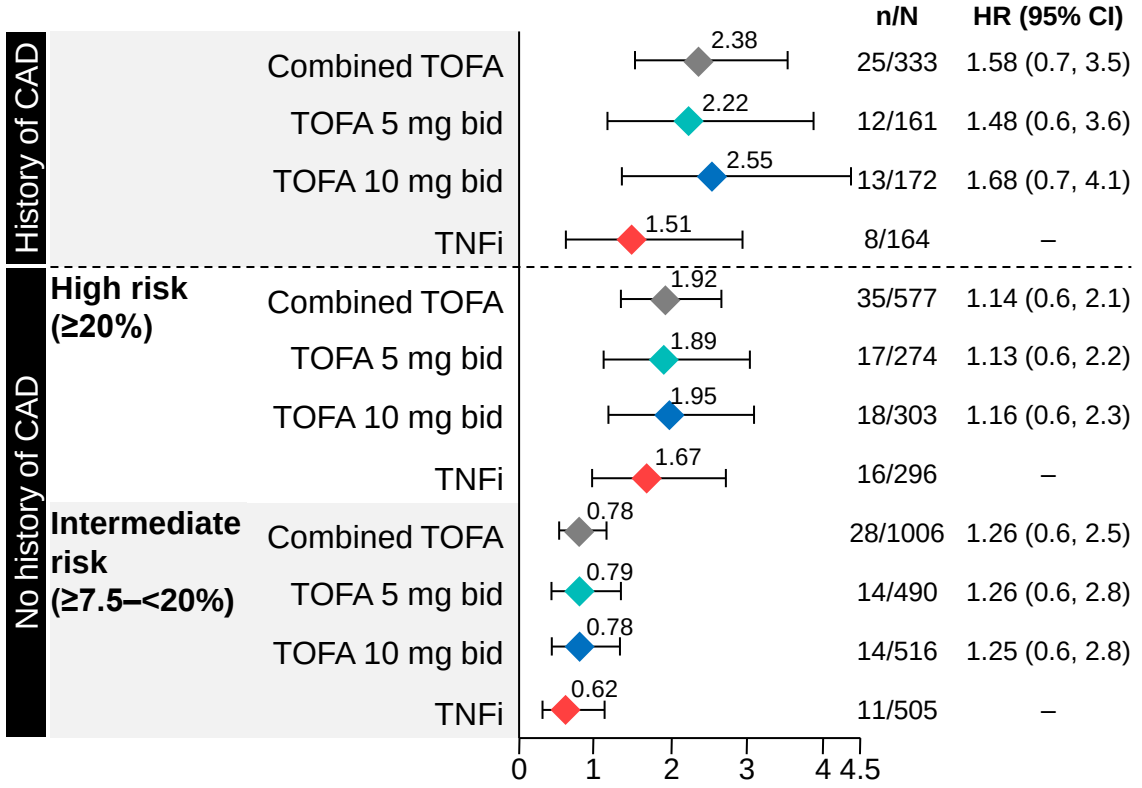
- Prospective, Phase 3b/4 noninferiority RCT in 4362 RA patients aged ≥50 years with ≥1 additional CV risk factor

Primary outcome: adjudicated MACE and malignancies[1]



[a]NNH = number of pt-y of exposure needed for treatment to have 1 more event relative to reference; calculated post hoc

Risk of MACE according to history of CAD and BL CV risk[2]



MACE and malignancies, not VTE, highest in patients with history of CAD/high BL CV risk

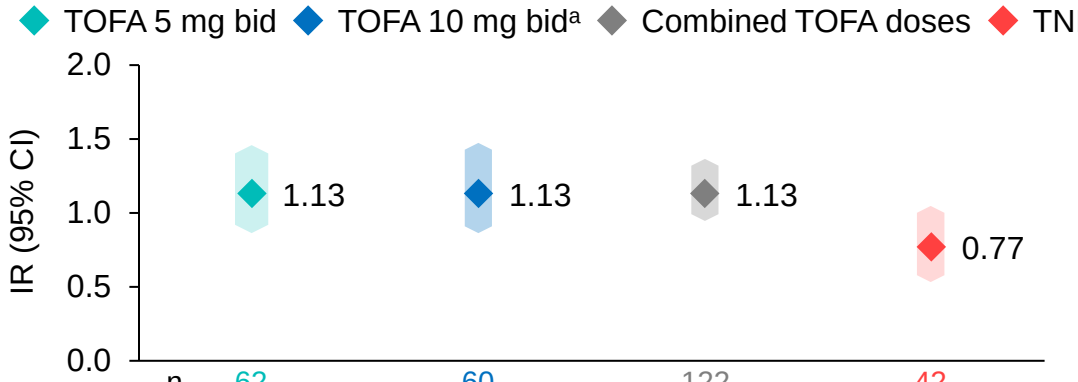
CAD, coronary artery disease; MACE, major adverse cardiovascular event; NNH, number needed to harm; NMSC, nonmelanoma skin cancer

1. Ytterberg SR, et al. ACR 2021 (virtual), #831; 2. Buch MH, et al. EULAR 2022, Copenhagen, POS0237

ORAL Surveillance:
Risk of malignancy with tofacitinib vs TNF inhibitors

- Multivariable risk factors: age ≥65 y and current/past smoking

IR (95% CI) malignancies excluding NMSC



	TOFA 5 mg bid	TOFA 10 mg bid[a]	Combined TOFA doses	TNFi
n	62	60	122	42
N	1455	1456	2911	1451
pt-y	5491	5312	10,803	5482
NNH vs TNFi	**276**	**275**	**275**	ref
HR vs TNFi (95% CI)	1.47 (1.00, 2.18)	1.48 (1.00, 2.19)	1.48 (1.04, 2.09)	ref

Frequencies and IRs for cancer subtypes of interest

n, IR/100 pt-y (95% CI)	TOFA 5 mg bid (n=1455)	TOFA 10 mg bid (n=1456)	TNFi (n=1451)
All malignancies excluding NMSC	**62**, 1.13 (0.87, 1.45)	**60**, 1.13 (0.86, 1.45)	**42**, 0.77 (0.55, 1.04)
Lung cancer	**13**, 0.23 (0.12, 0.40)	**17**, 0.32 (0.18, 0.51)	**7**, 0.13 (0.05, 0.26)
Breast cancer[a]	**10**, 0.22 (0.11, 0.41)	**7**, 0.17 (0.07, 0.35)	**10**, 0.24 (0.11, 0.43)
Lymphoma	**4**, 0.07 (0.02, 0.18)	**6**, 0.11 (0.04, 0.24)	**1**, 0.02 (0.00, 0.10)
Prostate cancer[b]	**1**, 0.09 (0.00, 0.52)	**8**, 0.68 (0.29, 1.34)	**3**, 0.24 (0.05, 0.69)
Colorectal cancer	**4**, 0.07 (0.02, 0.18)	**4**, 0.07 (0.02, 0.19)	**4**, 0.07 (0.02, 0.19)
Pancreatic cancer	**3**, 0.05 (0.01, 0.16)	**1**, 0.02 (0.00, 0.10)	**1**, 0.02 (0.00, 0.10)
Melanoma	**1**, 0.02 (0.00, 0.10)	**1**, 0.02 (0.00, 0.10)	**5**, 0.09 (0.03, 0.21)
NMSC	**31**, 0.61 (0.41, 0.86)	**33**, 0.69 (0.47, 0.96)	**16**, 0.32 (0.18, 0.52)
Squamous cell carcinoma	**15**, 0.29 (0.16, 0.48)	**22**, 0.45 (0.29, 0.69)	**8**, 0.16 (0.07, 0.31)
Basal cell carcinoma	**19**, 0.37 (0.22, 0.58)	**16**, 0.33 (0.19, 0.54)	**13**, 0.26 (0.14, 0.44)

[a]Female only: TOFA 5 mg bid, n=1169; TOFA 10 mg bid, n=1124; TNFi, n=1117
[b]Male only: TOFA 5 mg bid, n=286; TOFA 10 mg bid, n=332; TNFi, n=334

Numerical increase in some malignancies with tofacitinib vs TNF inhibitors

[a]Includes patients who switched from 10 to 5 mg bid as a result of 2019 protocol modification. NNH (95% CI) defined as the reciprocal of the IR difference (not shown) between TOFA and TNFi and interpreted as pt-y of exposure to TOFA required to have 1 more event relative to TNFi. If the 95% CI: of the IR difference includes 0, the 95% CI: of the NNH is disjointed

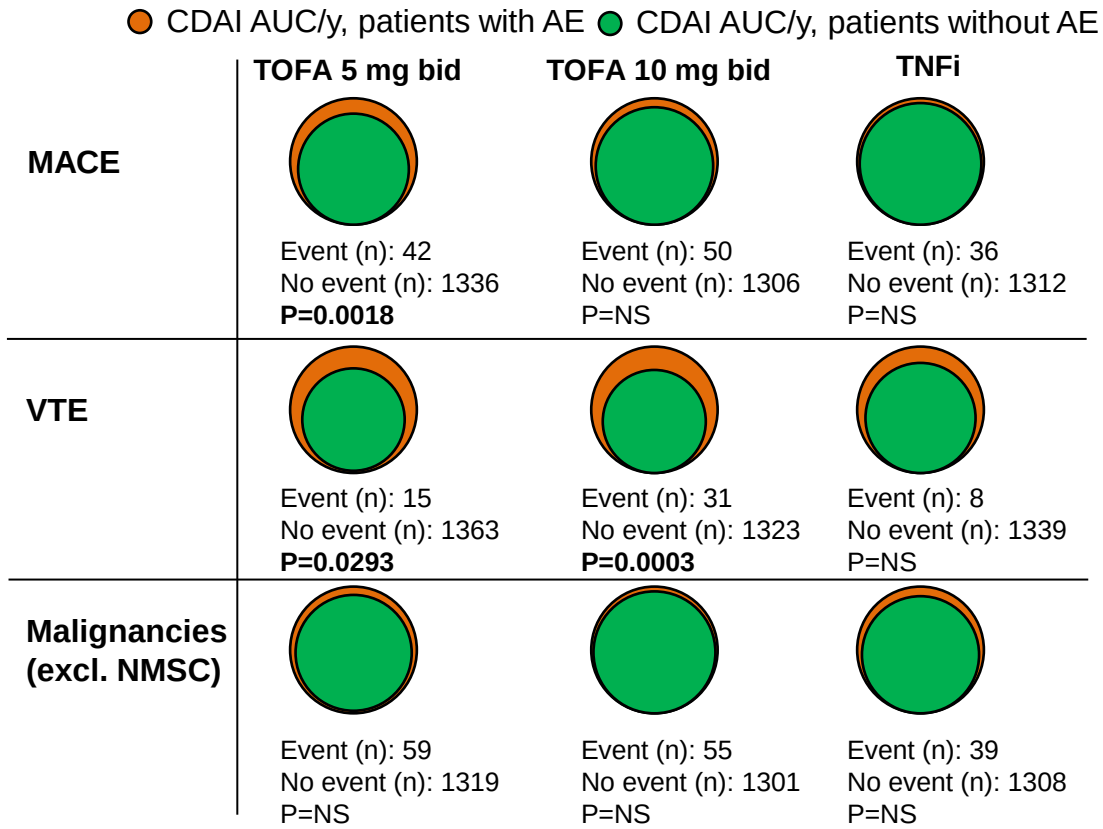
Curtis J, et al. ACR 2021, #1940

ORAL Surveillance: Post hoc analysis of risk factors for VTE and impact of disease activity on safety outcomes

Overall independent risk factors for pulmonary embolism across treatments (multivariable Cox regression)[1]

- Low overall statin use (23.4%): 35.7–40.6% patients with high risk/history of CAD; 35.7–44.2% patients with diabetes[3]
- Statin use had small impact as assessed in 5 mg bid group

Cumulative inflammation exposure (CDAI AUC/year) by AE



VTE risk factors were as shown; disease activity may contribute to some safety outcomes

[a]Indicator of underlying depression; [b]Proxy for elevated disease activity; [c]Impact considered inconclusive. VTE, venous thromboembolism

1. Charles-Schoeman C, et al. EULAR 2022, Copenhagen, POS0239; 2. Karpouzas G, et al. Ibid, POS0519;
3. Giles JT, et al. Ibid, POS0520

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), AND THROMBOSIS

See full prescribing information for complete boxed warning.

- **Increased risk of serious bacterial, fungal, viral, and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Interrupt treatment with XELJANZ/XELJANZ XR/XELJANZ Oral Solution if serious infection occurs until the infection is controlled. Test for latent TB before and during therapy; treat latent TB prior to use. Monitor all patients for active TB during treatment, even patients with initial negative latent TB test. (5.1)**
- **Higher rate of all-cause mortality, including sudden cardiovascular death with XELJANZ vs. TNF blockers in rheumatoid arthritis (RA) patients. (5.2)**
- **Malignancies have occurred in patients treated with XELJANZ. Higher rate of lymphomas and lung cancers with XELJANZ vs. TNF blockers in RA patients. (5.3)**
- **Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) with XELJANZ vs. TNF blockers in RA patients. (5.4)**
- **Thrombosis has occurred in patients treated with XELJANZ. Increased incidence of pulmonary embolism, venous and arterial thrombosis with XELJANZ vs. TNF blockers in RA patients. (5.5)**

---------- **INDICATIONS AND USAGE**----------

XELJANZ/XELJANZ XR/XELJANZ Oral Solution is a Janus kinase (JAK) inhibitor indicated for:

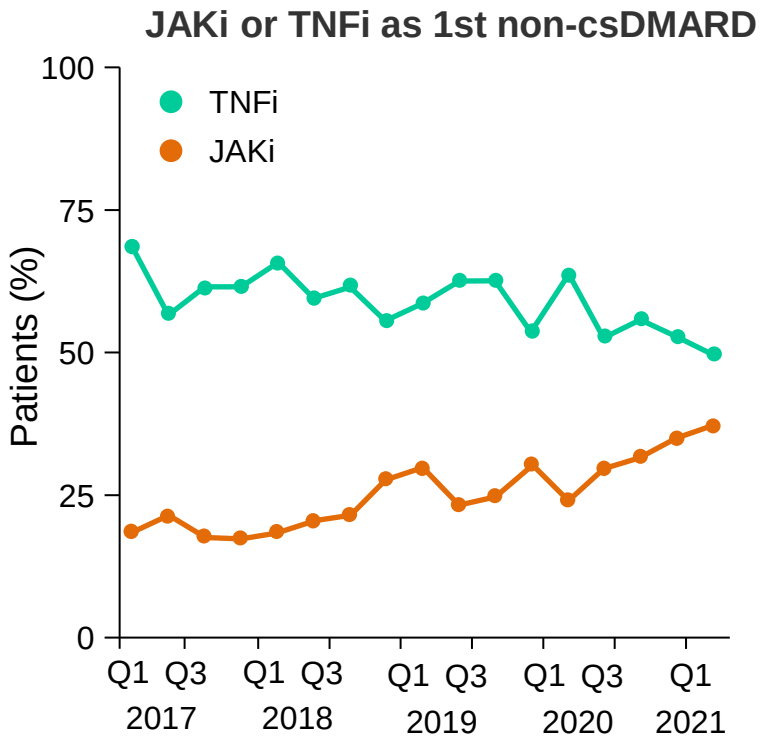
- Rheumatoid Arthritis: XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers.
  - *Limitations of Use:* Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1)
- Psoriatic Arthritis: XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers.
  - *Limitations of Use:* Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1)
- Ulcerative Colitis: XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response or intolerance to one or more TNF blockers.
  - *Limitations of Use:* Use of XELJANZ/XELJANZ XR in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1)
- Polyarticular Course Juvenile Idiopathic Arthritis: XELJANZ/XELJANZ Oral Solution is indicated for the treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older who have had an inadequate response or intolerance to one or more TNF blockers.
  - *Limitations of Use:* Use of XELJANZ/XELJANZ Oral Solution in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1)

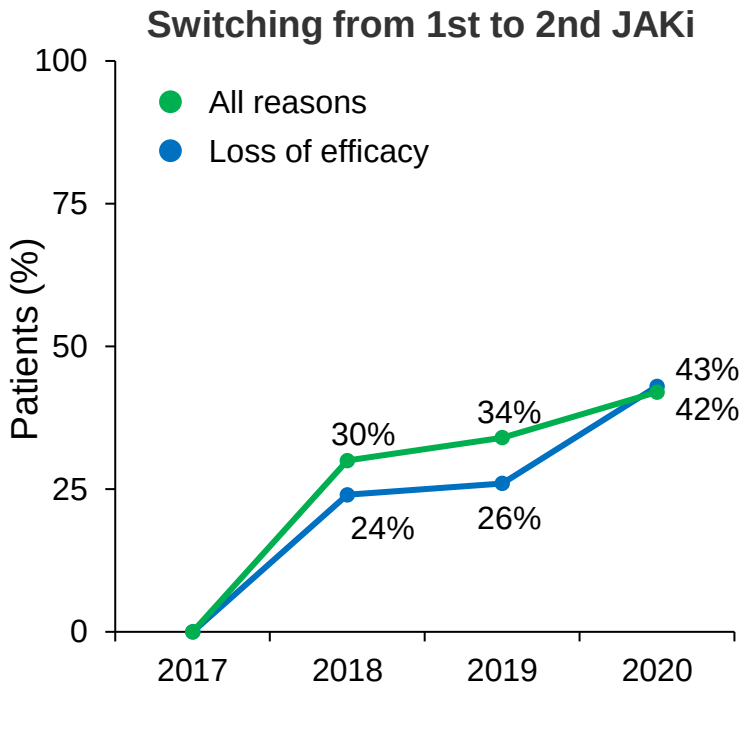
Oral Surveillance – Issues for Clinic

- All JAK inhibitors get a “boxed warning”
  - Risks apply to high risk (1133) pts: esp >65 yrs, smokers, Hx of MI
- New starts – use TNFi before JAKi
- VTE ↑Risk w/ age, obesity, inflammation, prior VTE → (no JAKi)
- Pts on JAKi – risks are low; discuss w/ pt; Stop JAKi? (no)
- Does 1133 indicate:
  - *Higher risks with JAKi?*
  - *Risks are lower with TNFi vs JAKi?*
- *Has this data affected your prescribing?*

OPAL dataset: Cycling jakinibs in patients with RA in clinical practice

- 3 JAKi available in Australia
  - TOFA Oct 2015; BARI Sep 2018; UPAD May 2020
- JAKi switching in RA Jan 2007–Mar 2021
- As of Mar 2021: 28% of 53,526 patients were being treated with a b/tsDMARD
  - Of these, 4048 (26.7%) received a JAKi
  - 47% TOFA; 28% BARI; 25% UPAD
- In 2020, JAKi comprised 44.5% of all initiations and 34.1% of first-line initiations (increase of 9.4/8.4%, respectively, from the prior 12-month period)
- Uptake of UPAD has been brisk (>75% of switches were to UPAD in past year)



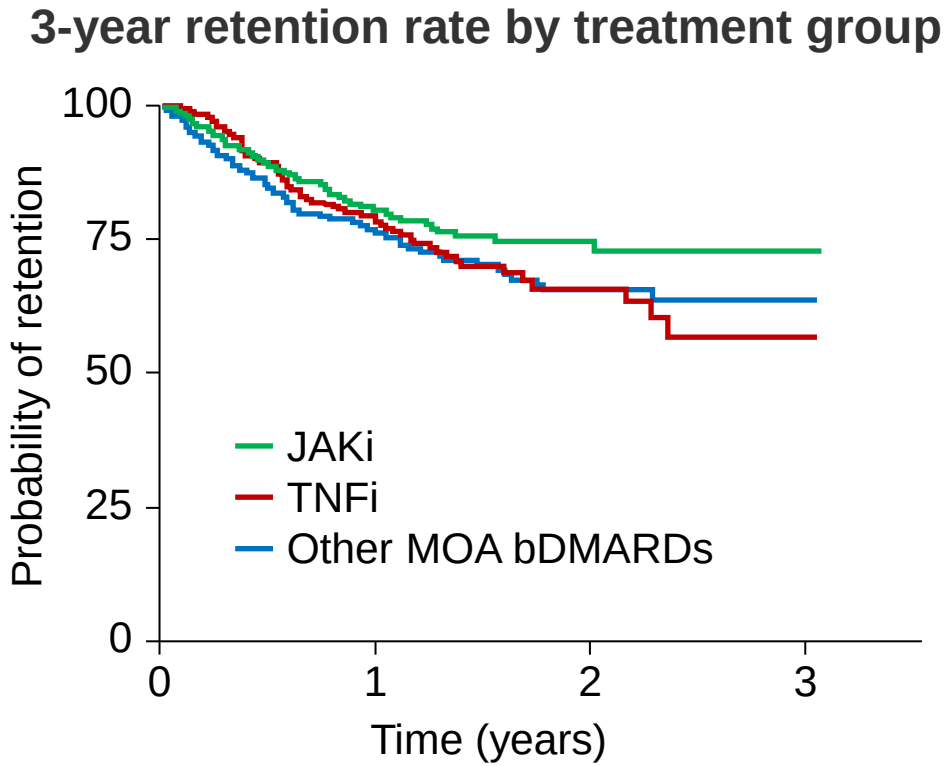


Considerable uptake and switching of JAKi in RA in clinical practice in Australia

Ciciriello S, et al. EULAR 2021, POS0223

Retention rates with jakinibs or biologic DMARDs in patients with RA

- GISEA:[1] Italian multicenter RA registry, N=1027 (2017–2020)
  - RA duration ~10 y; 67% ACPA+; baseline mean SDAI ~15
  - Retention of TNFi (n=365), JAKi (n=297), other MOA (n=365) bDMARDs
  - Higher retention with JAKi vs TNFi vs other MOA (P=NS)
    - 1 year: 80.6%, 78.9%, and 76.4%
    - 3 year: 73%, 56.8%, and 63.8%
- BiobadaBrasil registry:[2] 1177 RA patients starting bDMARDs or JAKi; drug retention over 4 years
  - <50%: IFX, ETN, ADA, RTX
  - >50–90%: GOL, CZP, ABA, TOFA, TCZ
- Canadian RA cohort:[3] 215 RA patients starting bDMARD or JAKi after DMARD-IR
  - Better retention for JAKi vs bDMARDs: HR 0.68 (95% CI: 0.47, 0.97), P=0.034

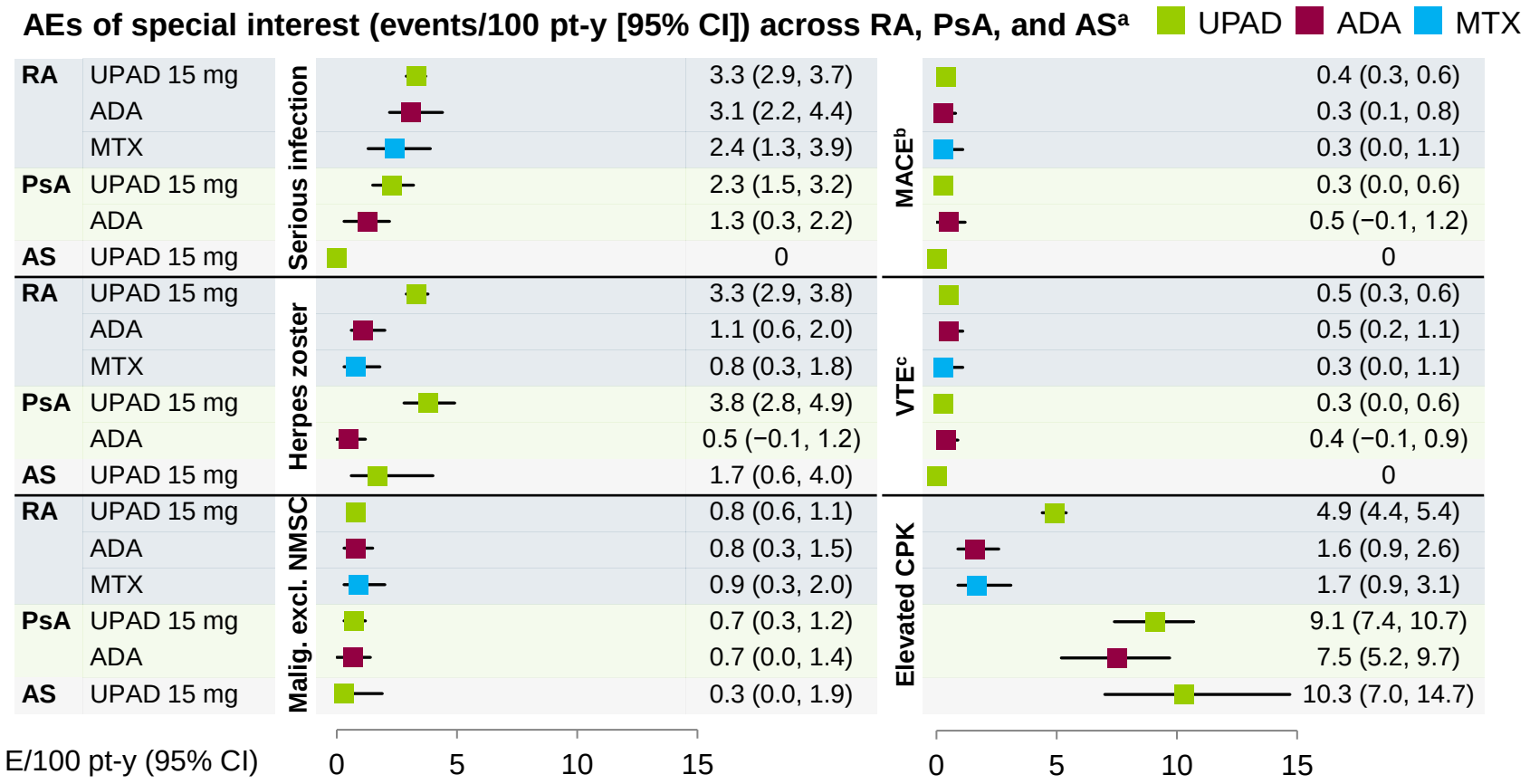


Jakinib retention is similar to, if not better than, bDMARD retention in patients with RA

1. Favali EG, et al. EULAR 2021, POS0675; 2. Bredemeier M, et al. Ibid, POS0676; 3. Machlab K, et al. Ibid, POS0207

Long-term safety of upadacitinib across multiple indications

- 5620 patients received ≥1 dose UPAD 15 mg
  - 3209 RA; 907 PsA; 182 AS
- Similar rates of SIE and OI
  - Pneumonia most common SIE
- Increased HZ and CPK in UPAD vs ADA or MTX
- Rates of HZ in UPAD similar across diseases
- GI perforations are rare
- No increased risk of death, MACE, or VTE



Safety signals for upadacitinib are comparable across rheumatologic indications

[a]RA: UPAD 15 mg qd (n=3209), ADA 40 mg eow (n=579), MTX (n=314); PsA: UPAD 15 mg qd (n=907), ADA 40 mg eow (n=429); AS: UPAD 15 mg qd (n=182).
[b]Adjudicated events, defined as CV death, nonfatal MI, and nonfatal stroke. [c]Adjudicated events including DVT and PE. CPK, creatine phosphokinase

Burmester G, et al. ACR 2021, #1691

UPA vs ABA in bDMARD-ir RA: SELECT-CHOICE Study

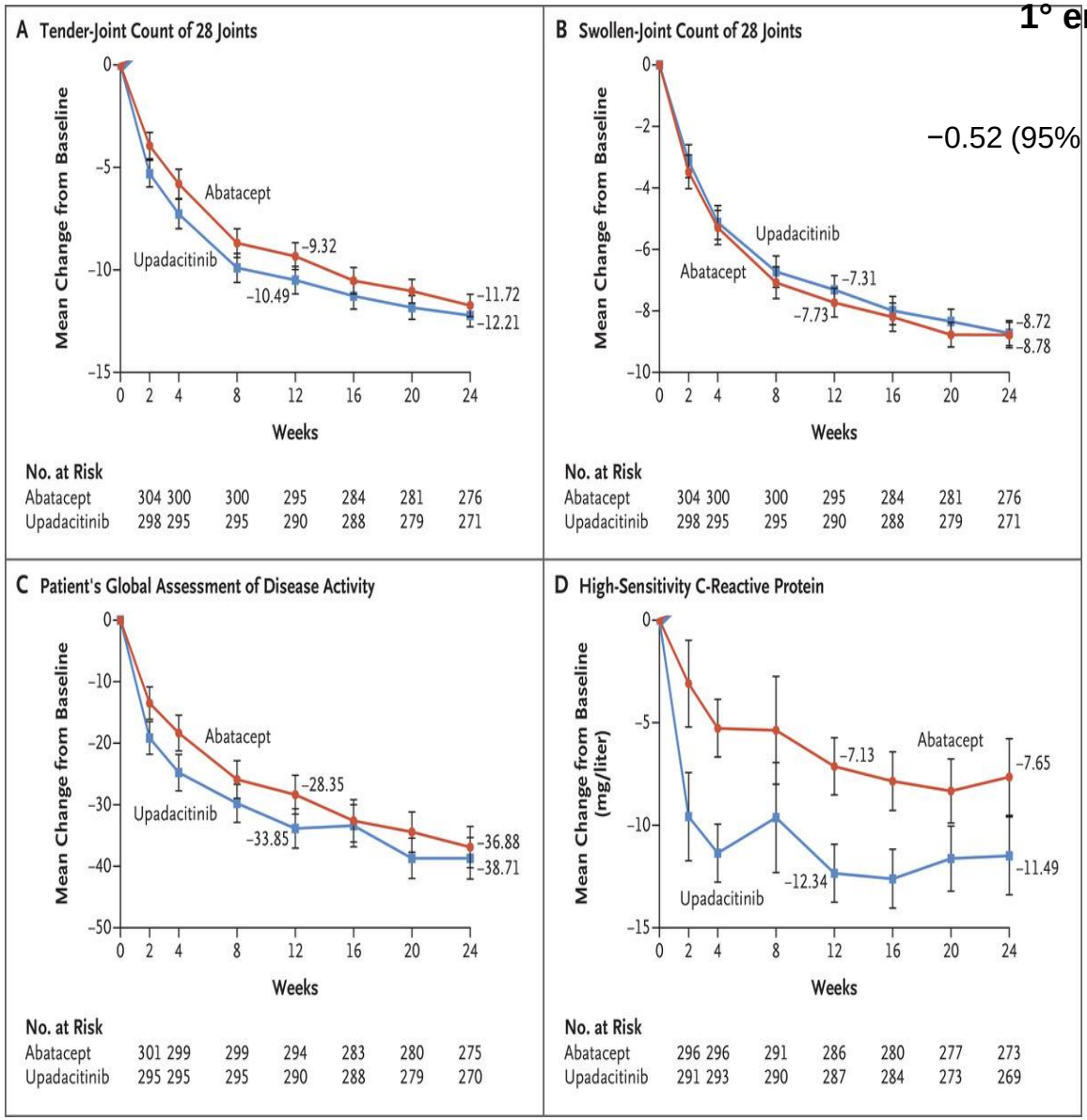
612 bDMARD-IR RA pts (mean Dz: 12 years)

~50% steroids; ~1/3 with ≥2 prior bDMARDs

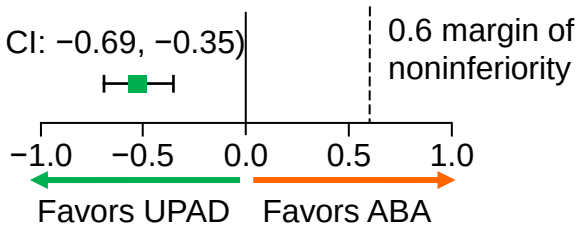
Continued background csDMARDs (could be adjusted at Week 12 in ACR20 non-resp)

Wk 24: similar HAQ, FACIT, and pain

n (%)	ABA (n=309)	UPAD (n=303)
Serious AE	5 (1.6)	10 (3.3)
Severe AE	10 (3.2)	19 (6.3)
AE leading to D/C	9 (2.9)	14 (4.6)
Opportunistic infection	1 (0.3)	4 (1.3)
Herpes zoster	4 (1.3)	4 (1.3)
Hepatic disorder	**5 (1.6)**	**23 (7.6)**
VTE	0	2 (0.7)
Gr 3/4 ↓ hemoglobin	**6 (2.0)**	**20 (6.6)**
Gr 3/4 lymphopenia	**26 (8.4)**	**45 (14.9)**
Gr 3/4 CPK elevation	**0**	**3 (1.0)**



1° endpoint: difference in ΔDAS28 (CRP) at Week 12

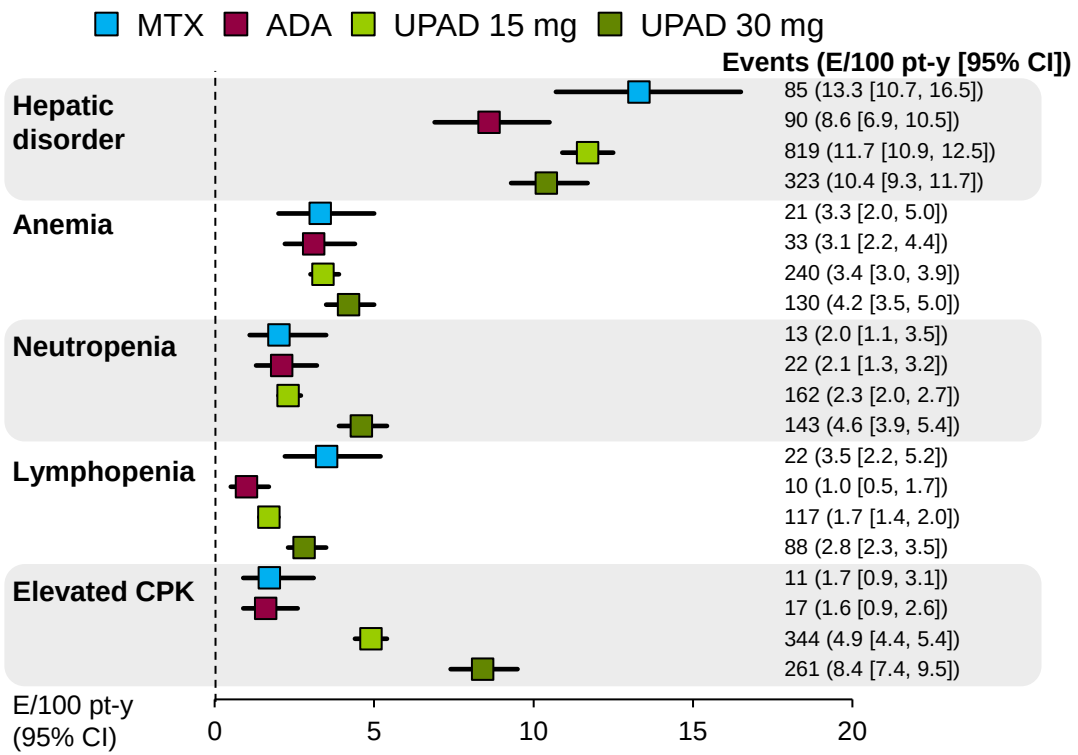


A Rubbert-Roth et al. N Engl J Med 2020;383:1511-1521.

Laboratory abnormalities with upadacitinib over 4.5 years exposure: Pooled data from 6 RCTs

- UPAD 15 mg (n=3209, 7024 pt-y) and 30 mg (n=1204, 3092 pt-y); MTX (n=314, 637 pt-y); ADA (n=579, 1052 pt-y)

TEAEs of special interest



Potentially clinically significant laboratory changes

	Variable, n (%)	MTX mono	ADA 40 mg	UPAD 15 mg	UPAD 30 mg
Hemoglobin, g/L	Gr 3 (70–<80 or ↓ 21 to <30)	28[a] (9.0)	24[b] (4.2)	254[d] (7.9)	169[f] (14.2)
	Gr 4 (<70 or ↓ ≥30)	16[a] (5.1)	16[b] (2.8)	101[d] (3.2)	78[f] (6.5)
Neutrophils, 10^9 /L	Gr 3 (0.5 to <1.0)	3[a] (1.0)	3[b] (0.5)	40[d] (1.2)	37[g] (3.1)
	Gr 4 (<0.5)	1[a] (0.3)	1[b] (0.2)	10[d] (0.3)	5[g] (0.4)
Lymphocytes, 10^9 /L	Gr 3 (0.5 to <1.0)	74[a] (23.7)	53[b] (9.2)	802[d] (25.1)	423[g] (35.5)
	Gr 4 (<0.5)	5[a] (1.6)	3[b] (0.5)	75[d] (2.3)	47[g] (3.9)
ALT, U/L	Gr 3 (3.0–8.0 × ULN)	26[a] (8.3)	13[c] (2.3)	152[e] (4.8)	71[h] (5.9)
	Gr 4 (>8.0 × ULN)	5[a] (1.6)	4[c] (0.7)	26[e] (0.8)	10[h] (0.8)
AST, U/L	Gr 3 (3.0–8.0 × ULN)	15[a] (4.8)	9[c] (1.6)	101[e] (3.2)	36[h] (3.0)
	Gr 4 (>8.0 × ULN)	1[a] (0.3)	5[c] (0.9)	18[e] (0.6)	8[h] (0.7)
CPK, U/L	Gr 3 (>5.0–10.0 × ULN)	2[a] (0.6)	3[c] (0.5)	65[e] (2.0)	36[i] (3.0)
	Gr 4 (>10.0 × ULN)	0[a] (0)	3[c] (0.5)	27[e] (0.8)	15[j] (1.3)

Lab abnormalities were generally higher with UPAD 15 mg than ADA, but similar to MTX; discontinuations for anemia, leukopenia, elevated CPK <0.2% in all treatment arms

[a]n=312, [b]n=576, [c]n=577, [d]n=3201, [e]n=3199, [f]n=1193, [g]n=1192, [h]n=1195, [i]n=1196, [j]n=1197

Charles-Schoeman C, et al. EULAR 2021, OP0128

ACR Guidelines - Facts or Foe?

- 8 guidelines - 403 recommendations
- 58% based on level C evidence
- 23% based on level A evidence

Table 1. Guideline Recommendations by Level (Quality) of Evidence

Guideline	No.	Year	Methodology	Level of Evidence, No. (%)[a]		
				A	B	C
GIOP	37	2010	ACC/AHA	13.0 (35)	7.0 (19)	17.0 (46)
JIA	102	2011-2013[b]	Oxford	1.7 (2)	12.2 (12)	88.1 (86)
Gout	88	2012[c]	ACC/AHA	18.5 (21)	27.4 (31)	42.1 (48)
LN	33	2012	ACC/AHA	8.0 (24)	2.0 (6)	23.0 (70)
OA	60	2012	GRADE	35.0 (58)	10.0 (17)	15.0 (25)
SpA	38	2015	GRADE	11.0 (29)	7.5 (20)	19.5 (51)
PMR	10	2015	GRADE	1.0 (10)	4.5 (45)	4.5 (45)
RA	35	2015	GRADE	4.6 (13)	6.1 (17)	24.3 (69)
Total	403			92.8 (23)	76.7 (19)	233.5 (58)
Median % (IQR)				23.0 (12-30)	18.0 (15-23)	50.0 (46-70)

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; GIOP, glucocorticoid-induced osteoporosis; GRADE, Grading of Recommendations and Assessment, Development, and Evaluation scoring system; IQR, interquartile range; JIA, juvenile idiopathic arthritis; LN, lupus nephritis; OA, osteoarthritis; Oxford, Oxford Centre for Evidence-Based Medicine; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; SpA, spondyloarthritis.

[a] Level A evidence to multiple randomized clinical trials (RCTs) or meta-analyses; level B to single RCT or nonrandomized studies; and level C to opinion of experts, case studies, or standard of care.

[b] Includes JIA guidelines of 2011 and focused 2013 update.

[c] Includes gout part 1 and part 2 guidelines.

JAMA Int Med 2017; https://buff.ly/2AD1dri

ACR 2021 RA Guidelines LOVE MTX

- **MTX** is recommended:
  - **(with low activity)** OVER HCQ or SSZ, LEF
  - **(with high activity)** OVER HCQ, SSZ, LEF, b/tsDMARD monoRx
  - **MTX** monoRx over Combination Rx with
    - dual/triple DMARD Rx
    - MTX+TNFi
    - non-TNFi OR tsDMARDs
  - Over steroids
- Start oral over SC MTX
- **Intolerance → split oral or SC or increase folate**
- Not at target on oral MTX → switch to SC MTX over starting another DMARD
- Max MTX before adding biologic or tsDMARD over adding HCQ/SSZ
- MTX ok with mild stable airway or parenchymal lung disease
- MTX ok with NAFLD and normal LFTs

WRONG!
Lower dose
Mucositis/n = Vit A
CNS Blahs = DM

L. Fraenkel. Arthritis Rheumatol. 2021. PMID: 34101376.

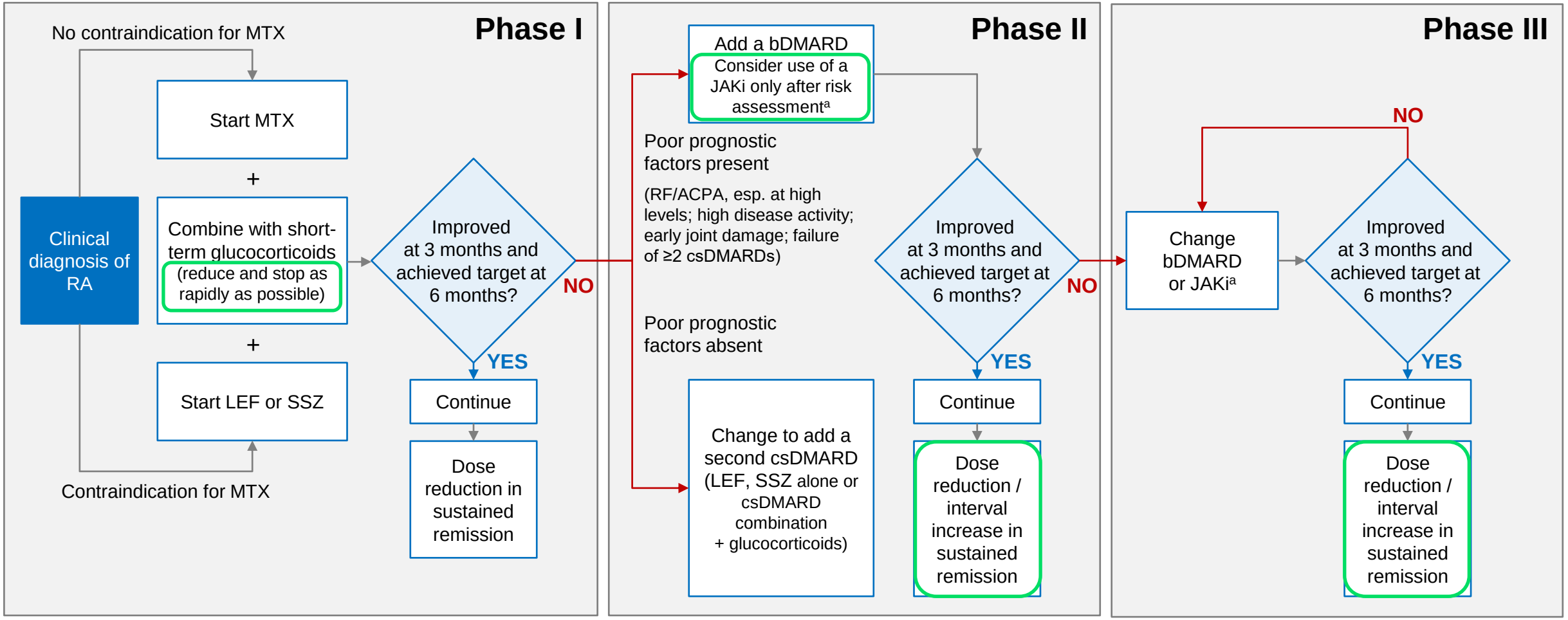
ACR 2021 Pharmacologic Treatment Recommendations for RA

81 Pico questions
37/44 conditional recs
Largely expert opinion

Specific Populations	Management (all conditional recommendations)	
Pulmonary disease + High Dz activity	(if mild – stable), ok to use MTX over other DMARDs	✓
Hepatitis B	Antiviral Rx strongly rec if HBcAb+ starting RTX or HBsAg+ with any biologic (frequent monitoring)	✓
Nonalcoholic fatty liver	MTX over other DMARD (w/ normal LFTs)	✓
Nodules	MTX over other DMARDs	?
Heart Failure	NY Class III or IV – use non-TNFi biologic or tsDMARD over TNFi	?
Lymphoproliferative Dz	RTX over other biologic or tsDMARD	?
Previous serious infx	Switch DMARDs than use GC; or use csDMARDs over biologic or ts DMARD	?
Hypogammaglobulinemia	On RTX, ok to continue RTX	
Nontuberculous mycobact-erial infection	Decrease GC use csDMARD over biologic or tsDMARD or ABA over other biologic or tsDMARD	

L. Fraenkel. Arthritis Rheumatol. 2021. PMID: 34101376.

2022 update of EULAR recommendations for the management of RA



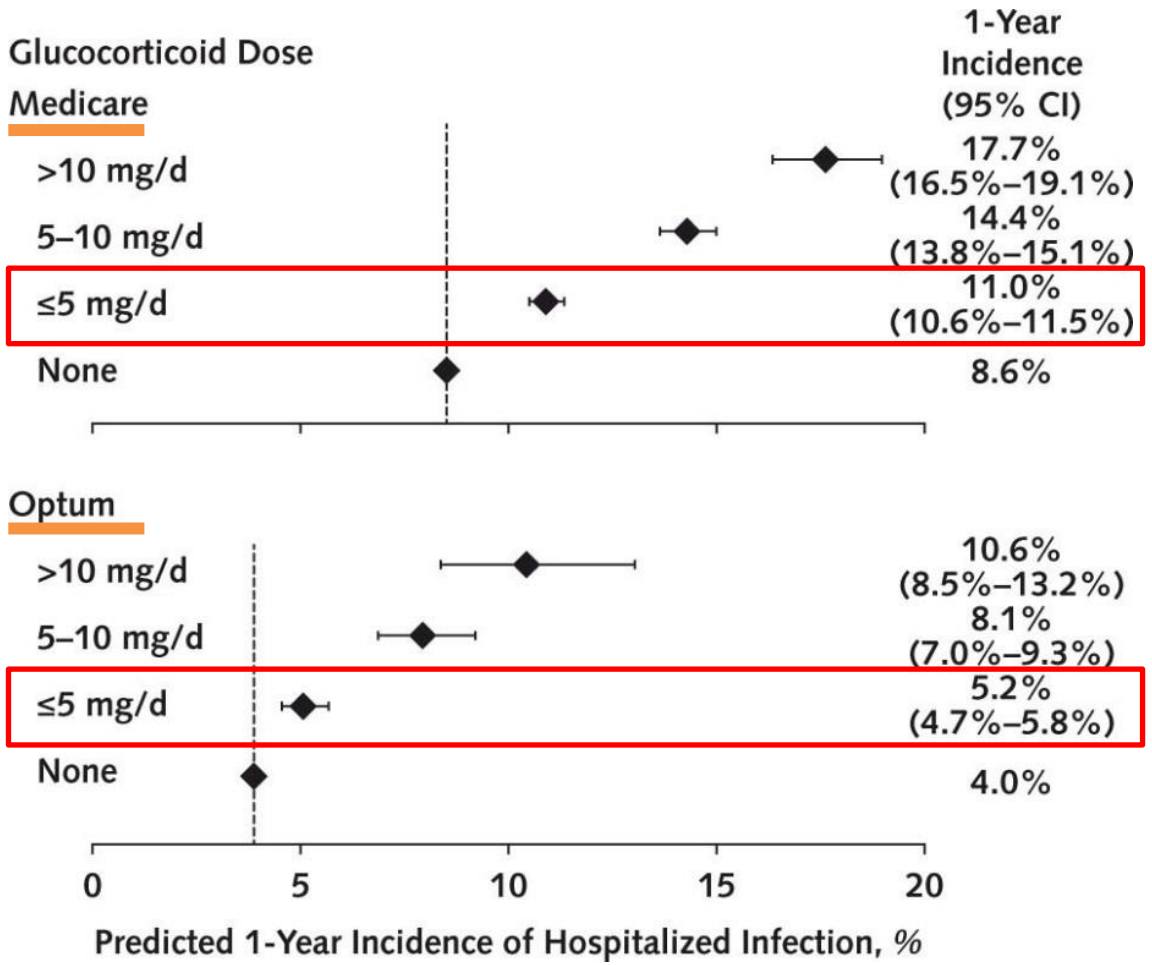
[a]The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAKi: age >65 years, history of current or past smoking, other CV risk factors, other risk factors for malignancy, risk factors for thromboembolic events

Smolen JS, et al. EULAR 2022, Copenhagen

Do you Play Steroid Poker?

- Prednisone – The Go-To Drug
  - Early RA, Bridge therapy, IA use
- Yet we know its toxicity
- Not so good at weaning/stopping steroids
- Despite aggressive biologics, most don't wean or stop steroids
- Doses < 5 mg/d are dangerous!
- "Steroids are acutely wonderful, chronically dangerous" - JC
- "Steroid are the best drug & worst drug we have" – P Merkel

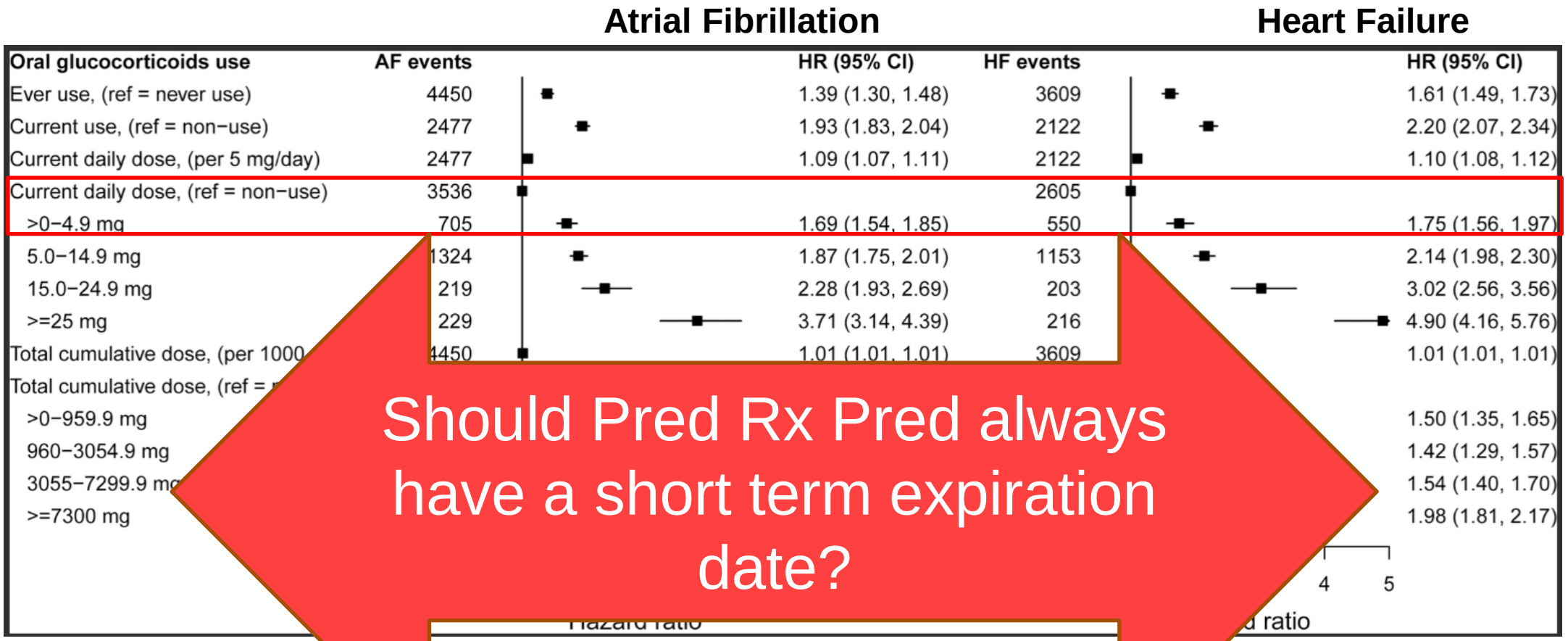
Risk for Serious Infection With Low-Dose Glucocorticoids in Patients With Rheumatoid Arthritis: a Cohort Study



Predicted 1-year incidence of hospitalized infection calculated from inverse probability–weighted cause-specific hazards models. Confidence intervals are not available for the reference group, which represents the baseline incidence at 1 y. Variables that were imbalanced across glucocorticoid categories after inverse probability weighting were added as covariates to weighted models (opioid use, outpatient visits, and hospitalizations in both data sets and emergency department visits in Medicare).

George M, et al. Ann Int Med. Published online: 22 September 2020doi:10.7326/M20-1594

UK: CPRD registry: CV risk with oral glucocorticoid Rx in immune-mediated inflammatory diseases pts (87,794 w/ PMR, IBD, RA, SLE, GCA, vasculitis)

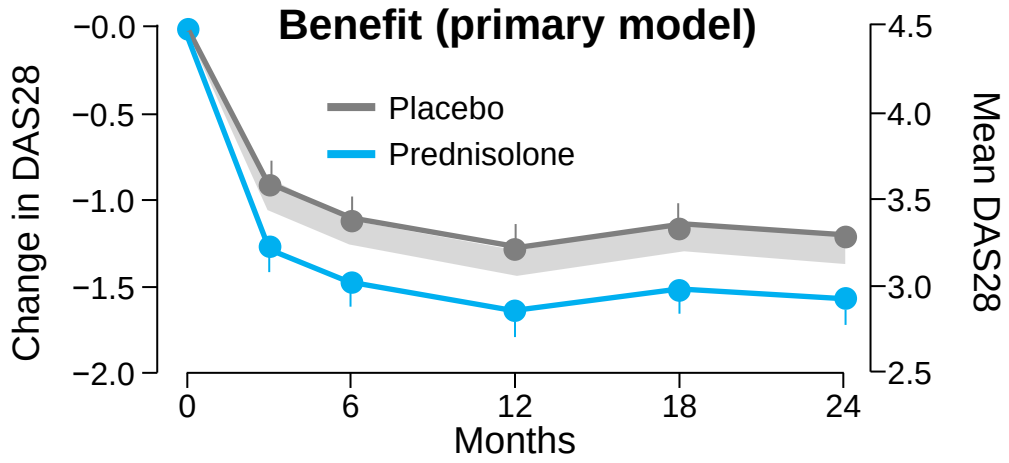


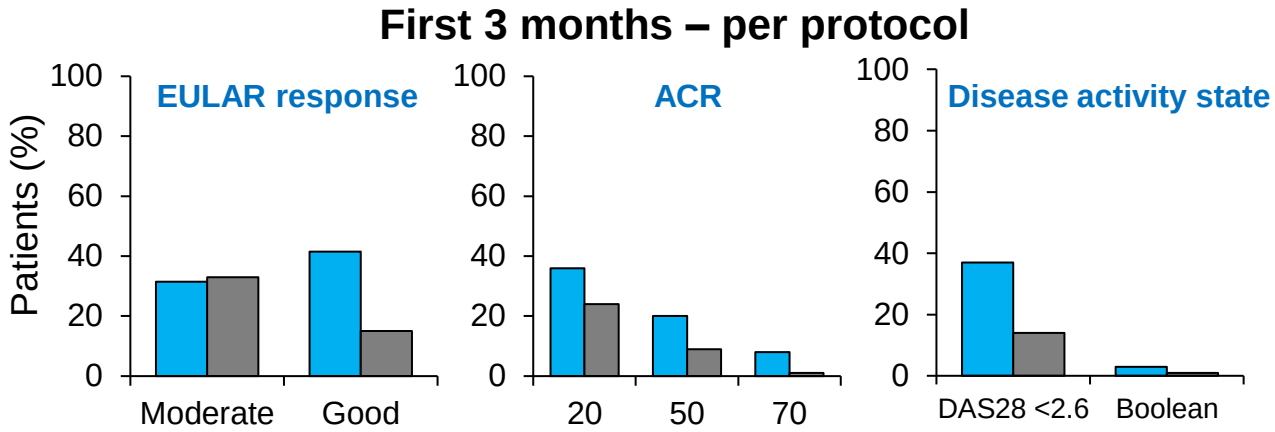
Should Pred Rx Pred always have a short term expiration date?

Pujades-Rodriguez M . PLoS Med 17(12): e1003432

GLORIA: Benefit and harm of long-term, low-dose prednisolone plus standard treatment in older RA patients

- Pragmatic double-blind RCT in RA patients aged ≥65 y with DAS28 ≥2.6 randomized to prednisolone 5 mg/day
  - All co-treatments/treatment changes except crossover allowed
  - Safety analysis n=449 (224 prednisolone, 225 PBO)
  - Efficacy analysis n=444
- 38% did not complete 2 years of follow-up
  - AEs 14%; active disease 4%; other reasons/COVID-19 20%
- Prednisolone vs placebo
  - DAS28: 0.37 points lower (95% CI: 0.23; P<0.0001)
  - Joint progression 1.7 points lower (95% CI: 0.7; P=0.003)
- Harm = ≥1 SAE or ≥1 other AE of special interest
  - Prednisolone 60% vs placebo 49%
  - RR 1.24 (95% CI: 1.04); P=0.02; NNH=9.5
  - Most marked difference between groups was for infection

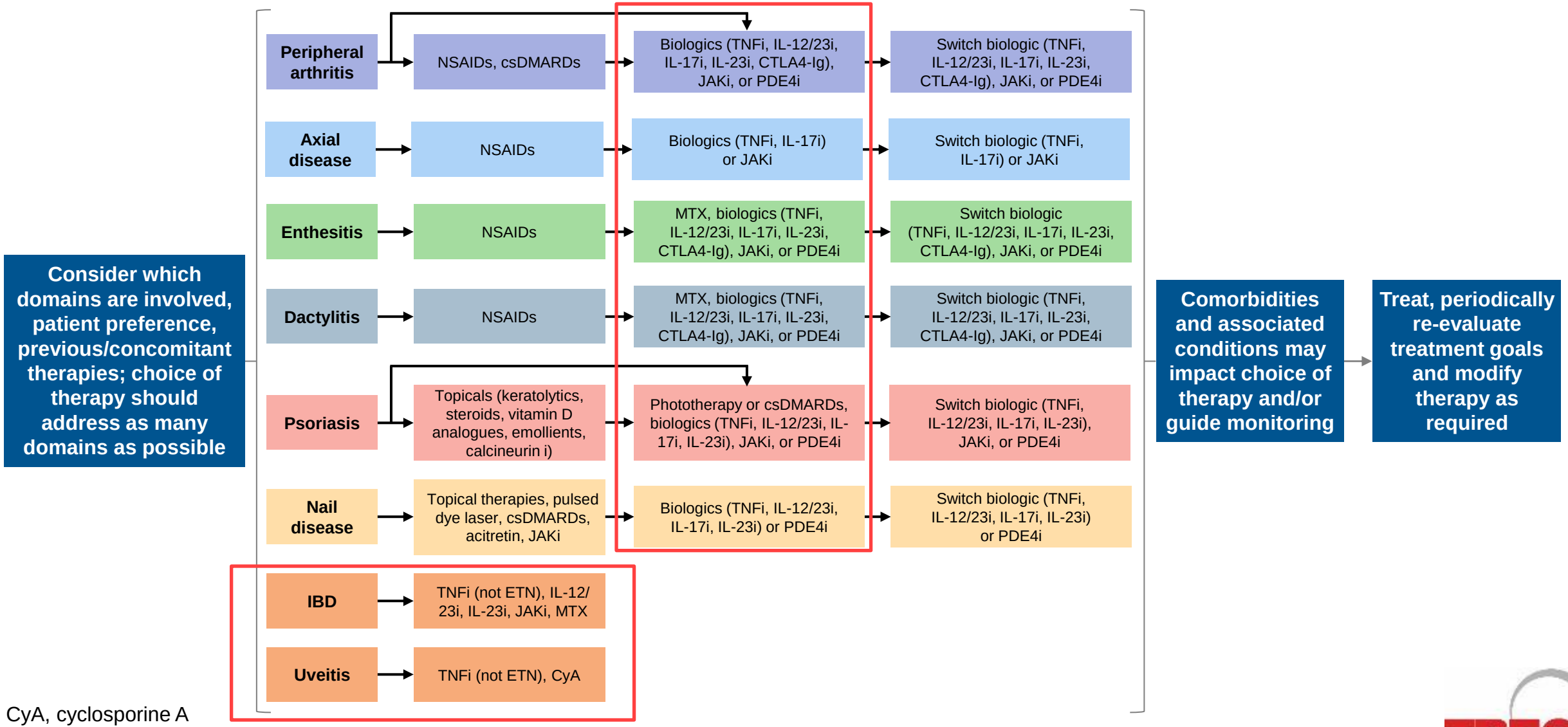




Small improvements in efficacy with low-dose prednisolone in early RA; toxicity is an issue

Boers M, et al. EULAR 2022, Copenhagen, OP0263;
Boers M, et al. Ann Rheum Dis 2022;doi:10.1136/annrheumdis-2021-221957

GRAPPA PsA treatment recommendations 2021



CyA, cyclosporine A

Coates LC, et al. EULAR 2021, OP0229

Update of the ASAS/EULAR recommendations on the management of axial spondyloarthritis

- **5 overarching principles:** unchanged
- **15 recommendations:** 8 unchanged; 3 minor edits; 2 significantly changed; 2 new
  - NSAIDs remain **1st-line** pharmacologic treatment
  - **Criteria for start of b/tsDMARD: ASDAS ≥2.1**
  - **b/tsDMARD:** TNFi, IL-17i, **or JAKi** (current practice to start with TNFi or IL-17i)
  - **Extra-musculoskeletal manifestations guiding therapeutic decision:**
    - Recurrent uveitis/IBD – TNFi preferred
    - Significant psoriasis – IL-17i preferred
  - **Treatment failure** should trigger re-evaluation of the diagnosis and consideration of the presence of comorbidities
  - If active axSpA confirmed: **switch** to another b/tsDMARD
  - **Tapering** of bDMARDs if sustained remission (no recommendation on tsDMARDs)

#	ASAS/EULAR Recommendations: New and significant changes
9	TNFi, IL-17i or JAKi should be considered in patients with persistently high disease activity despite conventional treatments; current practice is to start a TNFi or IL-17i
10	If there is a history of recurrent uveitis or active IBD, preference should be given to a monoclonal antibody against TNFα. In patients with significant psoriasis, an IL-17i may be preferred
11	Absence of response to treatment should trigger re-evaluation of the diagnosis and considerations of the presence of comorbidities
12	Following a first b/tsDMARD failure, switching to another bDMARD (TNFi or IL-17i) or a JAKi should be considered
13	If a patient is in sustained remission, tapering of a bDMARD can be considered

Sensible recommendations that are consistent with clinical practice

Ramiro S, et al. EULAR 2022, Copenhagen

Telemedicine & Digital/Virtual Learning

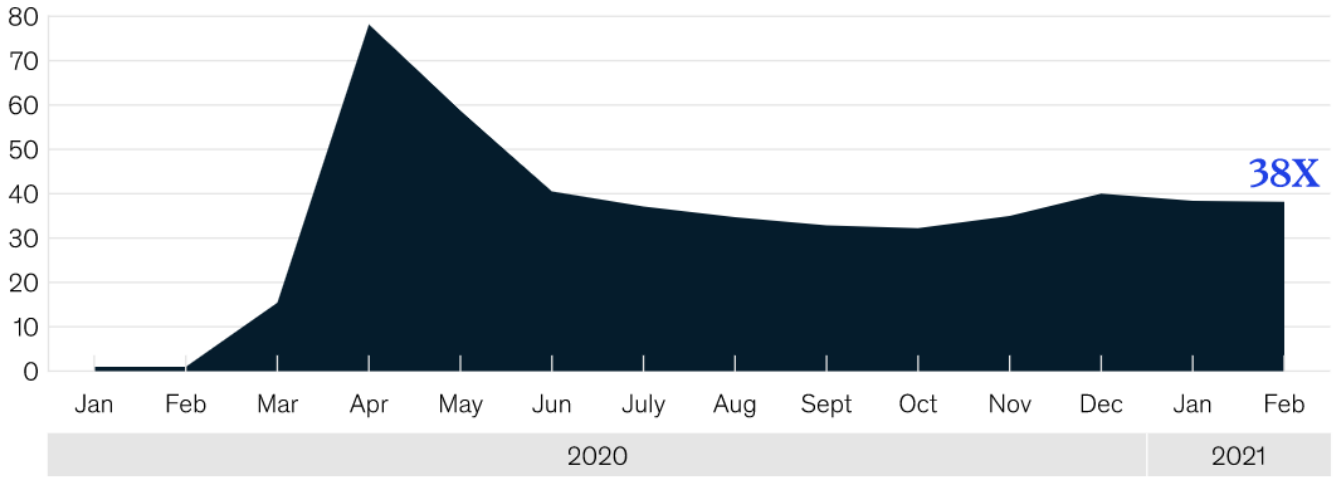
- Telemedicine makes up ~20% of current Clinic visits
- ACR position statements on Telemedicine
  - increase access and improve care… but it should NOT replace essential face-to-face assessments
  - protocols to protect the security and integrity of patient information
  - Geographical restrictions
- Virtual/Hybrid Education

https://www.rheumatology.org/About-Us/Newsroom/Press-Releases/ID/1087
JAMA. 2020;324(2):149-150

Telehealth Uptake

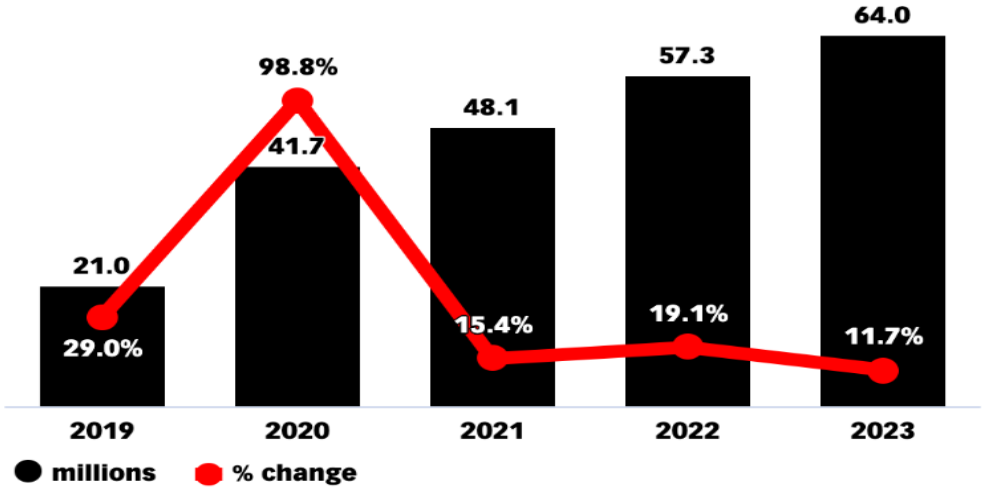
Growth in telehealth usage peaked during April 2020 but has since stabilized.

Telehealth claims volumes, compared to pre-Covid-19 levels (February 2020 = 1)[1]



Telemedicine Users

US, 2019-2023



Source: eMarketer, October 2020

www.eMarketer.com

Telehealth Uptake

KEY FINDINGS

Physician Adoption

Top 10 Specialties Using Telemedicine Frequently Treat Chronic Illnesses

There is a clear overlap between specialties that are using telemedicine the most, and those specialties that manage chronic illnesses, such as endocrinology and rheumatology

Treating long-term chronic conditions like diabetes and arthritis require frequent patient visits, but they don't always need to be in-person. For patients that require long-term care, telemedicine tools can reduce taxing trips to hospitals or clinics.

Top 10 Specialties Using Telemedicine

1. Endocrinology
2. Rheumatology
3. Gastroenterology
4. Nephrology
5. Cardiology
6. Urology
7. Neurology
8. Geriatrics
9. Hematology/Oncology
10. Pulmonology

Common Threads

- Chronic Care
- Complex Disorders
- Cognitive Care
- Pattern Recognition
- Biomarker
- Surrogate Marker
- Safety Labs
- Non-procedural

doximity

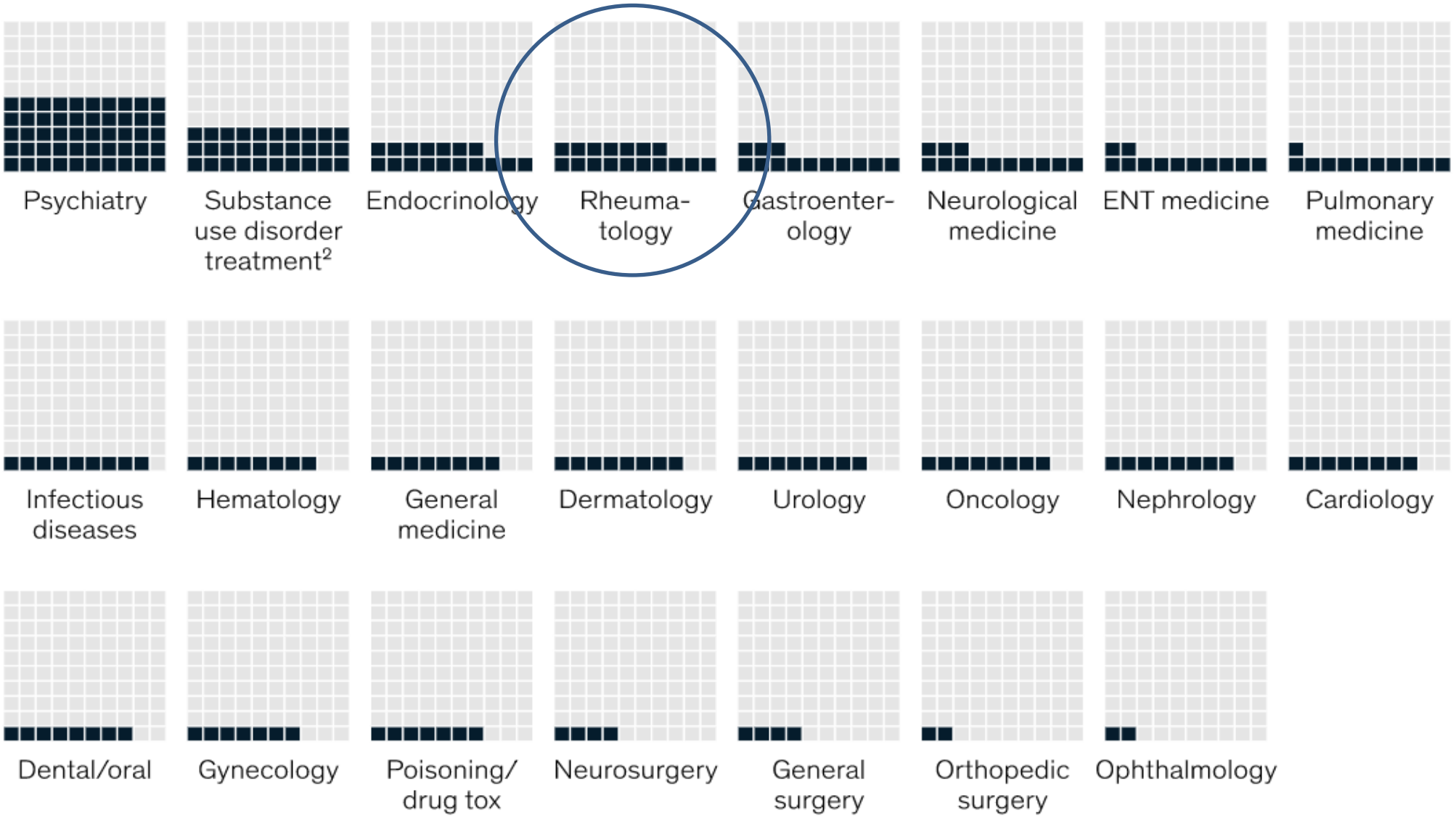
2020 STATE OF TELEMEDICINE REPORT

https://bit.ly/2RBIPr4

RheumNow

Substantial variation exists in share of telehealth claims across specialities.

Share of telehealth of outpatient and office visit claims by specialty (February 2021[1]), %



https://www.mckinsey.com/ By Oleg Bestsennyy 7/9/21

RheumNow

5 Reasons Telehealth Works

1. Fast adoption fostered by technology;
2. Lowered regulatory hurdles;
3. Improved financial reimbursements;
4. Video Telehealth can be integrated w/ F2F visits
5. Untapped potential with adoption by Pts and MDs

- Telemedicine market $29.3 billion in 2020, estimated to be $175.5B by 2026
- 59% pts more likely to use telehealth services now
- 33% would leave their physician for a telehealth MD

Forbes.com 5/4/20

RheumNow

Future of Combination Therapies

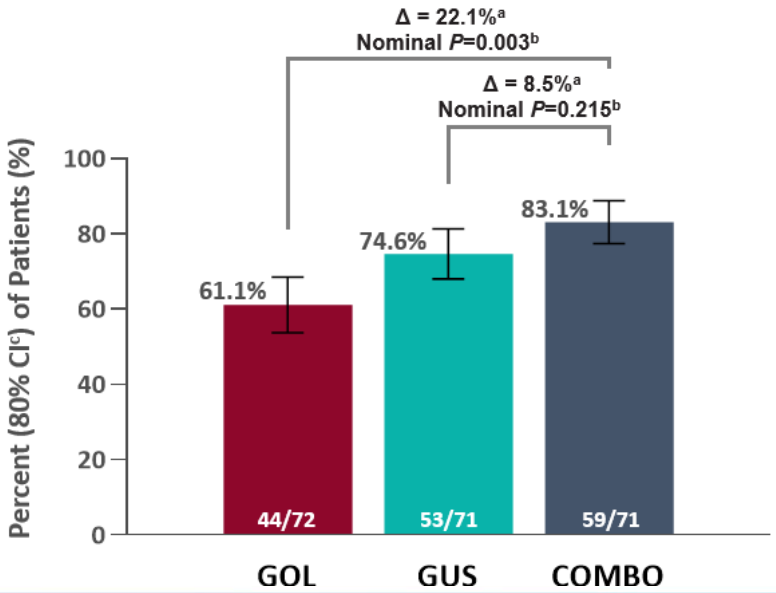
- “Combinations are good”
- 1980s Animal models, combo biologics highly effective
- TNF inhibitor + anakinra = no benefit; more SIE 6%
- TNF inhibitor + abatacept = no efficacy; more SAE (16 v 3%)
- $ Untold #s of pts taking apremilast + Biologic (TNFi, IL-17i)
- IL-23i + TNFi
  - VEGA Study (ECCO 2022)
  - AFFINITY (in progress)

VEGA Study in Ulcerative Colitis

- Phase 2a; Presented at ECCO 2022
- Combination Induction Therapy with Guselkumab and Golimumab in Active Ulcerative Colitis: Week 12 results of a Multicenter, Proof-of-concept Study

Primary Endpoint: Clinical Response at Week 12

Decrease from Baseline in the Mayo Score ≥30% and ≥3 Points with Either a Decrease in Rectal Bleeding Subscore ≥1 or a Rectal Bleeding Subscore of 0 or 1



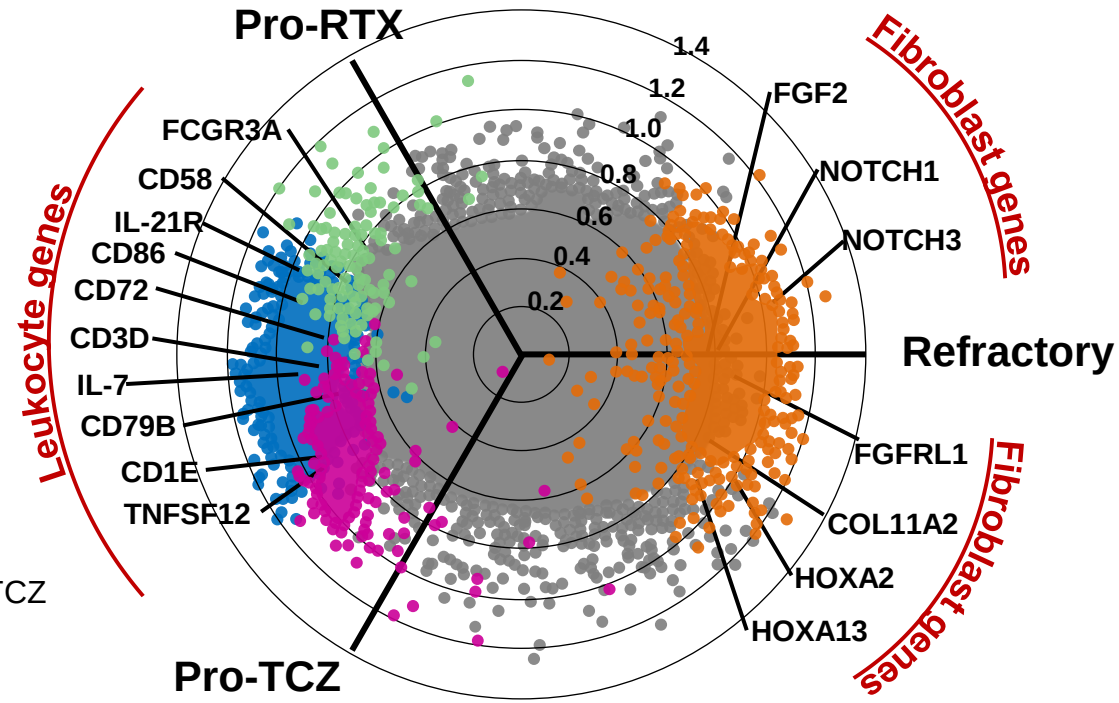
	Golimumab	Guselkumab	COMBO (Golimumab + Guselkumab)
Number of Patients	72	71	71
Adverse events (AEs)	38 (52.8)	31 (43.7)	29 (40.8)
Serious AEs	1 (1.4)	2 (2.8)	1 (1.4)
Serious infection[a]	0	0	1 (1.4)

Sands, B.E. ECCO 2022

R4RA: Synovial RNA-Seq analysis of fibroblast and stromal genes in treatment-resistant and refractory RA

- R4RA trial: 48-week study[1]
  - Patients with inadequate response to csDMARDs/≥1 TNFi randomized 1:1 to RTX or TCZ stratified by synovial B cell status
  - RNA sequencing of RA synovial tissue better predicted responses compared with histology
  - Low B cell signature correlated with response (TCZ > RTX)
- Post hoc analysis of mechanism of response[2]
- RTX: 6625 genes differentially expressed
  - Responder: Ag presentation, T/B cell gene signature (**green**)
  - Nonresponder: stromal/fibroblast genes (**orange**)
- TCZ: 85 differentially expressed genes
  - Responder: lymphocyte and Ig genes (**pink**)
  - Nonresponder: fibroblast signature (**orange**)

3-way differential gene expression analysis on baseline synovial biopsies



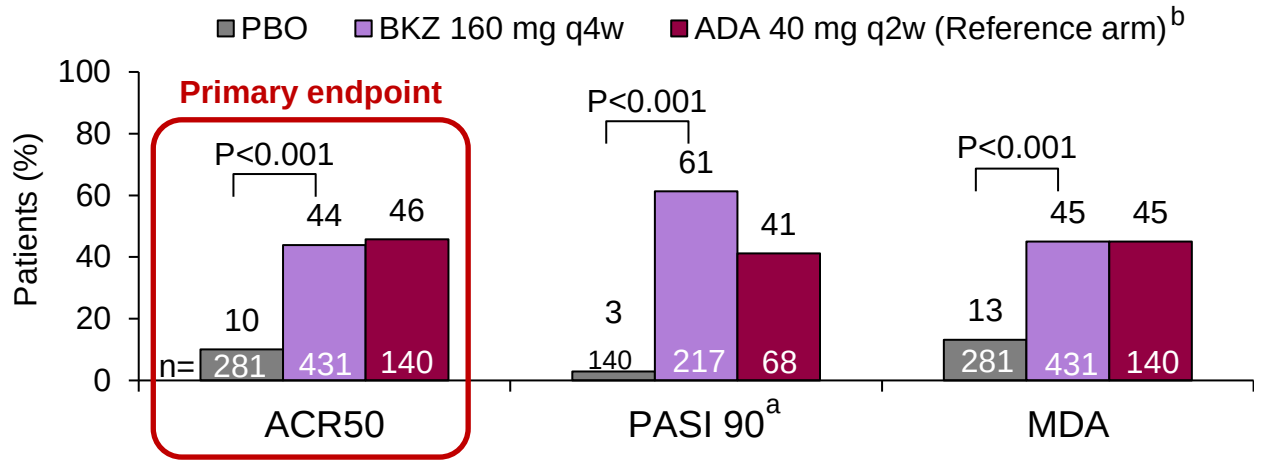
Synovial RNA sequencing may help identify cellular/molecular pathways of treatment resistance

1. Humby F, et al. Lancet 2021;397:305; 2. Surace A, et al. EULAR 2022, Copenhagen, OP0077

BE OPTIMAL: Phase 3 trial of bimekizumab for bDMARD-naïve PsA

- DBRCT in 852 patients with PsA, ≥3 T/SJC
  - Randomized 3:2:1 to BKZ 160 mg SC q4w, PBO, or ADA 40 mg SC q2w (reference arm)[b]
  - Double-blind to Week 16, after which PBO patients received BKZ, and all treatment-blind to Week 24
  - Mean age 49 y, 6 y since diagnosis, BMI 29 kg/m^2, 47% male
- **Primary endpoint:** ACR50 at Week 16
- All ranked secondary endpoints were met with BKZ treatment
- **PASI 100:**[a] BKZ **47.5%** vs PBO **2.1%** (nominal P<0.001) (ADA **20.6%**)
- **Safety:** to Week 16, no MACE, IBD, uveitis; *Candida* 2.6% BKZ, 0.7% placebo

ACR50, PASI 90, and MDA responses at Week 16 (randomized set; NRI)



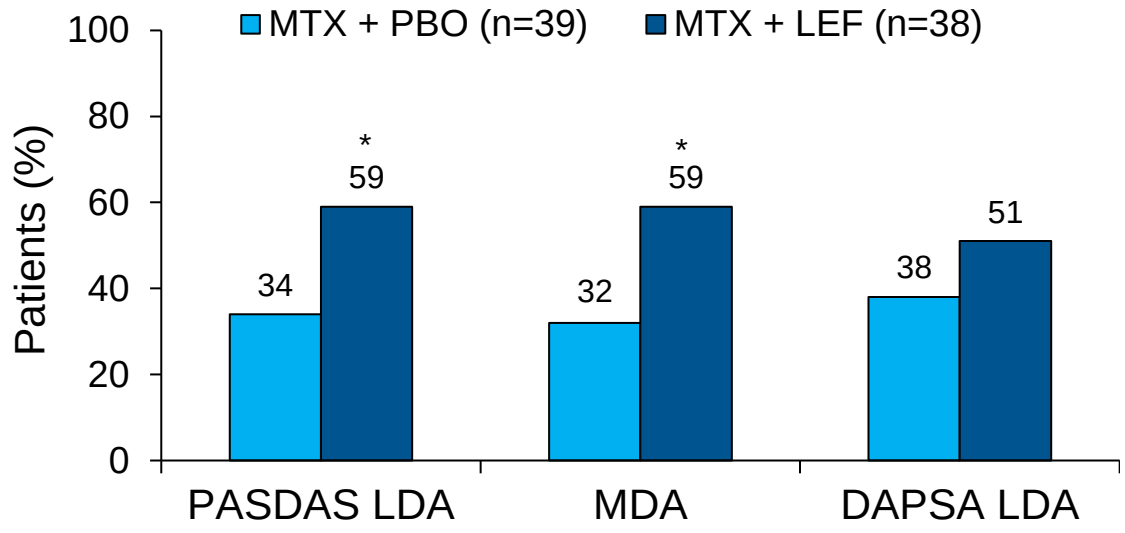
Bimekizumab effective in bDMARD-naïve PsA. Different from other IL-17 inhibitors?

[a]Reference arm; study not powered for statistical comparisons of ADA to BKZ or PBO; [b]In patients with psoriasis ≥3% BSA at BL.
BSA, body surface area; MDA, minimal disease activity
McInnes I, et al. EULAR 2022, Copenhagen, LB0001

COMPLETE-PsA: MTX alone or in combination with leflunomide for PsA

- DBRCT of 78 patients with active PsA (≥2 swollen joints) randomized 1:1 to MTX alone (MTX + PBO) (15→25 mg/week) or in combination with leflunomide 20 mg qd
- **Primary endpoint:** PASDAS at Week 16
  - **3.1** for MTX + LEF vs **3.7** for MTX alone (P=0.025)
  - Multiple secondary endpoints, including presence of active psoriasis, favored the combination
- More treatment discontinuations in the combination group than MTX alone (**10/39** vs **3/39**), most due to GI discomfort
  - More LFT elevation with combo[1]

Proportion of patients meeting different PsA responder criteria for low disease activity (LDA) at Week 16



*P<0.05

MTX + LEF superior to MTX alone in PsA, although there may be tolerability issues

LFT, liver function test

Mulder MLM, et al. EULAR 2022, Copenhagen, POS0078; 1. Mulder M, et al. Lancet Rheumatol 2022;4:E252–E261

SLE-BRAVE-I and -II: Efficacy and safety of baricitinib in SLE

- 2 Phase 3, 52-week, multicenter DBRCTs: SLE-BRAVE-I (n=760) and SLE-BRAVE-II (n=775)[1]
  - BARI 2 mg, 4 mg, or PBO + stable standard of care; glucocorticoid (GC) tapering encouraged
  - Primary endpoint: SRI-4 response at Week 52
  - Baseline SLEDAI-2K: 10.1 for both trials

	SLE-BRAVE-I			SLE-BRAVE-II		
Efficacy measure	**PBO (n=253)**	**BARI 2 mg (n=255)**	**BARI 4 mg (n=252)**	**PBO (n=256)**	**BARI 2 mg (n=261)**	**BARI 4 mg (n=258)**
SRI-4 at Week 52, n (%)[a]	116 (46)	126 (50)	142 (57)*	116 (46)	120 (46)	121 (47)
SRI-4 at Week 24, n (%)	99 (39)	114 (45)	117 (47)	98 (39)	104 (40)	108 (42)
Severe flares (n, events)	38 (15)	34 (13)	26 (10)	26 (10)	29 (11)	29 (11)
Time to first severe flare, HR (95% CI)	NA	0.8 (0.52, 1.32)	0.7 (0.40, 1.08)	NA	1.1 (0.65, 1.89)	1.1 (0.67, 1.94)
GC sparing at Week 52	36 (31)	31 (29)	36 (34)	33 (32)	34 (30)	36 (34)
LLDAS at Week 52	66 (26)	65 (26)	74 (30)	59 (23)	62 (24)	65 (25)

- Primary endpoint in SLE-BRAVE-II failed, as did all secondary endpoints in both trials

*P=0.05 vs PBO

- Pooled safety of Phase 2/3 trials: no increased VTE or malignancy; numerically more dose-related SIE, HZ, and MACE[2]

Failed trial of baricitinib in SLE: Drug? Placebo response? Adjudication?
No VTE signal in a disease where VTE may be expected

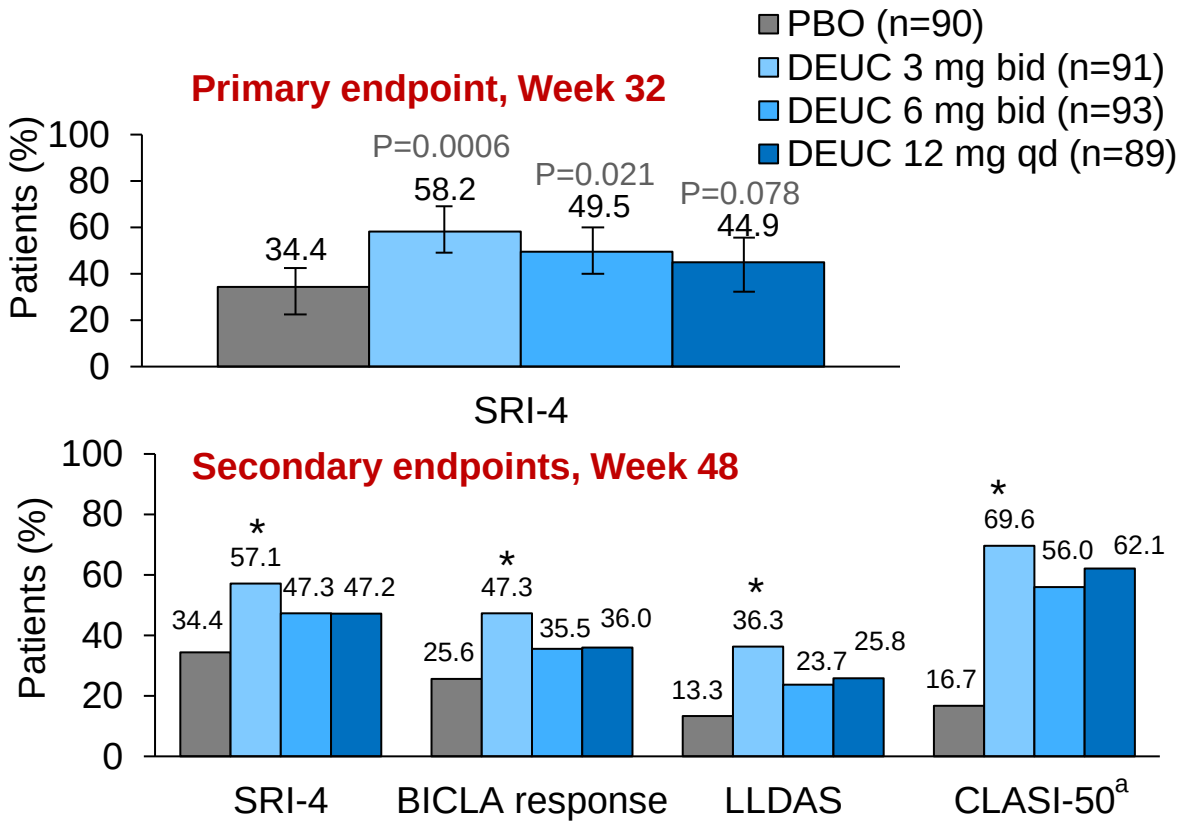
[a]Nonresponder imputation and multiple imputation. LLDAS, Lupus Low Disease Activity State; SRI-4, SLE Responder Index-4

1. Morand EF, et al. EULAR 2022, Copenhagen, POS0190; 2. Dorner T, et al. Ibid, POS0714

PAISLEY: Deucravacitinib Phase 2 in SLE

- TYK2 mediates signaling of type I IFN, IL-23, and IL-12: key cytokines in SLE
- DEUC: oral, selective, allosteric TYK2 inhibitor
- Phase 2, 48-week DBRCT in active SLE on SOC
  - PBO or DEUC (3, 6, 12 mg qd)
  - Oral GC tapering to 7.5 mg/day required from Wk 8–20
- SLICC criteria for SLE; + ANA/anti-DNA/or anti-Sm; SLEDAI 2K ≥6; ≥1 BILAG A or >2 B from MSK or MC domain
- Primary endpoint: % patients achieving SRI-4 at Wk 32
- No evidence of lab abs characteristic of JAKi (neutrophils, lymphocytes, creatinine, platelets, hemoglobin, ALT)
- Safety: increased acneiform rash DEUC 12 mg – no signal for SAE, infections (SIE, TB, HZ), malignancy, MACE, VTE

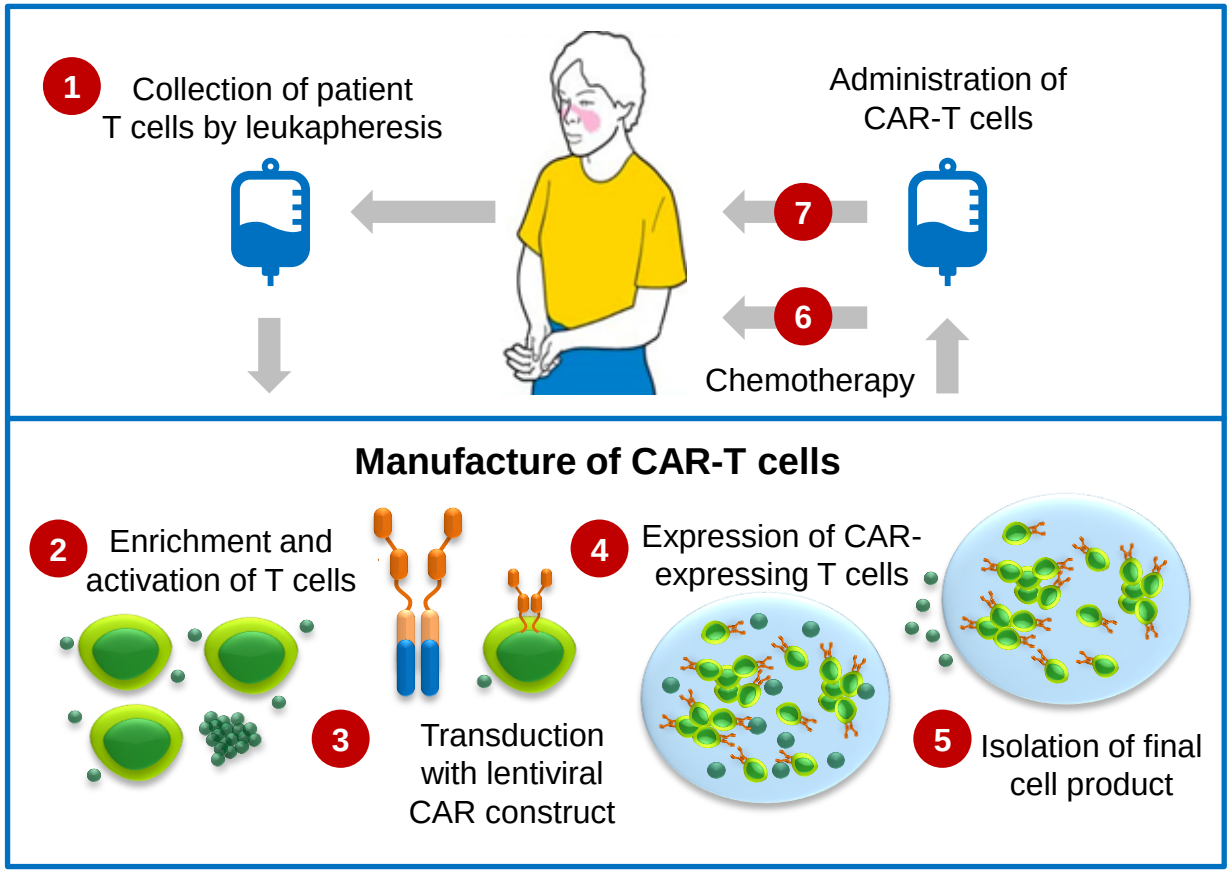
Efficacy outcomes (nonresponder imputation)

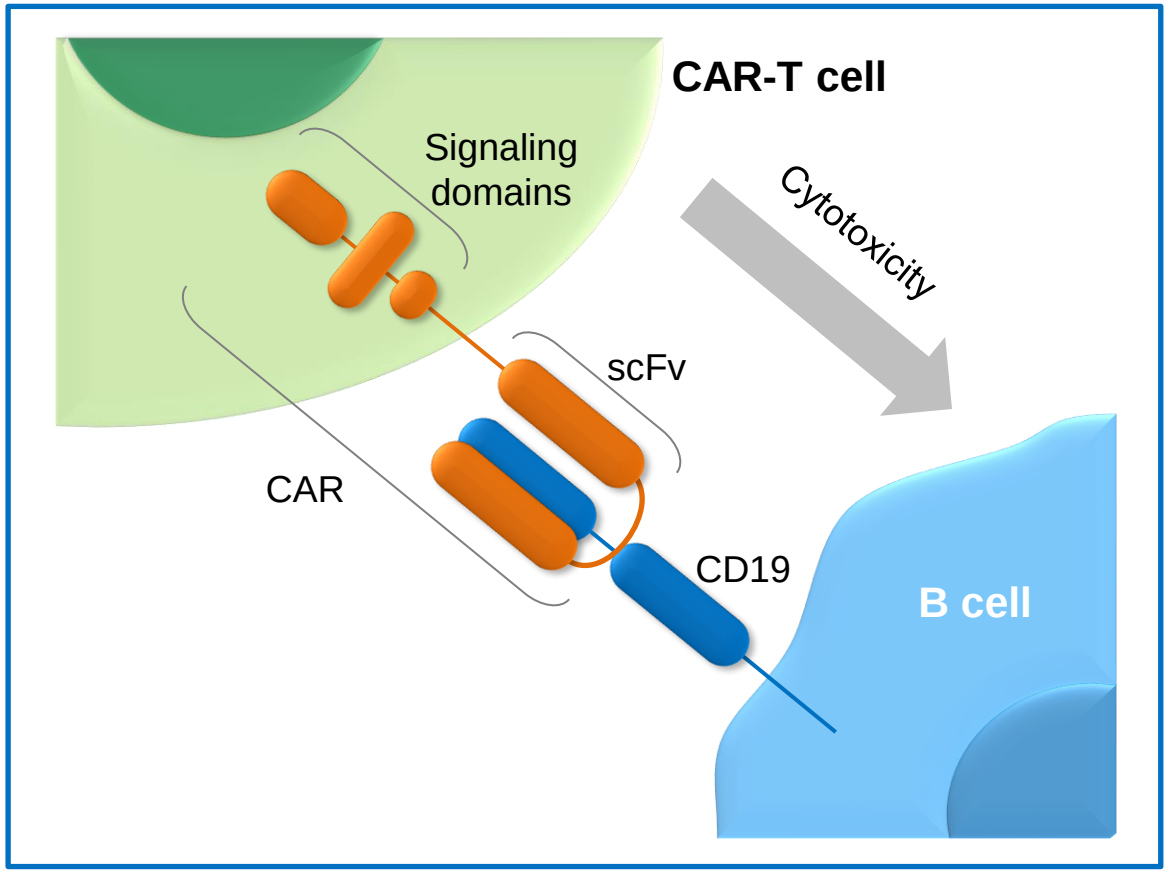


DEUC appears to be effective in a proportion of patients with MSK and MC manifestations

*Significant vs PBO in multiplicity-controlled prespecified analysis. [a]n patients with baseline CLASI-A score ≥10; MSK, musculoskeletal; MC, mucocutaneous; Sm, Smith; SOC, standard of care. Morand E, et al. EULAR 2022, Copenhagen, LB0004

Chimeric antigen receptor (CAR)-T cell treatment in SLE[1,2]





Anti-CD19 CAR construct = FMC63 scFv, CD8-derived hinge region, TNFRSF19-derived transmembrane domain, 4-1BB co-stimulatory domain, CD3ζ intracellular domain

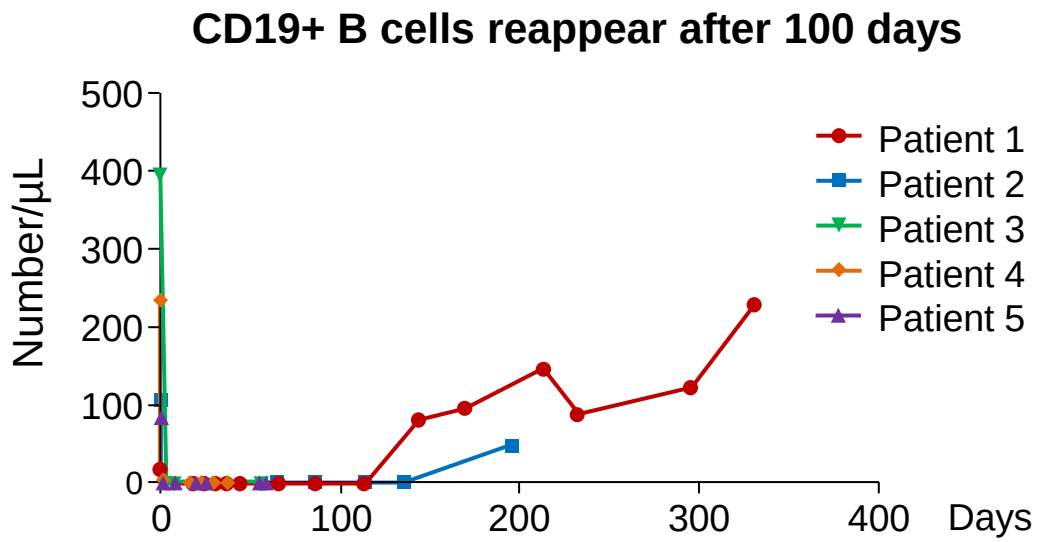
scFv, single-chain variable fragment

1. Adapted from: Hucks G, et al. Blood Cancer Journal. 2019;9:10
2. Adapted from: https://bpsbioscience.com/car-t-cell-therapy-technical-note

CAR-T cell treatment of refractory SLE

- Patients with severe multiorgan SLE refractory to all therapies treated with anti-CD19 CAR-T cells
  - Stopped all SLE therapies (except low-dose prednisolone), conditioned with CYC/fludarabine, and then given single infusion of 1 × 10^6 CD19–CAR-T cells/kg of body weight

Patient, age, sex	Follow-up (months)	Baseline SLEDAI-2K	Follow-up SLEDAI-2K
20 y, F	12	16	0, ANA/dsDNA neg
22 y, M	9	16	2, ANA/dsDNA neg
22 y, F	4	10	0
24 y, F	3	8	0
18 y, F	1	9	0



  - % total CAR/total T cells (at Day 9): 11.5–59.1%
  - Toxicity: fever; no other cytokine-release syndrome symptoms, neurotoxicity, or infections
  - All patients in remission and able to stop prednisolone and immunosuppressives

CAR-T cell therapy is a potential treatment for patients with refractory SLE

CYC, cyclophosphamide

Schett G, et al. EULAR 2022, Copenhagen, OP0279

COVID-19: Lessons in Rheumatology

1. **2020 GRA**: Rheumatologists establish the COVID-19 Global Rheumatology Alliance registry
2. **Telemedicine** Skyrockets and is then abandoned by Rheumatologists
3. **Reduced Risk**: Inflammatory arthritis well controlled (MTX, TNFi, JAKi, IL-6i etc)
4. **At Risk!** on Steroids , Rituximab, and active autoimmune disease
5. **"Immunosuppressed"** (active, uncontrolled, immunosuppressives) worse COVID outcomes
6. **Autoantibodies**: COVID-19 complicated by lupus anticoagulants, APL Abs and microthrombi
7. **Hydroxychloroquine**: fame, folly, and shortages
8. **Rheum Drugs**: Colchicine, IL-1 inhibitors, IL-6 inhibitors work in multiple (but not all) studies
9. **Baricitinib**: FDA approved for hospitalized COVID-19 (Bari > Remdesivir)
10. **Evusheld**: Not enough use in Rheum pts (on RTX)
11. **MIS-C**: a new Kawasaki-like disease appears in hundreds of COVID infected children
12. **US mortality** up (3.2 million deaths), 400,000 more than in 2019 (all due to COVID)

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Still's Diagnosis Calculator

- ○ Age less than 16 years
- ✓ **Age less than 35 years**
- ○ Daily or nightly fever (not measured)
- ○ Daily/nightly fever (between 100-102°F)
- ✓ **Daily/nightly fevers always above 102°F (>39°C)**
- ○ Muscle pains (myalgia)
- ○ Joint pains (arthralgia)
- ✓ **Swollen painful joints**
- ○ Many swollen joints (polyarthritis)
- ○ Carpal ankyloses (wrist fusion)*
- ○ Cervical ankyloses (neck fusion)*
- ○ Tarsal ankyloses (ankle fusion)*
- ✓ **Intermittent faint red/pink rash (arms, legs, trunk, neck only)**
- ○ Sore throat (preceding fevers, rash)
- ✓ **Pleuritis or pleural effusion**
- ○ Pericarditis or pericardial effusion
- ○ Generalized lymphadenopathy (many swollen lymph nodes)
- ✓ **Splenomegaly (enlarged spleen)**
- ○ Hepatomegaly (enlarged liver)
- ○ Elevated hepatic (liver) enzymes (AST, ALT)
- ○ Low albumin < 3.0 (hypoalbuminemia)
- ✓ **Negative tests for ANA (lupus) and RF (RA)**
- ✓ **Elevated "sed rate" (ESR) > 40 mm/hr**
- ✓ **Elevated WBC > 12.5**

	Cush Criteria	Yamaguchi Criteria	ILAR Criteria
Minimum Threshhold for Diagnosis:	10 points	>5 points>2 Major	A+B+C+ >1 D
Your score:	**12**	**5**	**B,C,D**

Sti...