DISCLOSURES- Michael Weinblatt,MD 2021

- **RESEARCH GRANTS**
- Bristol Myers Squibb
- Sanofi
- Lilly
- Amgen

- **CONSULTANT**
- Abbvie
- Aclaris
- Amgen
- Arena
- Bayer
- Bristol Myers Squibb
- Corrona
- Crescendo
- EQRx
- Genosco
- Glaxo Smith Kline
- Gilead
- Horizon
- Johnson and Johnson
- Kaleido
- Kiniksa
- Lilly
- Pfizer
- RPharma
- Roche
- Sanofi
- Scipher
- Set Points
- Tremeau
- XBiotech

- **OPTIONS**
- Canfite Inmedix
- Vorso Scipher

- Off label use Jak inhibitors in sarcoidosis and dermatomyositis

RA:2021 Outline

- Methotrexate
- Biologics
- Jak Inhibitors
- Other issues

METHOTREXATE

Toxicity of MTX in CIRT

Ann Intern Med Feb 2020

- RCT of MTX vs Placebo in pts with CV disease and DM or metabolic syndrome
- 6158 pts enrolled and 4786 randomized, 2391 received MTX median dose 15 mg/wk, median followup of 23 months, median BMI 31.5 kg/m2
- Adverse events
- GI 1.9, Lung 1.5, Infections 1.15 and Heme 1.1,Skin cancer 2.05
- Liver – 5 cirrhosis MTX, 0 Placebo
- All with BMI in obese range, all with DM, several with elevated transaminases at study entry, 3 had repetitive episodes prior to dx, duration of MTX was only several months for 3 pts
- Overall the adverse event profile in this study was similar to that observed with MTX in RA

MTX and Liver Disease

J Am Acad Derm 2012; 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 7.2 pso, 6.6 psa, 8.5 ra
- Conclusions- Independent of other risk factors psoriasis and psa increase risk of serious liver disease

Fibroscan and MTX ACR 2020 no 0205

- Cross sectional study of successive RA pts hospitalized over 12 months. 170 RA pts with mean disease duration of 15 yrs, 102 rx with MTX with mean dose of 10 mg/wk, mean duration of 9.5 yrs and cumulative dose of 5.3 gms
- No difference in fibroscan scores in those on mtx vs pts not on mtx. No impact of steroids or BMI

BIOLOGICS

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

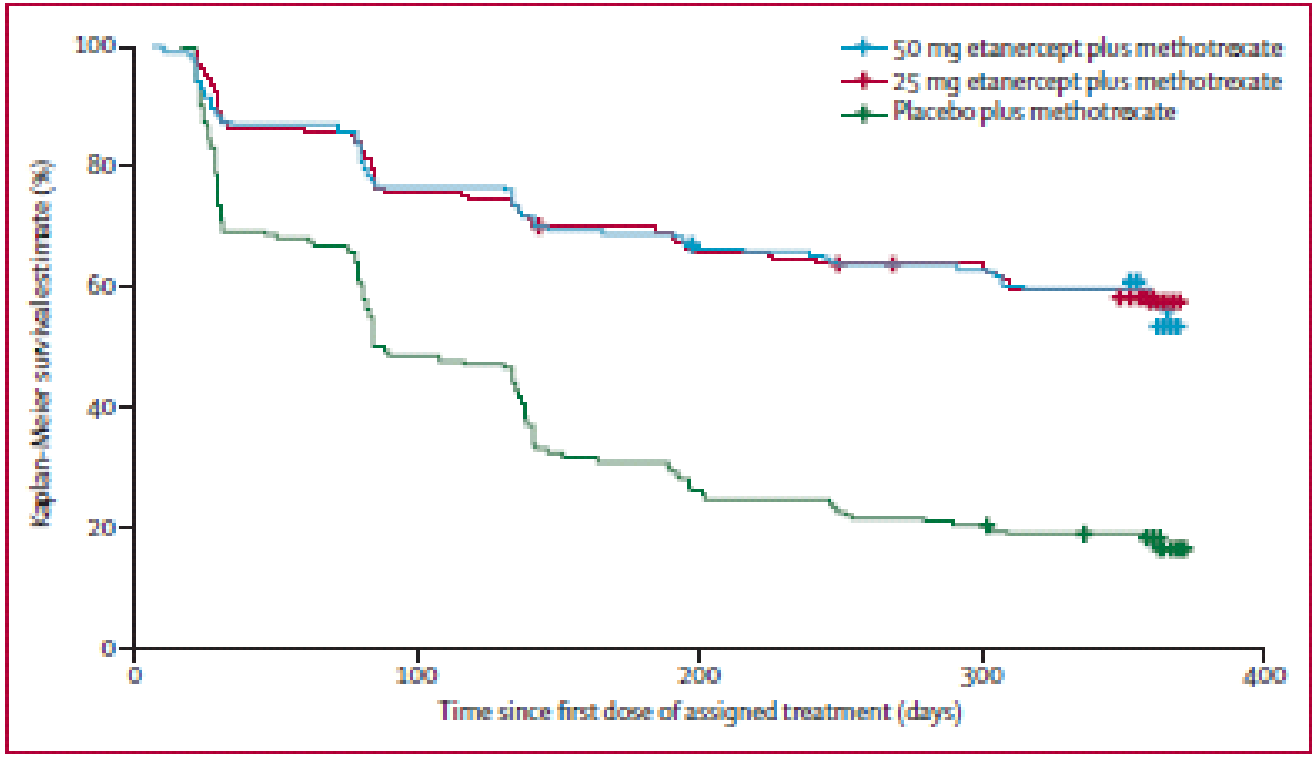


Figure e4: Time to loss of efficacy by treatment group

Withdrawal of Etanercept or MTX: Double Blind Study
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 +eta.

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

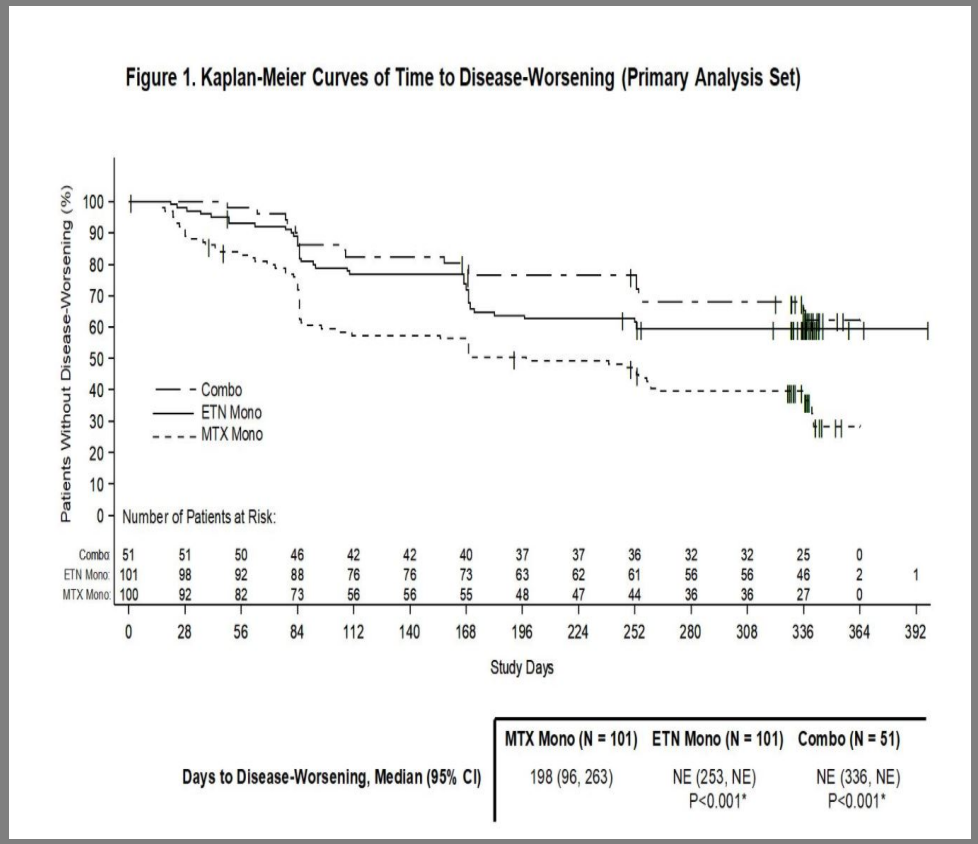
Results

SDAI remission

49.5% ETN, 28.7%MTX, Combo 52.9%

Recapture remission in >70% of pts

After stopping therapy monotherapy ETN was superior to MTX in remission and similar to Combo



Infliximab Drug Monitoring: Clinical Study JAMA 2012; 325:1744

- Open label study of 411 pts with RA, AS, Psa, IBD, pso initiating infliximab
- Randomized to received therapeutic drug monitoring with dose and interval adjustments based on serum drug levels and anti-drug antibodies vs standard dosing
- Primary outcome was clinical remission at wk 30
- Clinical remission was achieved in 51% and 53% of the TDM group vs standard of care.Mean Infiximab doses were the same at 4.9 mg/kg. Similar percentages developed HACA (18%)
- Conclusions
- Proactive TDM did not improve remission rates as compared to standard therapy

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”

JAK INHIBITORS

- Three now approved by the FDA
  - Tofacitinib 11 mg after biologic
  - Baricitinib 2 mg qd- after biologic
  - Upadacitinib 15 mg after biologic
  - Several more in development
  - All with comprehensive Phase 3 programs
  - monotherapy, in combo with mtx or other dmards, comparison to adalimumab mono or combined with MTX, comparison to mtx, biologic-naïve and experienced pts, radiographic studies
- All work quickly within a week- if not better by 8 wks move on
- Side effects in most cases directly related to mechanism of action
- MACE/ vte/Malignancy issues?

Tofacitinib in Sarcoidosis

ACR Open Rheum 2020;2:106

60 year old woman with 21 yr hx of sarcoidosis

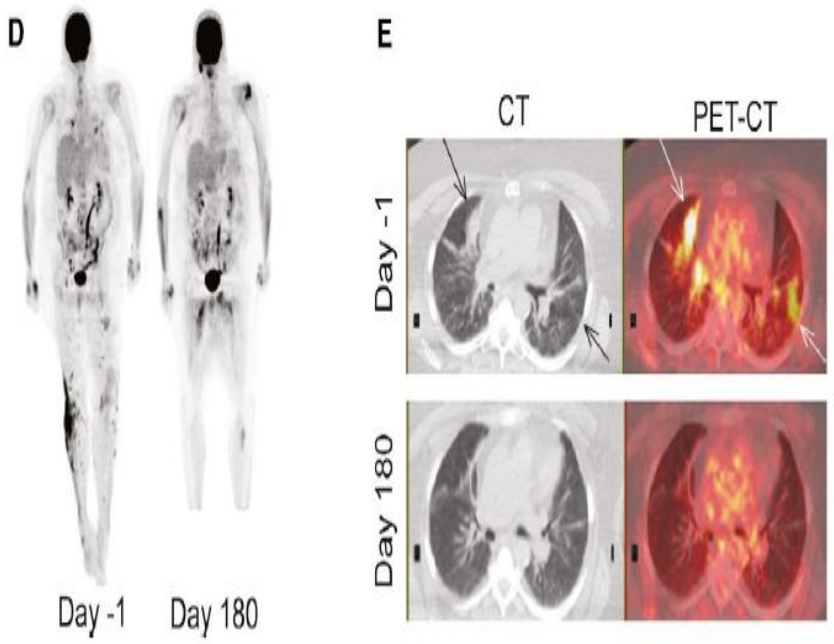
Prior rx included steroids, mtx, infliximab, mofetil, Rituxan, iIVIG

Involvement of skin and internal organs

Started on Tofa 10 mg

Improvement noted clinically, skin bx, CT and PET

One of several case reports of positive response with a JAK inhibitor in sarcoidosis



Tofacitinib is not approved for use in sarcoidosis

Tofacitinib in Dermatomyositis: Open Label Study

Arthritis Rheum 2021; 73:858

Open label study of tofacitinib in 10 pts with dermatomyositis

Active disease despite 12 weeks of prednisone and lack of response to one immunomodulatory drug. Maximum dose of prednisone at entry was Prednisone 20 mg/day

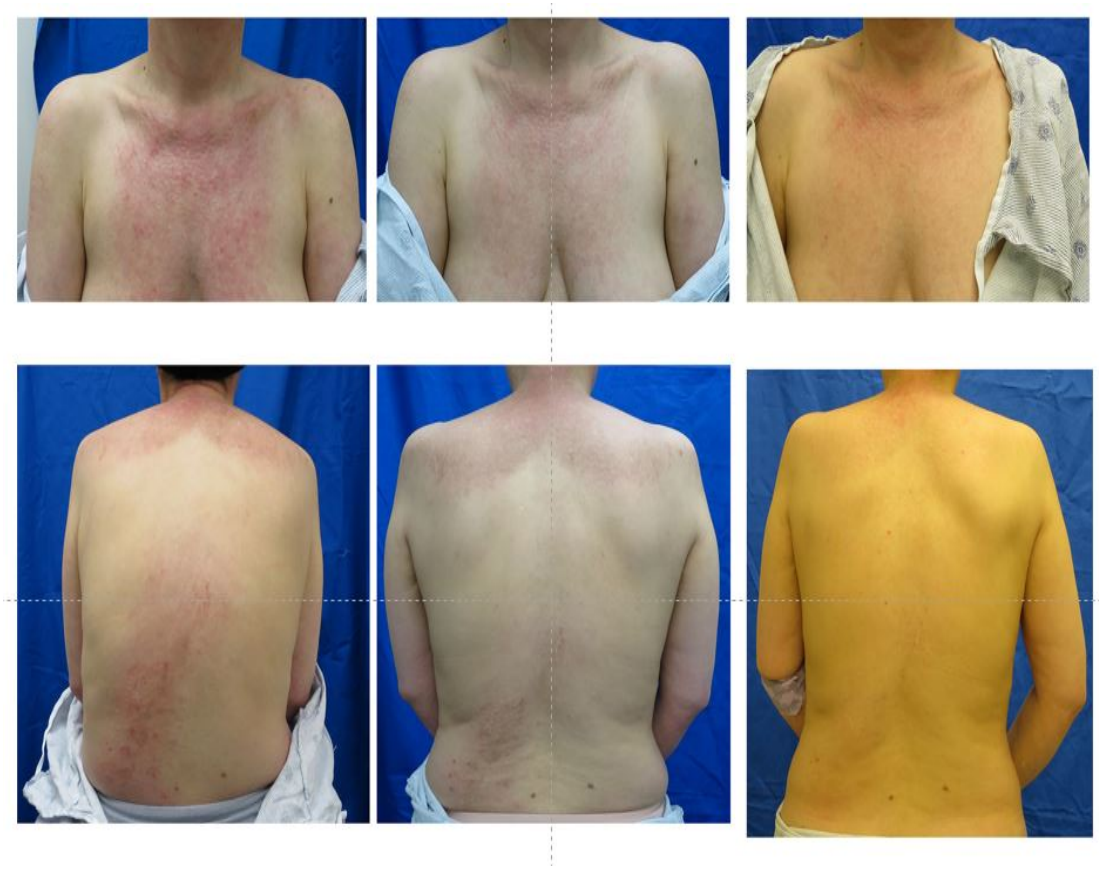
Primary outcome measure was improvement in 3/6 core set measures

All 10 pts met response criteria, 50% with moderate improvement

Skin was the predominant feature with only 1 pt with significant muscle weakness

Improvement in skin disease occurred as early as 4 weeks

Additional studies are needed to evaluate the impact of JAK inhibitors in pts with active muscle disease



Upadacitinib vs Adalimumab vs Placebo on Background MTX

Arthritis Rheum 2019; 71:1788

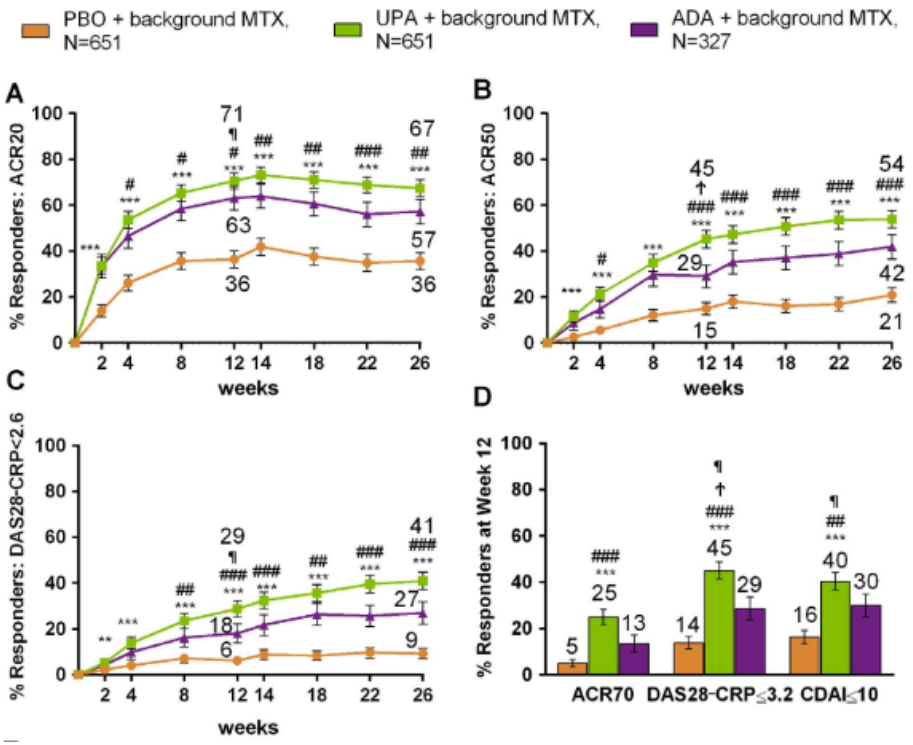
Upadacitinib vs Adalimumab on background MTX in 1629 pts. Primary outcome ACR 20 and DAS CRP <2.6 at wk 12 and inhibition in radiographic progression.

ACR 20 UPA 71%, ADA 63%, P 36%
ACR 50 UPA 45%, ADA 29%, P15

Significant inhibition of radiographic progression UPA vs Placebo

SAEs UPA 3.7%, ADA 4.3% P 2.9%
PE/DVT UPA 2, ADA 3, 1 P

UPA+MTX was superior to MTX+P in ACR 20 and DAS CRP<2.6 and superior to Ada+MTX in ACR 50 and DAS CRP<3.2, pain and HAQ at wk 12

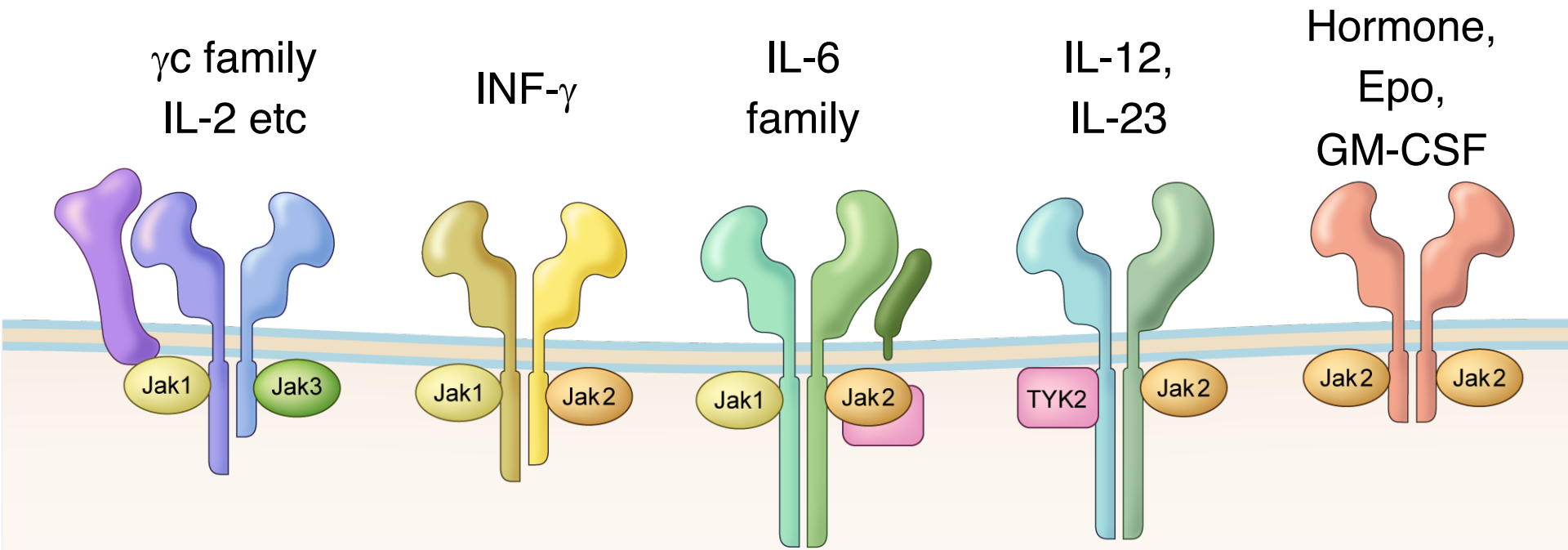


UPA vs Abatacept in RA

NEJM 2020;383:1511

- Double blind 24 wk study of UPA 15 mg qd vs IV ABA monthly in pts who were biologic experienced and background csDMARDs.
- Primary outcome – change in DAS CRP at wk 12 non inferiority – margin 0.6
- 612 RA treated, 90% completed 24 wks
- Wk 12 Non-inferiority and superiority met for UPA vs ABA
- Change in DAScrp -2.5 vs -2.0
- DAS crp <2.6 UPA 30% ABA 13%
- ACR 50 UPA 46% ABA 34%
- AE more treatment emergent Aes leading to study discontinuation with UPA (3.6%) vs ABA (2.6%)

Jaks and Signaling by Type I/II Cytokine Receptors



- Four Jaks: Jak1, Jak2, Jak3, Tyk2
- work in pairs, except homodimeric hormone receptors

JAK Inhibitors—AE profile

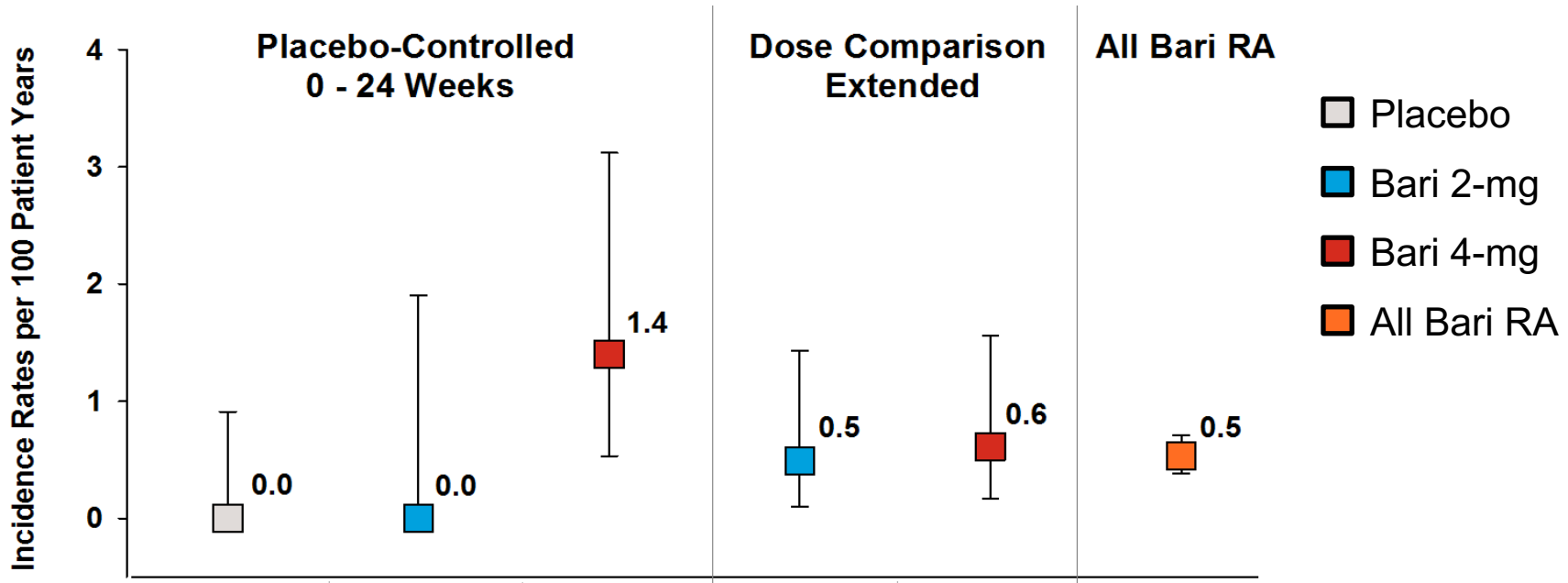
- Infections
  - Opportunistic infections
  - Zoster
- Lipid abnormalities
- Neutropenia /Anemia
- Increase serum creatinine –
- LFTs
- Malignancy
- Mace
- DVT/PE?
- Reproductive

Serious Infections with Tofa vs bDmards

Lancet Rheum 2020; 2:e84

- Study compared risk of serious infection in RA pts starting tofacitinib vs bDMARDS
- Analysis using 3 data sets- Medicare, Optum and Market Scan. 130,718 pt identified
- Adjusted HR Tofa vs Eta 1.41, vs Aba 1.2, vs Ada 1.06 and Infl 0.81
- Two fold higher risk of herpes zoster with Tofa as compared to the bDmards

Baricitinb:Total DVT/PE Incidence Rates by Analysis Set
Arthritis Rheum 2019; 71:1042



	Placebo	Bari 2-mg*	Bari 4-mg	Bari 2-mg	Bari 4-mg	All Bari RA
All Patients	1070	479	997	479	479	3492
With Events	0	0	6	3	4	42
Patient Years	406	194	418	615	657	7949

*Bari 2-mg data in the placebo-controlled analysis set is derived from 4 studies in which both baricitinib 2-mg and 4-mg were options during randomization. Events of DVT and PE were analyzed without adjudication.

VTE Risk with Jak inhibitors

Arthritis Rheum 2021; 75:779

- Meta-analysis of phase II/III studies of Jak inhibitors to evaluate risk of VTE
- 42 studies – 6542 Jak inhibitor pt exposure yrs (PEY) and 1578 placebo PEY
- VTE 15 Jak and 4 placebo group
- Incidence rates of VTE 0.68 Jak and 0.59 placebo
- Conclusion: Meta-analysis “does not provide support for the warnings of VTE risk for Jaks”

CV Outcome Study
Pfizer Press Release 1/21

- FDA Mandated CV Outcome Study
- Non inferiority Post Approval Study Tofa 5/10 vs anti-TNF therapy
- Primary outcome MACE/Ca
- 4362 RA >50 with CV Risk
- MACE
- 5 mg 10mg Anti tnf

No	47	51	37
HR	1.21	1.43	1.33

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

Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 7-10 June 2021

Share

Xeljanz: new recommendations for use

This DHPC is intended to inform healthcare professionals about the outcome of a signal procedure and new recommendations for use of Xeljanz (tofacitinib).

Final results from a recently completed study (A3921133) showed an increased risk of major adverse cardiovascular events and cancer in some patients, compared with TNF-alpha inhibitors (other medicines for rheumatoid arthritis). The PRAC is therefore advising healthcare professionals that Xeljanz should only be used in patients over 65 years of age, patients who are current or past smokers, patients with other cardiovascular risk factors, and patients with other malignancy risk factors, if no suitable treatment alternative is available.

EMA PRAC Statement: Tofa 7/10/21

Dear Healthcare Professional,

Pfizer Europe MA EEIG in agreement with the European Medicines Agency (EMA) and the <National Competent Authority>would like to inform you of the following:

Summary

- **In the completed clinical trial (A3921133) in patients with rheumatoid arthritis (RA) who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of myocardial infarction was observed with tofacitinib compared to TNF-alpha inhibitors.**
- **The study also showed an increased incidence of malignancies excluding NMSC, particularly lung cancer and lymphoma, with tofacitinib compared to TNF-alpha inhibitors.**
- **Tofacitinib should only be used in patients over 65 years of age, in patients who are current or past smokers, patients with other cardiovascular risk factors, and patients with other malignancy risk factors if no suitable treatment alternatives are available.**
- **Prescribers should discuss with the patients the risks associated with the use of Xeljanz, including myocardial infarction, lung cancer and lymphoma.**

FDA Communication 9/1/21

What is FDA doing?

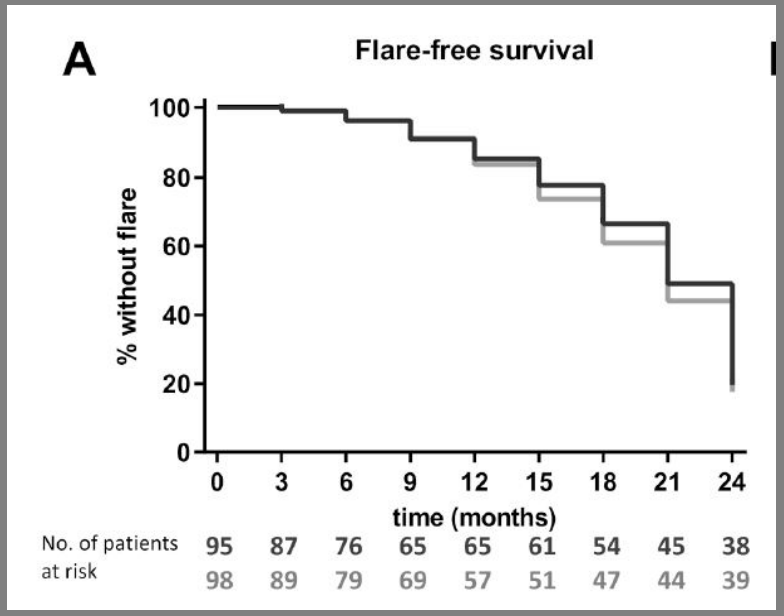
We are requiring revisions to the Boxed Warning, FDA's most prominent warning, for Xeljanz/Xeljanz XR, Olumiant, and Rinvoq to include information about the risks of serious heart-related events, cancer, blood clots, and death. Recommendations for health care professionals will include consideration of the benefits and risks for the individual patient prior to initiating or continuing therapy. In addition, to ensure the benefits of these three medicines outweigh the risks in patients who receive them, we are limiting all approved uses to certain patients who have not responded or cannot tolerate one or more TNF blockers. Changes will also be made to several sections of the prescribing information and to the patient Medication Guide.

RA Therapy Issues

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



Half dose vs Full dose CS DMARDS in RA pts in Remission

JAMA 2021: 325:1755

Open label non inferiority study

160 RA pts in remission for 12 months on stable cs DMARDs were randomized to receive half dose csDMARDS vs full dose

Primary outcome as proportion of pts with disease flare over 12 months.

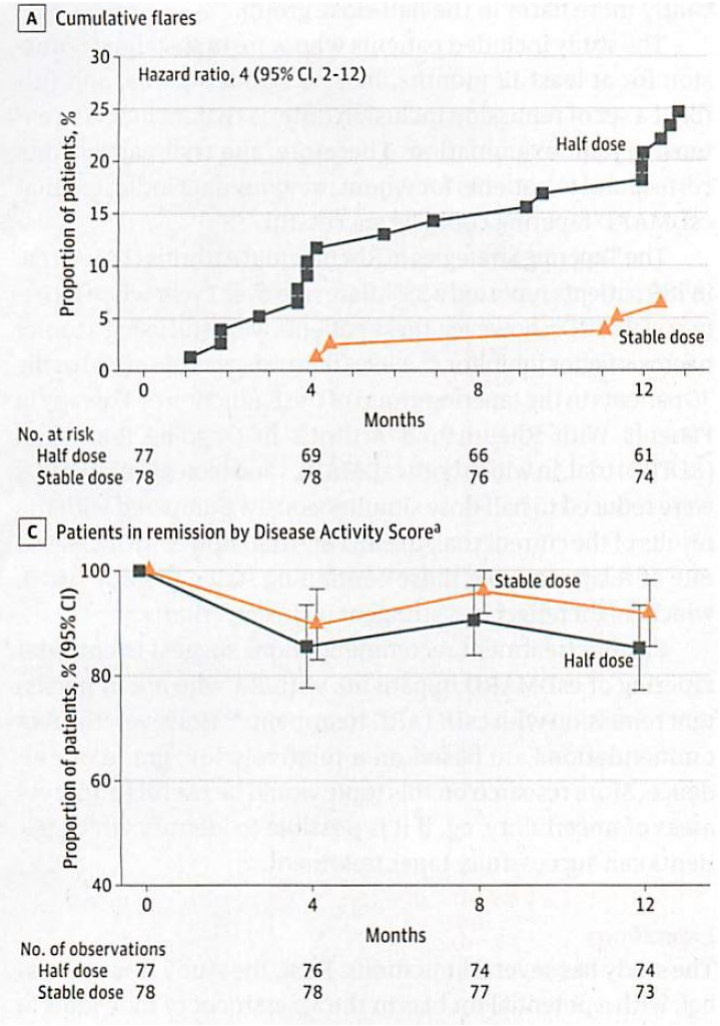
Flare defined as DAS ESR >1.6, increase of DAS>0.6 and at least 2 swollen jts

Results

Flare occurred in 19 pts (25%) of the half dose and 5 (6%) of the full dose group

Conclusion

Tapering to half dose CS DMARDs was not non inferior to maintaining remission as compared to full dose CS DMARDs



Steroids in Early RA

ACR 2020 no 2008

Study goal was to evaluate benefit and side effects of steroids (GC) in pts with early RA

474 pts were studied, mean age was 49 yrs, 71% woman and 69% CCP+

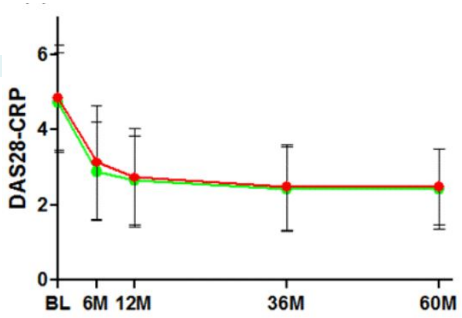
173 (38%) started GC and 294 (62%) did not receive GC

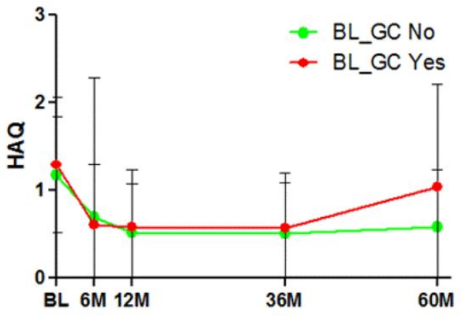
Factors associated with starting GC- elevation in CRP and negative CCP

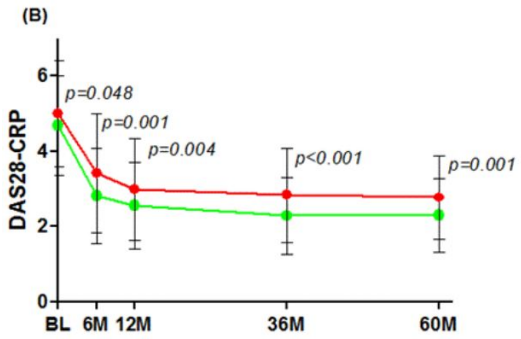
At 5 yrs no difference in response to therapy ie DAS CRP, HAQ

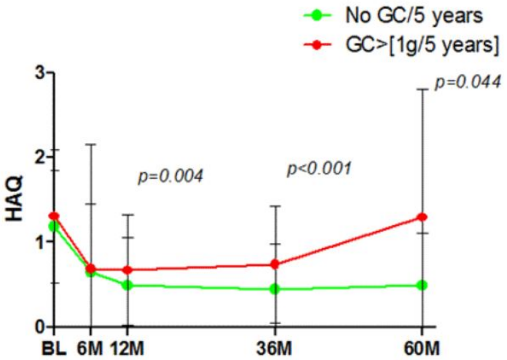
More infections in the GC group

Conclusion: Steroids did not add additional benefit in short and long term control of disease









Risk of serious toxicity with low dose steroids in RA ACR 2020 no 1998

Risk of steroids was studied in an early RA cohort

(ESPOIR cohort) <6 mo of disease duration

608 RA pts in the study, 397 received low dose prednisone (mean 2.8 mg) mean duration of rx was 44.6 mo.

95 serious events were observed

More events seen with GC vs no GC

Risk of events increased over time

6 months HR 0.39 and at 10 yrs 6.83

Conclusion: A dose and time- dependent impact of low dose GC on toxicity

Table 1. Primary outcome at 10 years (death, cardiovascular disease, severe infection or fracture) in the total sample and with and without glucocorticoid (GC) (univariate analysis).

	Total study population (n=608)	Without GC	With CG	P Value
Primary outcome	95 (15.6%)	24 (11.4%)	71 (17.9%)	**0.035**
Death	10 (1.6%)	1 (0.5%)	9 (2.3%)	0.103
Cardiovascular diseases	18 (3%)	3 (1.4%)	15 (3.8%)	0.177
Severe infections	35 (5.8%)	5 (2.4%)	30 (7.6%)	**0.009**
Fractures	32 (5.3%)	15 (7.1%)	17 (4.3%)	0.137

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American College of Rheumatology
Empowering Rheumatology Professionals

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

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Methotrexate monotherapy is conditionally recommended over methotrexate plus a tumor necrosis factor (TNF) inhibitor for DMARD-naive patients with moderate-to-high disease activity

Despite low-certainty evidence supporting greater improvement in disease activity with methotrexate plus a TNF inhibitor, methotrexate monotherapy is preferred over the combination because many patients will reach their goal on methotrexate monotherapy and because of the additional risks of toxicity and higher costs associated with TNF inhibitors. The recommendation is conditional because some patients, especially those with poor prognostic factors, may prioritize more rapid onset of action and greater chance of improvement associated with combination therapy (20–22) over the additional risks and costs associated with initial use of methotrexate in combination with a TNF inhibitor.

Glucocorticoids

Initiation of a csDMARD without short-term (<3 months) glucocorticoids is conditionally recommended over initiation of a csDMARD with short-term glucocorticoids for DMARD-naive patients with moderate-to-high disease activity

While the voting panel agreed that glucocorticoids should not be systematically prescribed, the recommendation is conditional because all members acknowledged that short-term glucocorticoids are frequently necessary to alleviate symptoms prior to the onset of action of DMARDs. Treatment with glucocorticoids should be limited to the lowest effective dose for the shortest duration possible. The toxicity associated with glucocorticoids was judged to outweigh potential benefits.

Hydroxychloroquine is conditionally recommended over other csDMARDs, sulfasalazine is conditionally recommended over methotrexate, and methotrexate is conditionally recommended over leflunomide for DMARD-naive patients with low disease activity

Hydroxychloroquine is conditionally recommended over other csDMARDs because it is better tolerated and has a more favorable risk profile in patients with RA. Sulfasalazine is recommended over methotrexate because it is less immunosuppressive, and the patient panel felt that many patients with low disease activity would prefer to avoid the side effects associated with methotrexate. The recommendations are conditional because methotrexate may be the preferred initial therapy in patients at the higher end of the low disease activity range and in those with poor prognostic factors (11). Methotrexate is recommended over leflunomide because of its greater dosing flexibility and lower cost.

ACR 2021 RA Guidelines

Table 3. Methotrexate administration*

Recommendations	Certainty of evidence
Oral methotrexate is **conditionally** recommended over subcutaneous methotrexate for patients initiating methotrexate.	Moderate
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‡
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
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

Treat-to-target

A treat-to-target approach is strongly recommended over usual care for patients who have not been previously treated with bDMARDs or tsDMARDs

This recommendation applies to dose optimization of methotrexate and to the subsequent addition of DMARDs when required. The recommendation is strong despite low-certainty evidence because of the recognized importance of systematic monitoring and adjustment of treatment to minimize inflammation to prevent joint damage, as well as other long-term sequelae including cardiovascular disease and osteoporosis.

A treat-to-target approach is conditionally recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs

The recommendation is conditional because of the uncertain incremental benefits of treat-to-target over usual care in this patient population. In this context, usual care refers to commonly employed practice patterns, i.e., adjustment of treatment based on shared decision-making, albeit typically without systematic monitoring of disease activity using validated measures to reach a predefined target. Moreover, 1) the number of remaining available treatment options, 2) the impact of noninflammatory causes of pain, comorbidities, and/or damage on the accuracy of validated

A treat-to-target approach is conditionally recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs

The recommendation is conditional because of the uncertain incremental benefits of treat-to-target over usual care in this patient population. In this context, usual care refers to commonly employed practice patterns, i.e., adjustment of treatment based on shared decision-making, albeit typically without systematic monitoring of disease activity using validated measures to reach a predefined target. Moreover, 1) the number of remaining available treatment options, 2) the impact of noninflammatory causes of pain, comorbidities, and/or damage on the accuracy of validated

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.

A treat-to-target approach is conditionally recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs

The recommendation is conditional because of the uncertain incremental benefits of treat-to-target over usual care in this patient population. In this context, usual care refers to commonly employed practice patterns, i.e., adjustment of treatment based on shared decision-making, albeit typically without systematic monitoring of disease activity using validated measures to reach a predefined target. Moreover, 1) the number of remaining available treatment options, 2) the impact of noninflammatory causes of pain, comorbidities, and/or damage on the accuracy of validated

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 (26–29). 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) (13,30). The recommendations from these studies (13,31) 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 (17,18) may require a modification of this recommendation when peer-reviewed results are published.

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 (37).

Nonalcoholic fatty liver disease (NAFLD)

Methotrexate is conditionally recommended over alternative DMARDs for DMARD-naive patients with NAFLD, normal liver enzymes and liver function tests, and no evidence of advanced liver fibrosis who have moderate-to-high disease activity

Given the concerns about the risk of hepatotoxicity associated with methotrexate therapy in patients with NAFLD, use of methotrexate should be restricted to patients with normal liver enzymes and liver function tests and without evidence of liver disease or liver fibrosis (Stage 3 or 4). Noninvasive testing to diagnose and stage liver fibrosis as well as consultation with a gastroenterologist or hepatologist should be considered in patients prior to initiating methotrexate (49). In addition, more frequent monitoring should be performed in this patient population (every 4 to 8 weeks). The recommendation is conditional because patients' and clinicians' risk tolerance varies.

Methotrexate is conditionally recommended over alternative DMARDs for the treatment of inflammatory arthritis for patients with clinically diagnosed mild and stable airway or parenchymal lung disease, or incidental disease detected on imaging, who have moderate-to-high disease activity

Studies indicate that preexisting lung disease is a risk factor for methotrexate-related pneumonitis (39,40). However, the overall risk of worsening lung disease attributable to methotrexate is uncertain, and alternative DMARDs have also been associated with lung disease (41–45). The recommendation is in favor of methotrexate because of its important role as an anchor treatment in RA and the lack of alternatives with similar efficacy and/or superior long-term safety profiles. The recommendation is conditional because some clinicians (rheumatologists and pulmonologists) and patients will prefer an alternative option rather than accept any additional risk of lung toxicity. Patients with preexisting lung disease should be informed of their increased risk of methotrexate pneumonitis prior to initiating treatment with methotrexate.

While consensus was easily reached on the majority of statements, 2 issues required prolonged discussion and debate. The decision on whether patients with an inadequate response to methotrexate should escalate to a bDMARD, tsDMARD, or triple therapy engendered much discussion with contrasting points of view. In the end, a recommendation was made in favor of a bDMARD or tsDMARD because of the more rapid onset of benefit and concerns related to the poor tolerability and durability of triple therapy in real-world practice (13,14). In particular, the patient panel highlighted the importance of a rapid onset of benefit after already having had an inadequate response to methotrexate. The conditional recommendation to initiate methotrexate therapy for patients with preexisting mild, stable lung disease was also rigorously debated. While minimizing the risk of toxicity is paramount, the voting panel favored a conditional recommendation to initiate methotrexate therapy in this clinical setting because of the vital role of this DMARD in the overall treatment of RA and lack of other comparable therapies without pulmonary risks.

On February 4, 2021, the FDA released a Drug Safety Alert noting a possible increased risk of major cardiovascular events and malignancies (excluding non-melanoma skin cancer) in patients with RA (over the age of 50 years with at least 1 risk factor for cardiovascular disease) participating in a randomized controlled trial designed to compare the safety of tofacitinib to adalimumab (18). Recommendations will be reviewed once peer-reviewed results are published. Rapidly evolving comparative effectiveness and safety signals associated with JAK inhibitors highlight the need to engage in a shared decision-making process when adjusting DMARDs (16,59). In addition, although previous recommendations cautioned against the use of TNF inhibitors in patients with skin cancer (1), the results of more recently published studies examining specific DMARD-related risks of non-melanoma skin cancer and melanoma do not support making a definite recommendation for or against specific DMARDs (60,61).

RA:2021

- MTX remains the cornerstone of therapy– maximize the dose and go to sq or split dose oral as the dose is escalated. Add another drug if not in low disease activity at max dose of MTX
- Adherence and tolerability an issue with triple therapy
- Biologics or JAK inhibitors induce a significant response in MTX partial responders in combo with MTX or as monotherapy. MTX reduces antibodies to biologics
- If no response with a biologic or JAK inhibitor go to another molecule
- Consider reduction of MTX in combo pts in LDA after 6 months of desired clinical state. Consider dose reduction or dose interval increase of biologics in LDA
- Complete discontinuation of therapy generally not effective!
- 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 risk and mechanism needs to be determined with JAKs
- Access barriers for our pts remains the greatest threat to successful treatment!