
In the name of God

Update for treatment of rheumatoid arthritis
(Small molecules targeting JAKs)

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2 May 2019

Introduction

- Biologic therapies have revolutionized the treatment of RA with targeted suppression of key inflammatory factors .
- However not all patients respond to treatment.
- The cytokine network in RA is complex and targeting a single cytokine does not exclusively terminate the disease.
- Biologics are susceptible to immunogenicity, which may result in a loss of efficacy over time .

Rheumatology (Oxford). 2019 Apr 14

Small-molecule inhibitors

- Advances in our understanding of signal transduction pathways has resulted in the development of small-molecule inhibitors.

- These drugs target intracellular cytokine pathways and represent an attractive pharmacological alternative to biologics.

- The Janus kinase (JAK)signal transducer and activator of transcription (JAK-STAT) pathway operates downstream of >50 cytokines and growth factors and is regarded as a central communication node for the immune system .

Four JAKs exist: JAK1, JAK2, JAK3 and non-receptor tyrosine-protein kinase TYK2.

Rheumatology (Oxford). 2019 Apr 14

Small molecule

Within the fields of molecular biology and pharmacology:

A small molecule is a low molecular weight (< 900 daltons) organic compound that may regulate a biological process.

- Most drugs are small molecules.
- Larger structures such as nucleic acids and proteins, and many polysaccharides are not small molecules.
- Although their constituent monomers (ribo- or deoxyribonucleotides, amino acids, and monosaccharides, respectively) are often considered small molecules.
- Pharmacology usually restricts the term "small molecule" to molecules that bind specific biological macromolecules and act as an effector, altering the activity or function of the target.

Wikipedia

Proposed Algorithm to Reach and Sustain the T2T in RA

Phase	Standard strategy	Alternate strategy
First-line treatment	Start initial csDMARD (methotrexate) plus short-term glucocorticoids	If methotrexate is contraindicated, use an alternate csDMARD (leflunomide or sulfasalazine)
Second-line treatment	Continue csDMARD and add a bDMARD (combination csDMARD + bDMARD) or continue csDMARD and add a tsDMARD (combination csDMARD + tsDMARD)	If no poor prognostic factor[b] is present, switch to another csDMARD monotherapy or add another csDMARD
Third-line treatment	Use any other bDMARD or tsDMARD, in combination with continued csDMARD	Not applicable
Remission phase	Consider tapering existing therapy by reducing doses or by extending intervals between treatment	Continue therapy based on patient or physician preference

Daniel Aletaha; Josef S. Smolen. JAMA Oct 2018

Management recommendation

- About 50% to 60% of patients will not meet treatment goals after the first DMARD course.
- More than 60% of these will require at least a third DMARD course.
- However, with the correct treatment strategy, LDA or remission is currently a realistic goal for more than 75% to 80% of patients with RA.

Daniel Aletaha; Josef S. Smolen. JAMA Oct 2018

Classification of cytokines

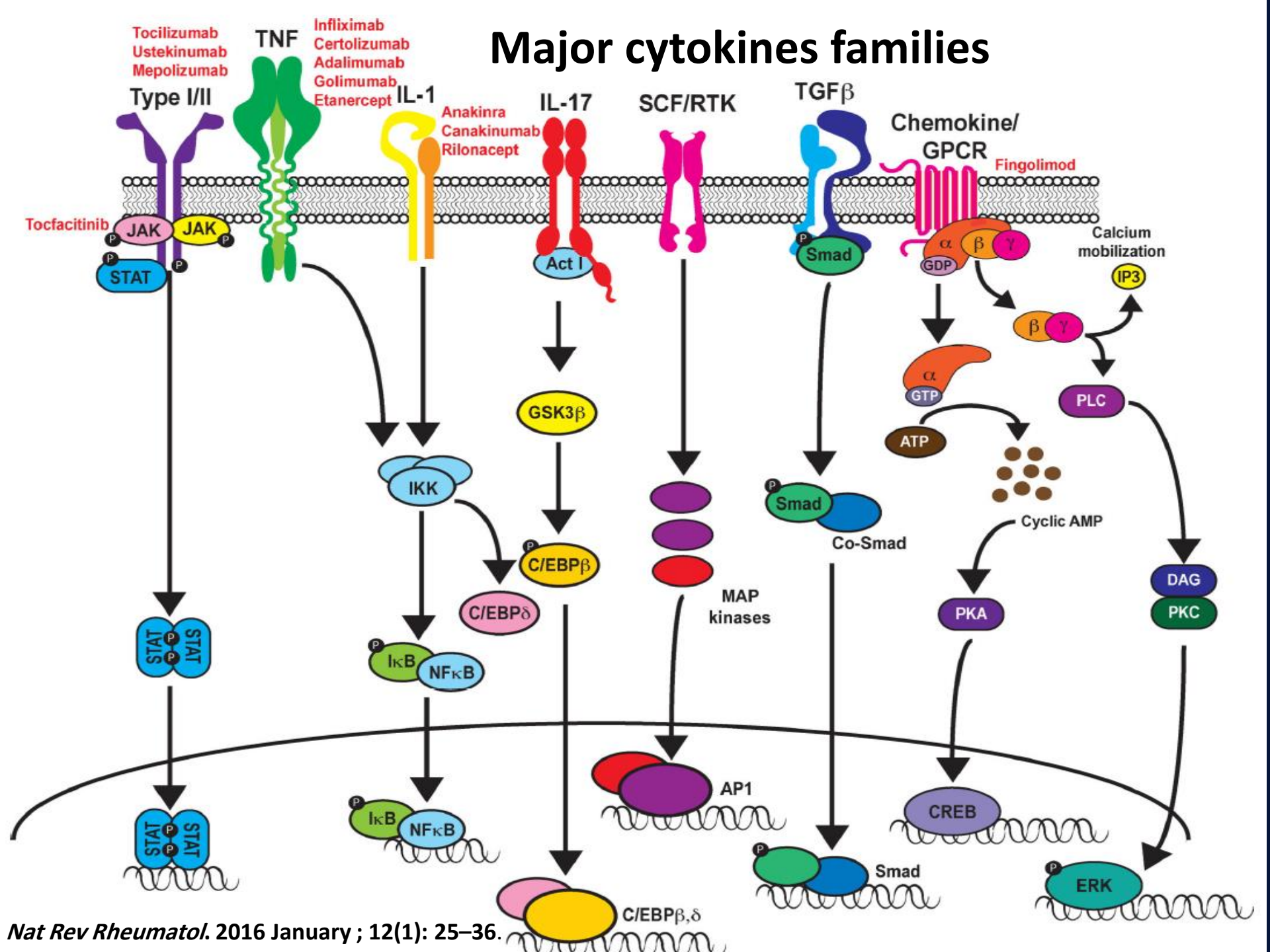
- **Cytokines are better classified based on the type of receptors they bind.**
- **This classification also allows us to highlight similarities in their signal transduction cascades.**

It is possible to identify 5 distinct classes of receptors:

1. **Type I and type II cytokine receptors**
2. **The tumor necrosis factor (TNF) receptor family**
3. **The interleukin (IL)-1 receptor**
4. **IL-17 family of receptors**
5. **Transforming growth factor receptor superfamily**

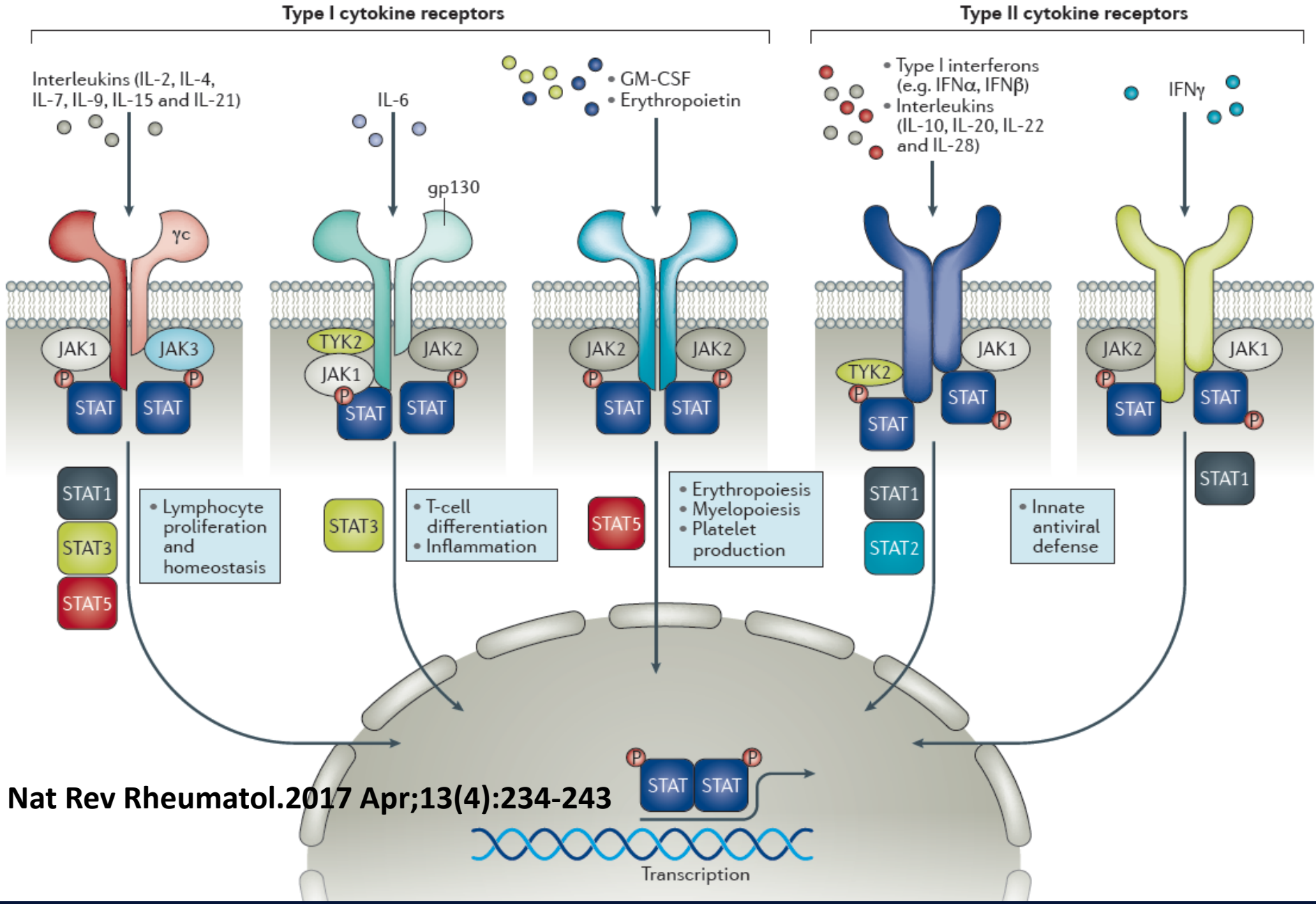
M. Gadina et al. / Journal of Autoimmunity 85 (2017) 20-31

Major cytokines families



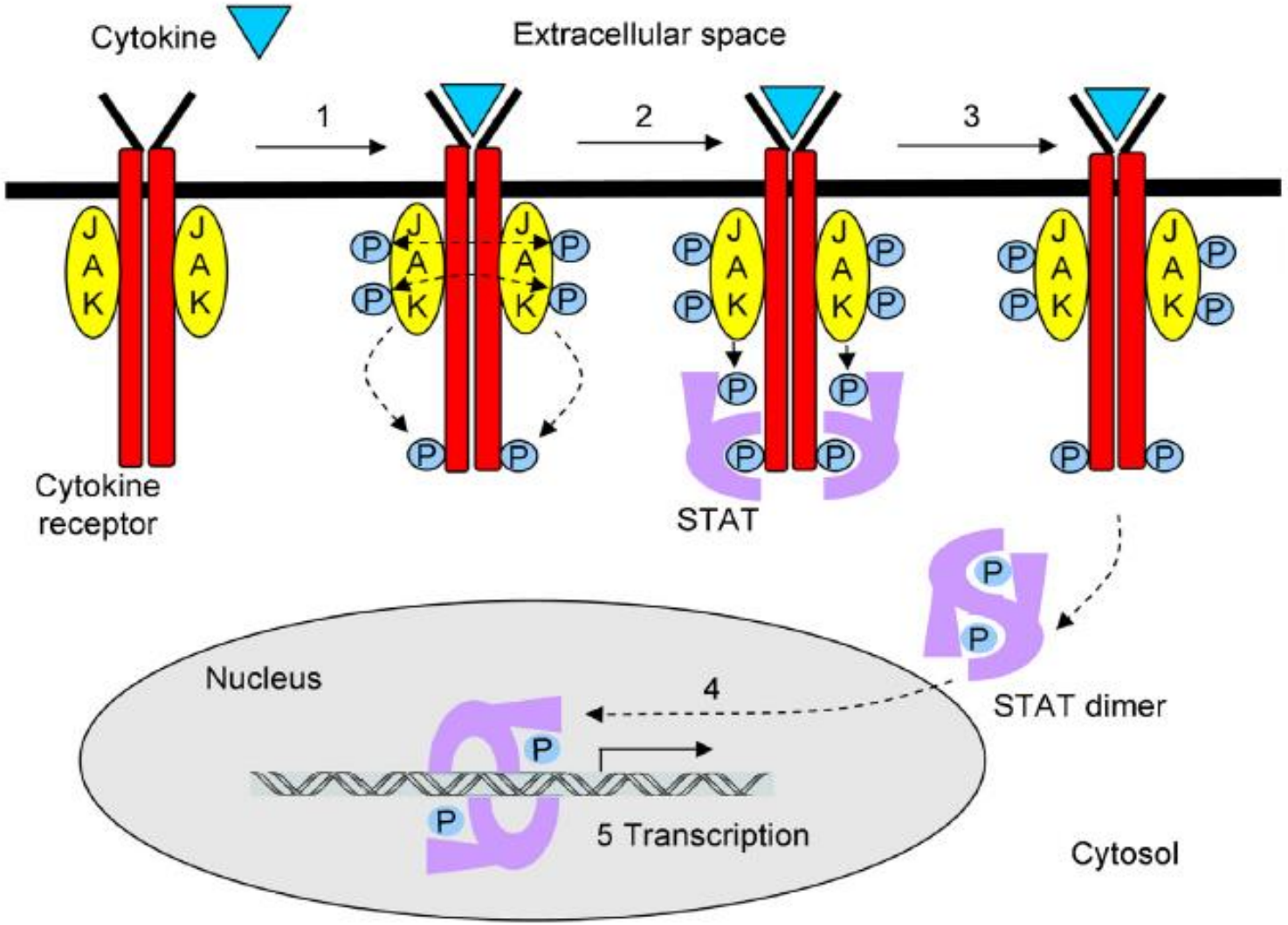
Nat Rev Rheumatol. 2016 January ; 12(1): 25–36.

JAK–STAT signalling in host defense and cellular homeostasis



Nat Rev Rheumatol.2017 Apr;13(4):234-243

The JAK-STAT signal transduction pathway



R. Roskoski Jr. / Pharmacological Research 111 (2016) 784–803

JAKinibs

- Many JAKinibs have been developed over recent years , often subcategorized as first-generation and newer JAKinibs.
- The first-generation JAKinibs do not display high specificity, demonstrating activity against three or even all four of the JAK family members (also termed as pan-JAK inhibitors).
- Selectivity against specific JAKs is a desirable feature of the newer JAKinibs, primarily in terms of mitigating side effects.

Rheumatology 2019;58:i43i54

Janus kinase inhibitors currently used/being studied for RA

Drug	Trade name	Other names	Target
Tofacitinib	Xeljanz	CP-690,550	JAK1-JAK3
Baricitinib	Olumiant	INCB028050 LY3009104	JAK1, JAK2
Upadacitinib		ABT-494	JAK1
Filgotinib		GLPG0634/GS-6034	JAK1
Peficitinib		ASP015K	JAK3, JAK1
Decernotinib		VX-509	JAK3

Immunotherapy 2019

Janus kinase inhibitors currently used/being studied for RA

Drug	Development stage for RA
Tofacitinib	Available in multiple countries
Baricitinib	Available in multiple countries
Upadacitinib	Completed Phase III, approvals pending
Filgotinib	In Phase III
Peficitinib	In Phase III
Decernotinib	Phase IIb completed

Immunotherapy 2019

Tofacitinib in rheumatoid arthritis

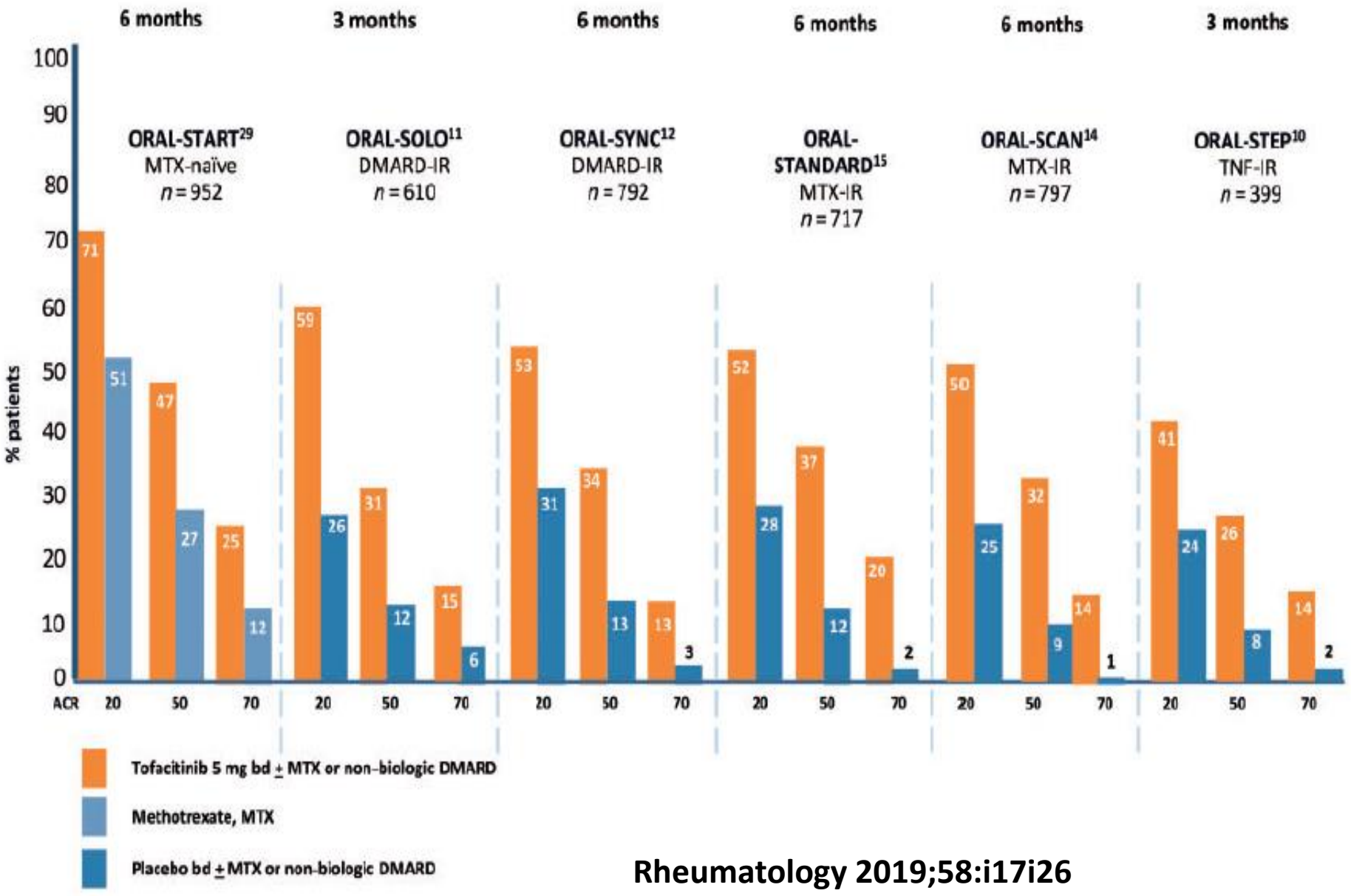
Four Phase II b and seven Phase III RCTs all showed significant efficacy for tofacitinib .

Phase III clinical trials have established that:

- **Tofacitinib in RA is superior to MTX.**
- **Effective in MTX- and csDMARD-refractory, active RA.**
- **Non-inferior in combination with MTX comparing with adalimumab plus MTX .**
- **TOFA is effective in people with active RA who have failed to respond to multiple bDMARDs of different mechanisms of action.**

Rheumatology 2019;58:i17i26

Tofacitinib: ACR responses at the time of primary end point for pivotal phase III clinical trials for moderate to severe RA



Rheumatology 2019;58:i17i26

Pharmacokinetic of tofacitinib

- Tofacitinib is rapidly absorbed .
- It eliminated after administration with reaching peak plasma concentrations within 0.5 to 1 h .
- Its half-life is about 3 h.

The clearance mechanisms for tofacitinib in humans appear to be both nonrenal (hepatic metabolism, 70%) and renal (30%) excretions of the parent drug.

Therapeutics and Clinical Risk Management 2018:14 15–29.

Tofacitinib

- **Tofacitinib is FDA-approved for daily dosing at 5 mg twice daily or with the extended-release formulation at 11 mg once daily.**
- **Tofacitinib is metabolized via cytochrome P-450 (CYP) 3A4 and a lesser degree via CYP2C19.**
- **Strong inhibitors of CYP 3A4 increase the effect of tofacitinib, increasing the toxicity.**
- **Inducers of CYP3A4 decrease the effect of tofacitinib.**

Rheum Dis Clin North Am.2018 Aug;44(3):371-391

Clinically relevant medication interactions with tofacitinib

CYP Subset	Inhibitors	Inducers
CYP3A4	Clarithromycin	Rifampin
	Erythromycin	Phenytoin
	Ketoconazole	Carbamazepine
	Itraconazole	
	Diltiazem	
	Verapamil	
	Nelfinavir	
	Ritonavir	
CYP2C19	Fluoxetine	Rifampicin
	Fluvoxamine	Phenytoin
	Isoniazid	Carbamazepine
	Ritonavir	

Rheum Dis Clin North Am.2018 Aug;44(3):371-391

Pharmacokinetics of Tofacitinib

- **The pharmacokinetics of tofacitinib are not apparently affected by age, body weight, gender, or race.**
- **Tofacitinib has no apparent impact on the pharmacokinetics of concomitant oral contraceptives, or metformin .**
- **If coadministered with ketoconazole or fluconazole, the dosage of tofacitinib should be reduced to 5 mg once daily .**
- **Coadministration with rifampin in healthy volunteers reduced tofacitinib levels .**

Curr Treat Options in Rheum (2015) 1:305–319

Cigarette Smoking Does Not Affect Treatment Response to Tofacitinib in RA

- **Current smoking does not affect the response and drug survival for tofacitinib in RA.**
- **However, it is obvious that smoking is related with high morbidity and mortality in RA, since it increases pulmonary disabilities and the risks of atherosclerosis and malignancies.**
- **Moreover, it is known to increase the risk for RA, and the clinical and radiological progression of RA.**
- **Therefore, the cessation of tobacco use should be still advised to all smoker RA patients.**

2018 ACR/ARHP Annual Meeting

Dosage adjustment of Tofacitinib

- The recommended dosage of tofacitinib is 5 mg administered twice daily, with or without food.
- No dosage adjustment is needed when tofacitinib is coadministered with methotrexate.
- Adjustment of dosage is not needed when given to patients with mild [creatinine clearance (CLCR) 50–80 mL/min] or moderate (CLCR 30–49 mL/min) renal impairment or mild hepatic impairment (Child Pugh A) .

Drugs.2017 Dec;77(18):1987-2001

TOFA Versus Biologic Treatments in Patients With Active RA Who Have Had an IR to TNFi : Results From a NMA

- In the absence of head-to-head comparisons of bDMARDs with tofacitinib in patients with RA and an IR to TNFi, a NMA was performed based on currently available evidence from RCTs.

- **This analysis concluded that oral tofacitinib 5 mg BID has efficacy and rates of AEs comparable with currently available bDMARDs during a 24-week period.**

- However, longer-term follow-up data are required to fully understand the benefit–risk profile of tofacitinib compared with bDMARDs for the treatment of RA.

Clinical Therapeutics/Volume 38, Number 12, 2016

Tofacitinib Therapy for RA: A Direct Comparison Study between Biologic-naïve and Experienced Patients

- We prospectively enrolled and followed 113 patients who had a high or moderate clinical disease activity index (CDAI) (36 biologic-naïve patients and 77 biologic-experienced patients).
- Patients received 5 mg of tofacitinib twice daily.
- Effectiveness and adverse events were examined at month 6 of treatment.
- Although tofacitinib can provide an effective treatment option for intractable RA patients, its impact on outcomes is lower in patients with previous biologic failure.

Intern Med 57: 663-670, 2018

Effect of GC on the Clinical and Radiographic Efficacy of Tofacitinib in Patients with RA

(A Posthoc Analysis of Data from 6 Phase III Studies)

- **MTX plus GC appeared to inhibit radiographic progression to a numerically greater degree than MTX alone.**
- **Concomitant use of GC with tofacitinib did not appear to affect clinical or radiographic efficacy.**

J Rheumatol. 2018 Feb;45(2):177-187.

Baricitinib (Olumiant)

- Baricitinib selectively inhibits JAK1 and JAK 2.
- Baricitinib demonstrated a 100-fold selectivity for JAK-1 and JAK-2 over JAK-3 and inhibited IL-6– and IL-23–stimulated STAT phosphorylation.
- BARI decreased concentrations of MCP-1, IL-17, and IL-22.
- Baricitinib (Olumiant) was approved by the EMA in 2017 for use as 4mg and 2mg tablets once daily for the treatment of moderate to severe active RA .
- On May 31, 2018, FDA approved baricitinib 2 mg once daily for the treatment of adults with moderately to severely active RA who have had an inadequate response to 1 or more TNF antagonist therapies.
- **Baricitinib is not recommended for use in combination with other JAK inhibitors; biologic DMARDs; or potent immunosuppressant drugs, such as azathioprine and cyclosporine.**

Annals of Pharmacotherapy 2019

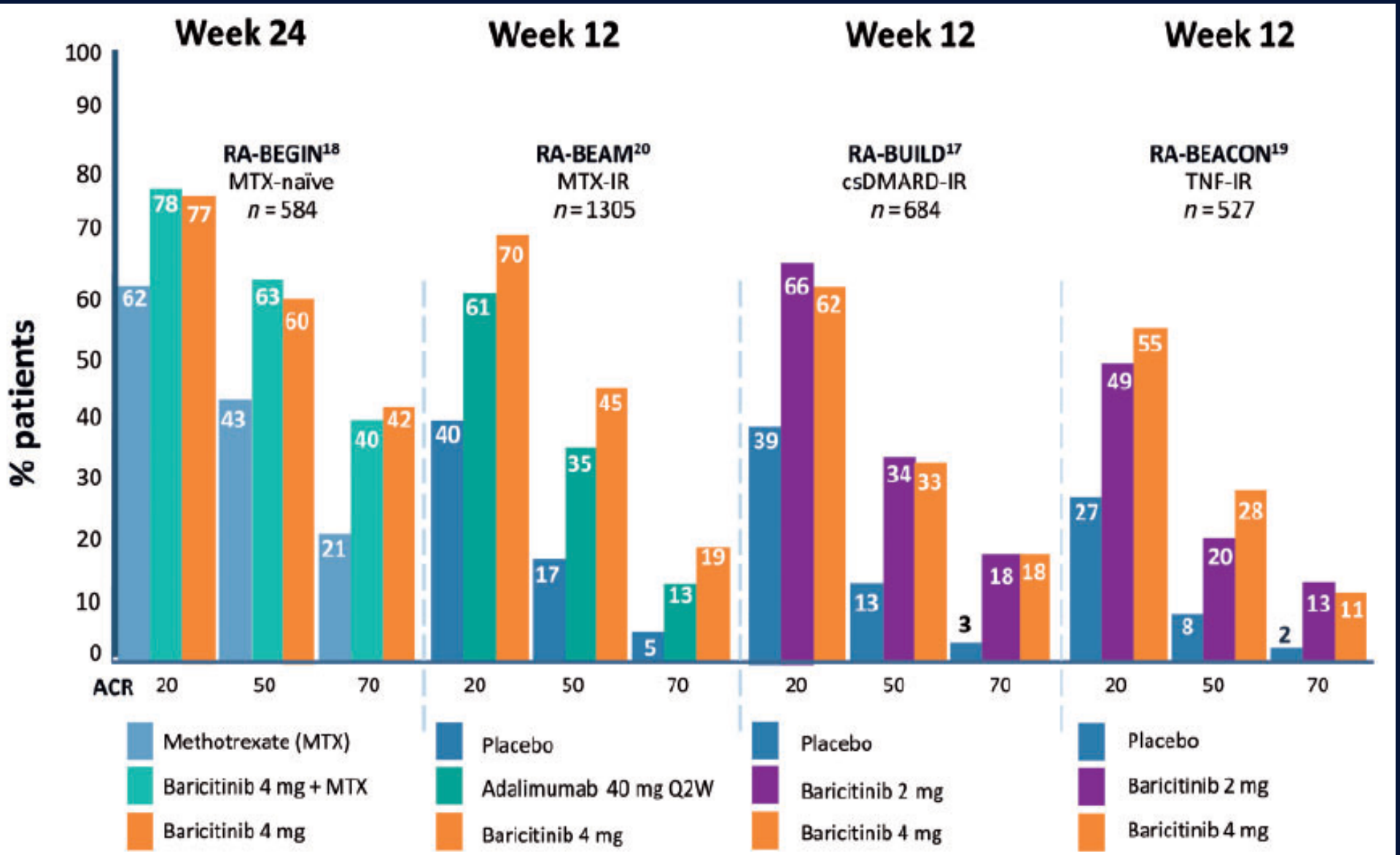
Pharmacokinetics of baricitinib

- Peak plasma concentrations occur in about 1 hour, with a 0.5-hour delay if consumed with fatty meals.
- Metabolism is primarily through CYP3A4, and renal clearance occurs through filtration and active secretion.
- The half-life is approximately 12 hours.
- Approximately 75% of the dose is eliminated in the urine and 20% in the feces.
- Of the eliminated drug, 69% and 15% are excreted unchanged in the urine and feces, respectively.

Annals of Pharmacotherapy 2019

Baricitinib: ACR responses at the time of primary end point for pivotal phase III clinical trials for moderate to severe RA

Rheumatology 2019;58:i17i26



Efficacy and safety of baricitinib for active RA in patients with an IR to cs-DMARDs or b-DMARDs

(A meta-analysis of randomized controlled trials)

The present meta-analysis demonstrated that:

- 4 mg baricitinib once daily was beneficial in patients with active RA with an inadequate response or intolerance to conventional synthetic or biological DMARDs.

- More high-quality RCTs are required to determine the sustained efficacy and the safety of baricitinib..

Exp Ther Med. 2018 Sep;16(3):2449-2459

Safety profile of baricitinib

An integrated analysis on the safety profile in the 3492 patients who received BARI across the trials concluded:

- No differences in rates of death, AEs leading to drug discontinuation, malignancies, major adverse cardiovascular event (MACE), or SI were seen for 4 mg versus placebo or for 4 mg versus 2 mg.

- Notably, higher rates of infections overall were more common in BARI 4 mg compared with placebo, specifically the incidence of herpes zoster.

- Deep vein thrombosis/pulmonary embolism were reported with 4 mg but not placebo.

Immunotherapy 2019

No increased risk of VTE with tofacitinib

- **No increased risk of VTE with tofacitinib Unlike the JAK inhibitor baricitinib, which is associated with an increased risk of VTE at high doses.**

- **No increased risk of VTE has been found in patients with rheumatoid arthritis (RA) using the JAK inhibitor tofacitinib compared with those using TNF inhibitors.**

- **In a cohort of 50,865 patients with RA in the USA, the occurrence of VTE was <1 per 100 patients, and although the number of reported VTEs was numerically higher in patients using tofacitinib than in those using TNF inhibitors, this difference was not statistically significant (P = 0.13–0.70).**

Nat Rev Rheumatol. 2019 Jan 7.

Comparison of the efficacy and safety of TOFA and BARI in patients with active RA

(a network meta-analysis of RCTs)

In a network meta-analysis of 12 RCTs:

- **The authors concluded that the number of serious AEs between tofacitinib and baricitinib did not differ significantly.**

- **The most efficacious 10 mg tofacitinib dosing was not significantly associated with a risk of serious AEs.**

Z Rheumatol.2018 Sep 6

Safety of JAK inhibitors

- Safety profiles of these JAK inhibitors in randomized controlled trials and their long-term extension studies have been demonstrated.
- However, real world evidence remains to be established to bridge the gap between randomized controlled trials and rheumatology clinics.
- Fundamentally, no difference in the screening, prevention, and monitoring of infections between JAK inhibitors and biological DMARDs exists.
- **However, increased risk of herpes zoster is probably common to all JAK inhibitors.**
- No indication of increased risk for malignancy in patients with RA treated with JAK inhibitors has been reported.

Rheumatology 2019;58:i34i42

A systematic review and meta-analysis of infection risk with small molecule JAKi in RA

- This study has not demonstrated a significant increased risk of SI with licensed-dose JAKi compared with placebo.
- The herpes zoster incidence with JAK inhibitors is higher than expected in the RA population.
- Zoster risk is greatest with baricitinib, although differences were not statistically significant.

Rheumatology (Oxford).2019 Apr 14.

Opportunistic infections in tofacitinib

- In short-term therapy, no opportunistic infections were reported.
- Between 6 and 12 months, in tofacitinib 5 mg and 10 mg therapies cases appeared of opportunistic infections such as HZ, TB,cryptococcal pneumonia, candidiasis, CMV, and VZ.
- At 24 months' observation, the rate of herpes zoster infection was 4.5%.

Therapeutics and Clinical Risk Management 2018:14 15–29

Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis

- Using health plan data from 2010 to 2014, patients with RA initiating tofacitinib or biologics with no history of HZ or HSV were identified, as were incident cases of HZ or HSV.

- **The rate of zoster associated with tofacitinib was approximately double that observed in patients using biologics.**

Ann Rheum Dis. 2016 Oct;75(10):1843-7

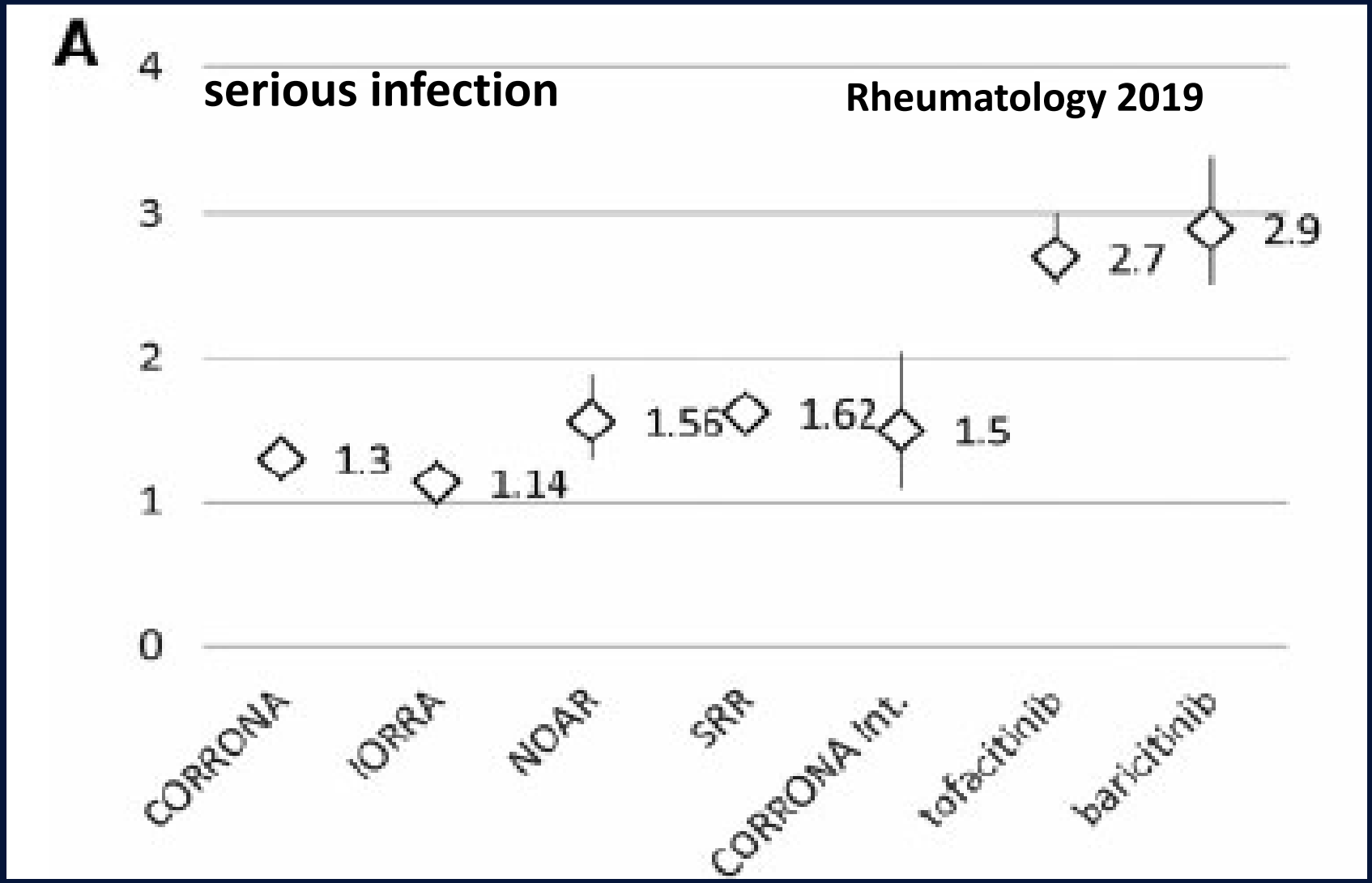
Herpes Zoster in Tofacitinib: Risk is Further Increased with Glucocorticoids but not MTX

- In tofacitinib users, HZ occurred at a rate of approximately 4% per year.
- It was further doubled with GC exposure.
- Concomitant MTX did not confer additional risk.
- Zoster vaccination may decrease risk.

Arthritis Care Res (Hoboken).2018 Oct 8

Incidence rates of serious adverse events in patients with RA

(Incidence rates per 100 patient-years and 95% CIs)



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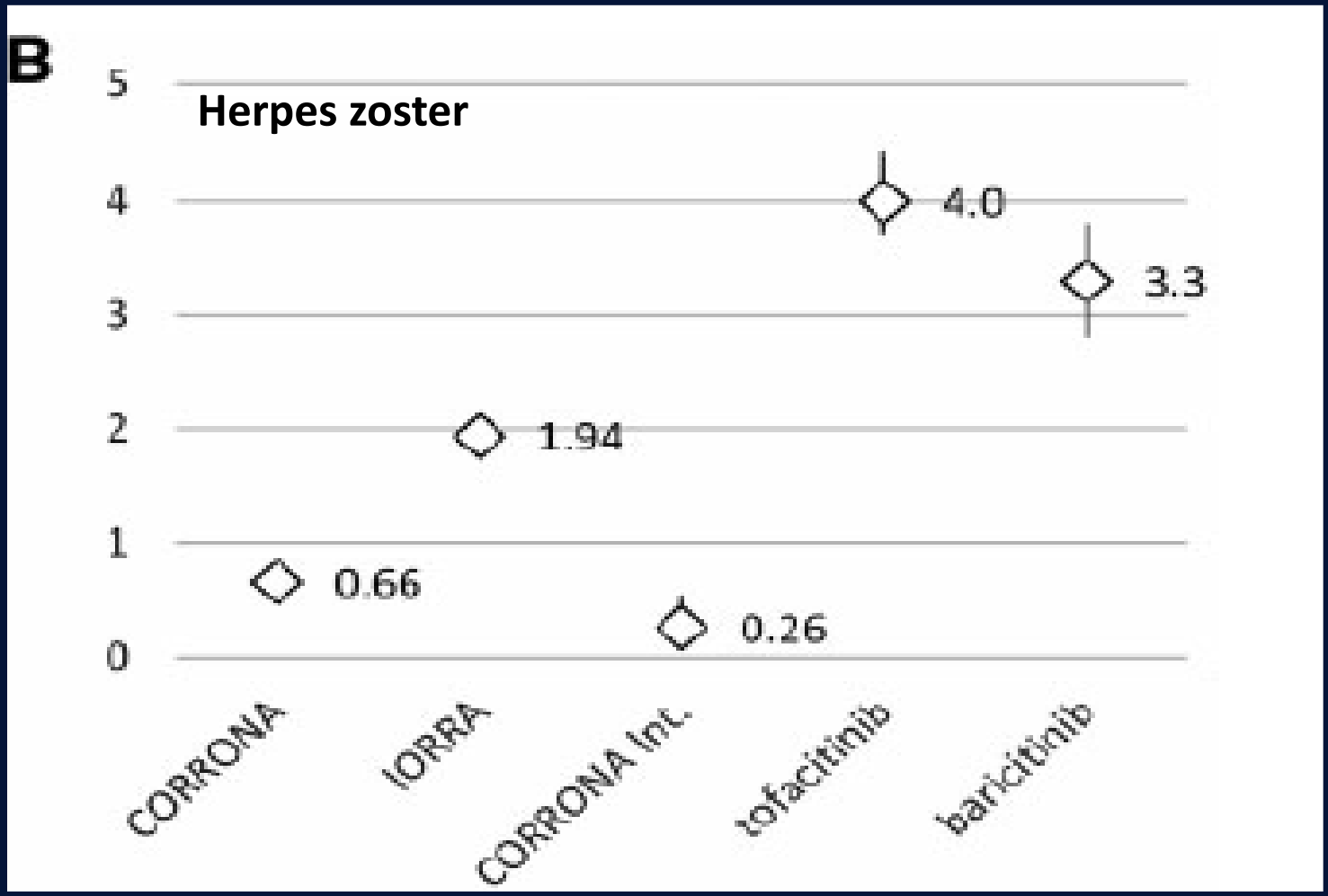

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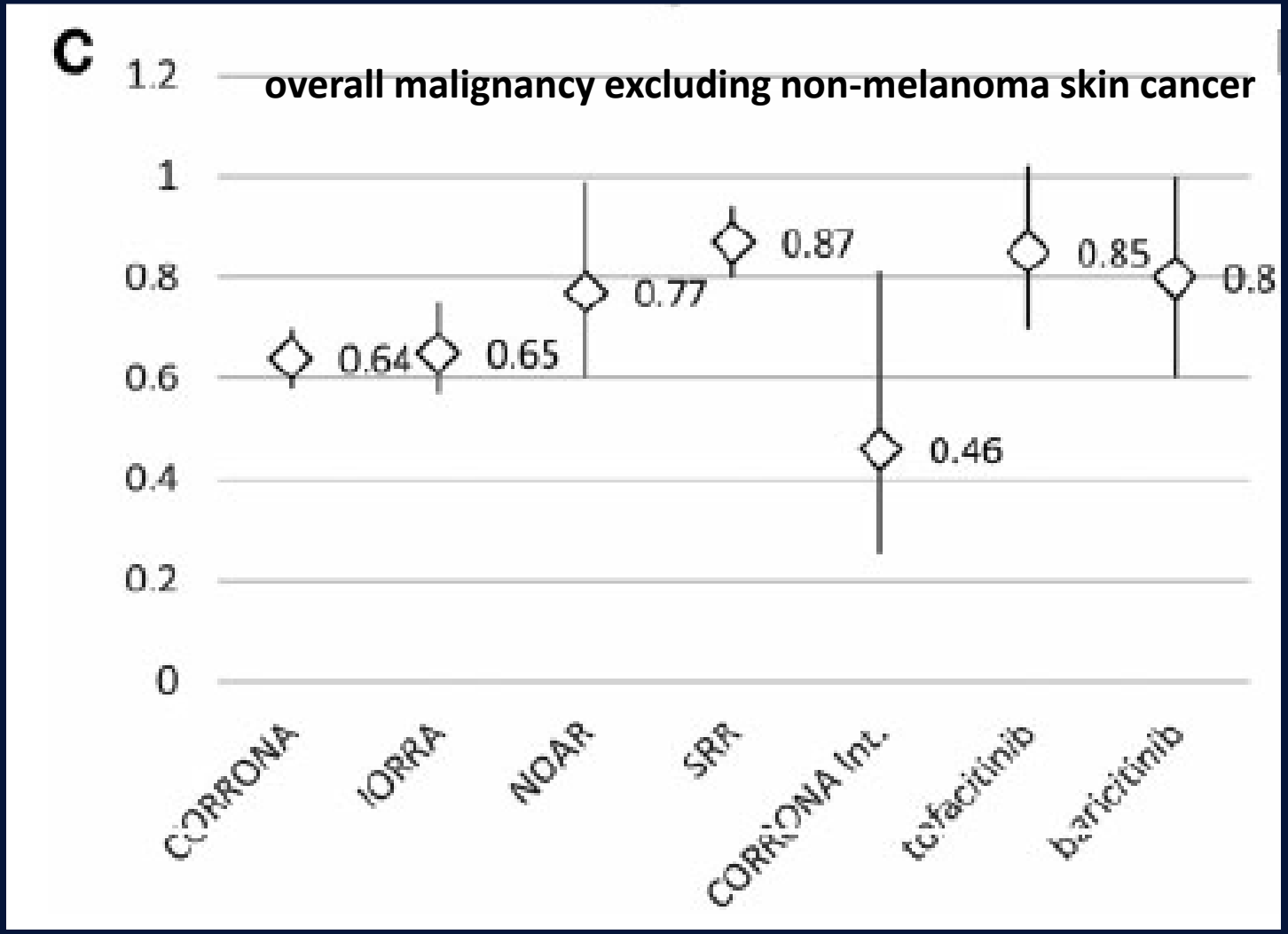

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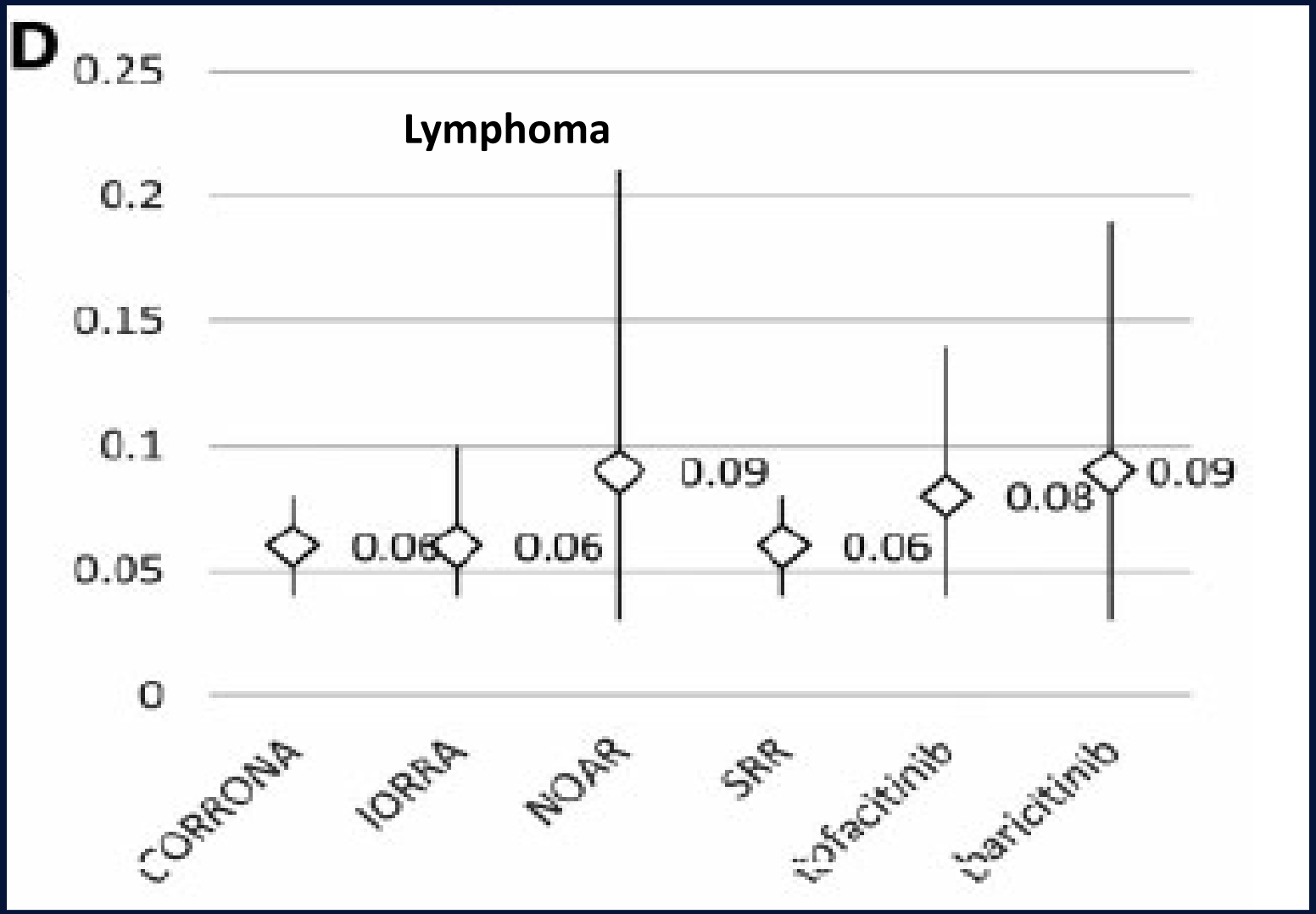


Changes in laboratory parameters

- **In patients treated with tofacitinib, initial decreases in the number of neutrophils, lymphocytes, NK cells and platelets are observed while haemoglobin levels increase.**

- **No new safety risks of laboratory parameters were identified in the long-term extension (LTE) study .**

- **In the case of baricitinib, initial decrease in neutrophil counts, no changes in lymphocyte counts, initial peak at 2 weeks and returning to baseline in platelet counts, initial decrease and returning to baseline in haemoglobin levels.**

- **The differential changes in haemoglobin levels between the two drugs are explained by their selectivity for each JAK, as erythropoietin stimulates erythrocyte production via the JAK2 signaling pathway.**

Rheumatology 2019;58:i34i42

Changes in laboratory parameters

- Elevation of liver transaminase, CK, HDL, LDL and creatinine levels are commonly observed in patients treated with tofacitinib and baricitinib.

- Similarities and differences of these changes in laboratory parameters are quite interesting from a point of differential biological roles of each JAK.

Rheumatology 2019;58:i34i42

Pregnancy and breastfeeding

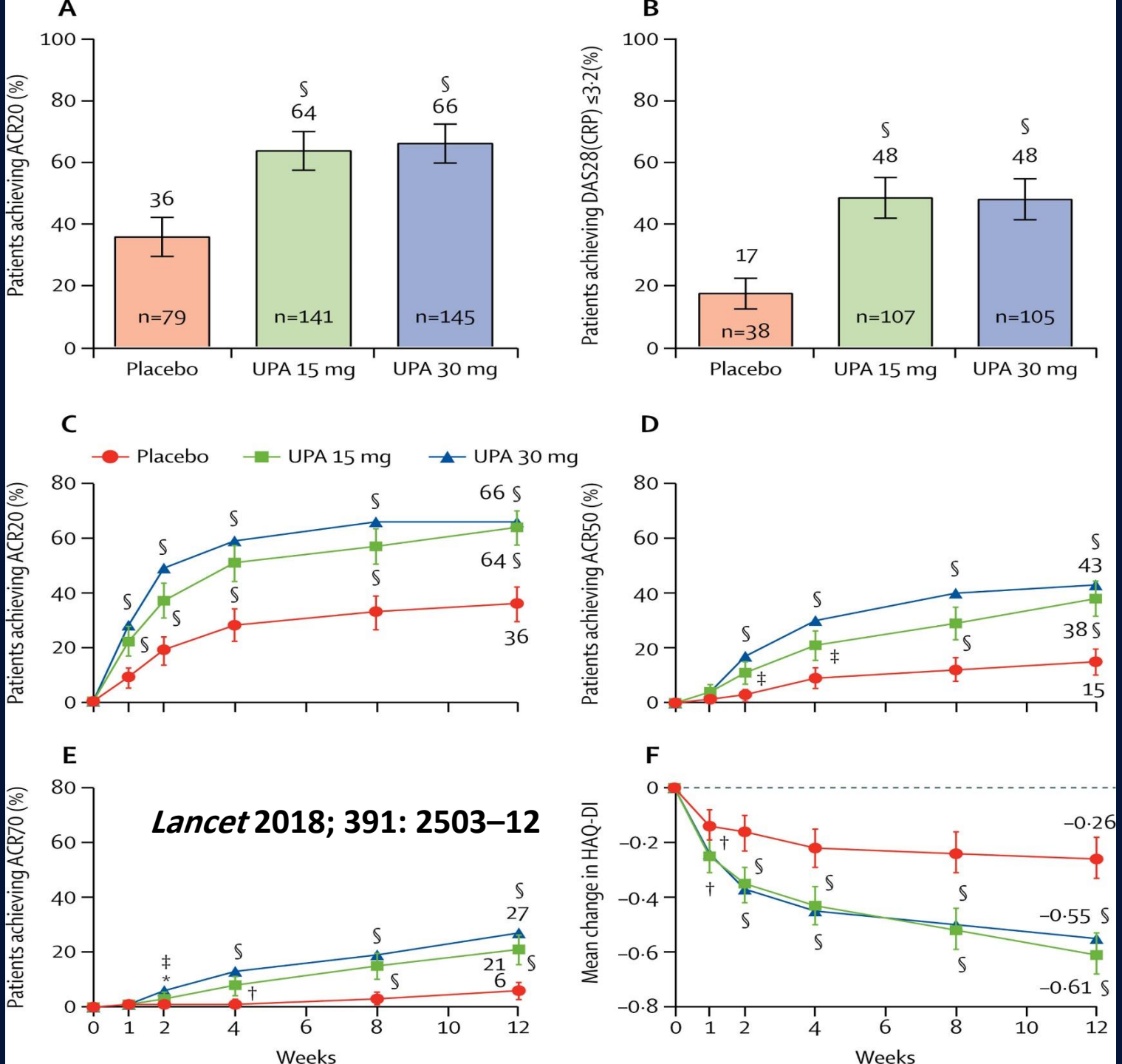
- JAK inhibitors are contraindicated during pregnancy.
- Women of child-bearing age should use effective contraception during and at least 1 week after treatment.
- JAK inhibitors poses risks to newborns/ infants and thus should not be used during breastfeeding.

Rheumatology 2019;58:i34i42

Safety and efficacy of upadacitinib in patients with RA and IR to csDMARDS (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial

- In this csDMARD-IR population with moderate to- severe RA, once-daily doses of upadacitinib (15 mg or 30 mg), when administered in combination with csDMARDs, showed improvements in clinical signs and symptoms of RA.
- In keeping with the goals of the T2T strategy, a significantly larger proportion of patients in the upadacitinib groups achieved a state of low disease activity or clinical remission, compared with placebo.
- Overall, upadacitinib showed a favourable benefit-to risk profile.
- However, the proportions of participants with infections or premature discontinuation due to adverse events were higher in the upadacitinib groups than in the placebo group.

Lancet 2018; 391: 2503–12


A
Patients achieving ACR20 (%)
100
80
60
40
20
0
36
64 §
66 §
n=79
n=141
n=145
Placebo
UPA 15 mg
UPA 30 mg
B
Patients achieving DAS28(CRP) ≤3·2(%)
17
48 §
48 §
n=38
n=107
n=105
Placebo
UPA 15 mg
UPA 30 mg
C
Placebo
UPA 15 mg
UPA 30 mg
Patients achieving ACR20 (%)
66 §
64 §
36
D
Patients achieving ACR50 (%)
43 §
38 §
15
E
Patients achieving ACR70 (%)
27 §
21 §
6
0 1 2 4 6 8 10 12
Weeks
F
Mean change in HAQ-DI
0
−0·2
−0·4
−0·6
−0·8
−0·26
−0·55 §
−0·61 §
0 1 2 4 6 8 10 12
Weeks
Lancet 2018; 391: 2503–12

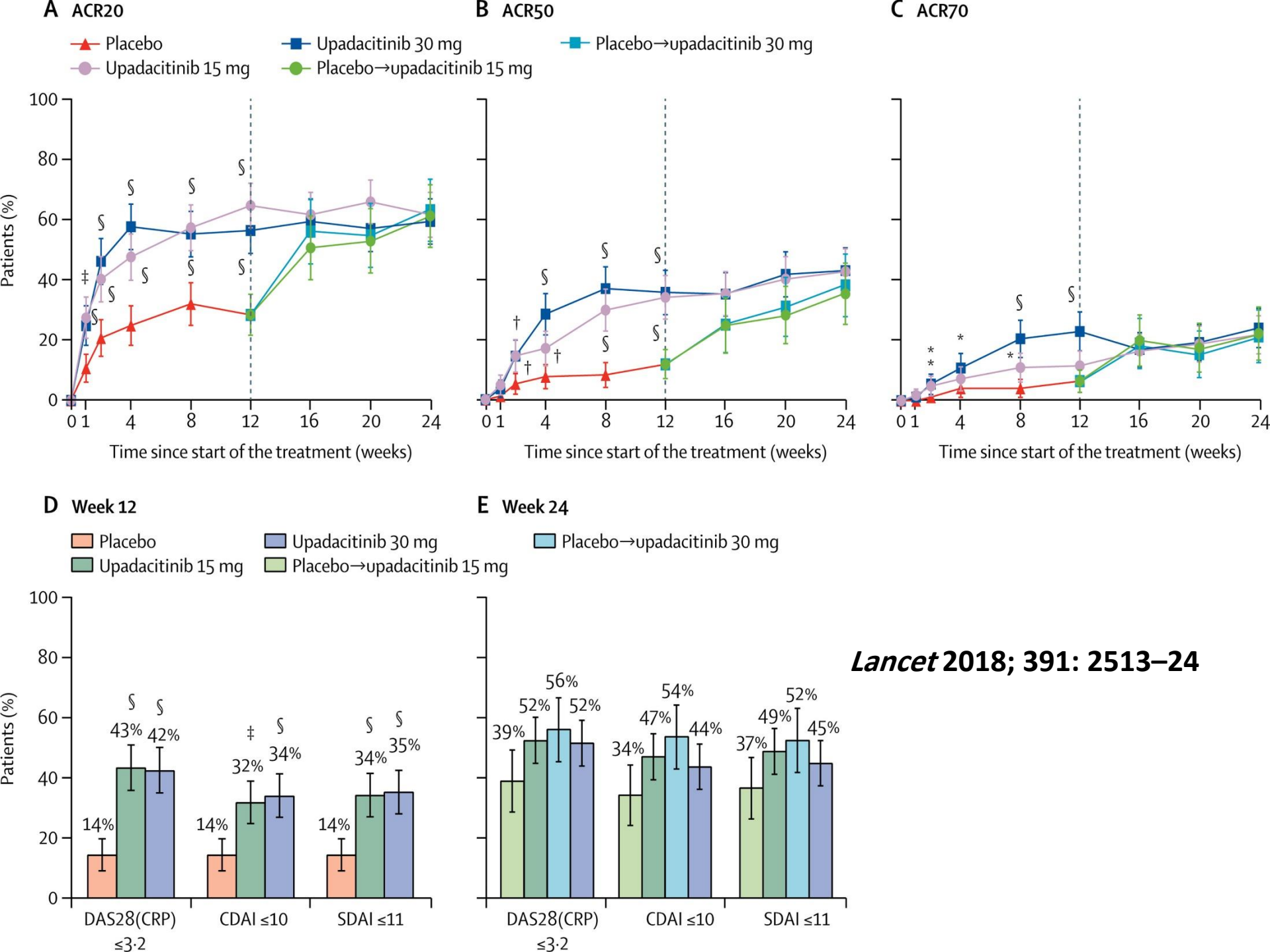
Safety and efficacy of upadacitinib in patients with active RA refractory to bDMARDs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial

- Once-daily upadacitinib administered using the extended-release formulation was effective in treating RA symptoms in patients with moderate-to-severe active disease with inadequate response to bDMARDs.

- In this population, both doses of upadacitinib had similar efficacy, with higher frequency of some safety events in the higher dose group.

- Integrated data from the complete phase 3 programme will allow a more comprehensive analysis of the performance and benefit–risk profile of the 15 mg and 30 mg doses of upadacitinib in different RA populations.

Lancet 2018; 391: 2513–24



***Lancet* 2018; 391: 2513–24**

Upadacitinib

- Phase IIb and two of the Phase III trials that were published at the time were included in this review, which looked at patients with inadequate response to both csDMARDS and previous biologics.

- Rapid, statistically significant improvement in ACR20 (as early as week 1), ACR50, ACR70 and DAS28CRP scores were seen in both 15 and 30 mg extended release daily dosing groups.

- Four cases of pulmonary embolism were reported in SELECT-BEYOND, all with known additional risk factors.

Immunotherapy 2019

Filgotinib

- Phase IIb trials completed showed dose-dependent results, with 100 mg daily, 200 mg daily and 100 mg bid having the most significant results.
- When studied as monotherapy in DARWIN 2, significantly higher ACR20/50 was seen at all doses at 12 weeks and were maintained at 24 weeks.
- A good tolerability profile and encouraging safety data were observed across trials, although further Phase III trials are needed.

Immunotherapy 2019

Peficitinib (JAK1-3, more selective for JAK3)

- Three Phase IIb trials were included, all of which used five doses ranging from 25 to 150 mg once daily dosing.
- PEFI as monotherapy was significantly efficacious in methotrexate (MTX)-IR patients at doses 100–150 mg OD at 12 weeks in terms of ACR20, 50 and DAS28 scores.
- When used in csDMARD- and MTX-IR, higher ACR percentages coincided with PEFI in a dose-dependent manner, although statistical significance was not consistently reached.

Immunotherapy 2019

Decernotinib (JAK3)

- Phase II/IIb trials testing its efficacy as monotherapy, in combination with methotrexate, and with other csDMARDs were reviewed.

- DECER monotherapy was also found to be efficacious with significant ACR 20/50/70 and DAS28 scores at doses 50–150 mg BID compared with placebo in patients with unsuccessful disease control on >1 csDMARD therapy.

- When studied in combination with MTX, all doses were significantly efficacious.

Immunotherapy 2019

Safety of other JAKinibs

- Data for peficitinib are very limited, but it seems that the data are largely similar to those for tofacitinib.
- Interestingly, the side-effect profile for decernotinib appears comparable with those observed for other JAKinibs.
- Decernotinib being a selective JAK3 inhibitor, which might therefore be predicted to have fewer off-target side effects.

Rheumatology 2019;58:i43i54

Safety of other JAKinibs

- Safety data for upadacitinib appear similar to those for tofacitinib, although haemoglobin was found to be decreased with high doses.
- The early data suggest that filgotinib appears to have a slightly different safety profile in relation to the laboratory abnormalities.
- Filgotinib had no increase in liver function tests or decrease in haemoglobin levels or number of lymphocytes or NK cells was observed in the trials conducted for RA patients.
- Additionally, despite the fact that both LDL and HDL were increased during treatment with filgotinib, the LDL:HDL ratio fell .
- Further studies are needed to confirm these findings.

Rheumatology 2019;58:i43i54

Are Janus Kinase Inhibitors Superior over Classic Biologic Agents in RA Patients?

There are some advantages over classical biologics that Jakinibs potentially may have.

- The first one is the blockade of a wide spectrum of cytokines that may cover many existing and potential inflammatory pathways.
- Secondly Jakinibs are small nonprotein substances lacking potential to generate antidrug response and therapeutic effect may be more stable.
- It is also worth underlining that treatment with Jakinibs is not associated with allergic reaction, making this treatment safer compared with typical biologics.
- Finally Jakinibs as small chemical compounds are easy to synthesize, which indicates that in the future the price for treatment may be substantially lower than biologics.

BioMed Research International Volume 2018

Conclusion

- Similar efficacy and safety are seen overall within the class for most of the JAK inhibitors.
- Proven efficacy across various RA patient groups including MTX-naive, MTX -IR, biologic-naive and anti-TNF IR patients.
- Benefit has been found in use as monotherapy and also in combination with csDMARD(s), especially MTX.
- Adverse events include gastrointestinal upset, infections, cytopenias, elevated cholesterol and transaminitis.

Immunotherapy 2019

Conclusion

- It is noteworthy that the efficacy of tofacitinib was comparable to that of adalimumab.
- Efficacy of baricitinib was superior to adalimumab at week 12 for the ACR20 response.
- No signs of increased risk for malignancy and opportunistic infection have been reported except for herpes zoster in patients with RA treated with JAK inhibitors.
- post-marketing surveys is needed to determine their risk–benefit ratio and selection of the most appropriate patients for such therapy, which would help us understand the positioning of these drugs.

Rheumatology, Volume 58, Issue Supplement_1, February 2019


Thank you for your attention