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VIEWPOINT

RMD commentary, JAK kinase inhibitors: a preferred alternative to TNF inhibitors?

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The JAK kinase inhibitors (JAKis) represent an exciting class of therapies in rheumatology, and they are effective across a wide variety of immune-mediated diseases, in haematology (myelofibrosis, polycythemia vera and acute graft-versus-host disease), dermatology and gastroenterology (ulcerative colitis), interferonopathies, sarcoidosis and recently COVID-19 (baricitinib). Their use in rheumatoid arthritis (RA) has convincingly demonstrated an early onset of benefit and anecdotally, better adherence. In a combined analyses of the phase III RA randomised controlled trials (RCTs) and long-term extensions (LTE) with tofacitinib, approximately 78% remained on therapy at 2 years and 51% at 5 years.[1] Orally administered, they are convenient and easy to use, without concerns regarding immunogenicity. And they have the shortest half-lives of all of our therapeutic classes.

It is interesting that the approved JAKis demonstrate different selectivity profiles in vitro, modulating distinct cytokine signalling pathways to different degrees and duration. Yet, they do not potently or continuously inhibit any individual cytokine pathway over 24 hours.[2] It is unclear which cell types and which signalling pathways are affected at any given time or for how long. Despite different selectivities, clinical responses are similar, especially across agents in RA, psoriatic arthritis (PsA) and spondyloarthritis (SpA). Four are EMA approved in RA (tofacitinib, baricitinib, upadacitinib and filgotinib), 3 by FDA (except filgotonib); tofacitinib in polyarticular JIA; tofacitinib in PsA with upadacitinib expected, as are tofacitinib and upadacitinib expected in SpA. Indications of efficacy based on open-label series or early trials are evident in systemic lupus erythematosus, dermatomyositis, systemic sclerosis, Sjogren's syndrome and non-infectious uveitis.

Perhaps even more compelling are the uniformly strong data available with all the JAKis studied in methotrexate incomplete responder (MTX-IR) patients with RA, resulting in clinically meaningful improvements (≥minimum clinically important differences (MCID)) across all patient-reported outcomes (PROs): patient global assessment of disease activity (PtGA), Pain, HAQ, and health-related quality of life (HRQOL) by SF-36 physical component summary and domain and FACIT-F scores, by 54%–74% of patients, with 11%–51% reporting scores≥normative values at 3 months.[3–5] Importantly, the number needed to treat (NNT) based on these results is generally ≤10, considered an economically as well as clinically important result, and less than 10 with adalimumab+MTX.[6–8] Similarly, in the JAKis RCTs in biologic DMARD incomplete responders (bDMARD-IR) patients with RA, NNTs again are generally ≤10 for the major PROs and quite similar to those for ACR 20% and 50% responses in ORAL-STEP, RA-BEACON and SELECT-BEYOND trials.[9–12]

A similar argument may be made regarding the first therapeutic agent after initial csDMARD failure. Here, the choice appears more obvious, but a bDMARD was preferred by 69% versus 31% of attendees after 'The Great Debate' at the ACR 2020 Convergence. Was this due to familiarity with use of TNF inhibitors (TNFis) over the past 22 years compared with a maximum of 7 years' experience with tofacitinib in the USA? RCT data in RA have shown more rapid onset of benefit with JAKis than TNFis with benefits in pain and PtGA reported at 2.5 days and maximal efficacy at 3 months rather than 4–6 months.[3] Superiority of both baricitinib 4 mg+MTX and upadacitinib 15 mg+MTX versus adalimumab+MTX has been demonstrated in MTX-IR patients with RA[13 14], as well as non-inferiority

Table 1 Remission rates in csDMARD-IR patients: at 3 and 6 months

Tofacitinib 5 mg and 10 mg[52]	DAS28(CRP): 18–22%	DAS28(CRP): 25–40%
	SDAI: 4–7%, CDAI: 5–6%	SDAI: 7–15%, CDAI: 7–15%
	Boolean: 2–7%	Boolean: 6–12%
Baricitinib 2 mg and 4 mg[53 54]	DAS28(CRP): 19–26%	DAS28(CRP): 31–35%
	SDAI: 8–9%, CDAI: 8–10%	SDAI: 15–17%, CDAI: 15–16%
	Boolean: 7%	Boolean: 12–13%
Upadacitinib 15 mg[55]	DAS28(CRP): 28–31%	DAS28(CRP): 39–41%
	SDAI: 12–14%, CDAI: 13%	SDAI: 15–20%, CDAI: 13–21%
	Boolean: 7–10%	Boolean: 9–19%
Filgotinib 100 mg and 200 mg[56 57]	DAS28(CRP): 24%	DAS28(CRP): 35–48%
	SDAI: 9–13%, CDAI: 11–12%	SDAI: 18–23%, CDAI: 19–21%
	Boolean: 7–10%	Boolean: 14–19%

CDAI, Clinical Disease Activity Index; DAS28(CRP), Disease Activity Score28(CRP); SDAI, Simplified Disease Activity Index.

with tofacitinib 5 mg+MTX and filgotinib 100/200 mg+MTX in this population.[15 16] Remission rates at 3 and 6 months from these trials certainly support the choice of a JAKi (table 1).

RCTs in csDMARD-naive patients with RA have demonstrated the superiority of JAKi monotherapy (tofacitinib, baricitinib, upadacitinib and filgotinib) to MTX, by disease activity measures as well as PROs with even larger improvements in this less treatment experienced population.[17–20] In ORAL-START and SELECT-EARLY, patients reporting improvements ≥MCID in PtGA, Pain, HAQ, HRQOL and FACIT-F scores ranged from 47% to 88%, with NNTs generally ≤10 and 23%–58% reporting scores≥normative values at 3 or 6 months.[21 22]

The safety profiles of the approved JAKs (ruxolitinib, tofacitinib, baricitinib, upadacitinib, filgotinib) have been well characterised based on RCTs in their respective approved indications as well as ongoing work (table 2). Their profile is similar to the TNFis with a few notable exceptions: higher incidence of herpes zoster infections; despite elevations of HDL and LDL, a 'less atherogenic profile', due to increased cholesterol efflux capacity associated with decreases in CRP[23–25]; GI perforations, more common than TNFis but less common than with tocilizumab, and the newly emerging profile of venous thromboembolic events (VTEs): deep vein thromboses (DVTs) and pulmonary embolisms (PEs). Laboratory changes require monitoring but typically are not clinically relevant. They include transient changes in lymphocytes and platelets with baricitinib, NK cells and neutropenia (tofacitinib and baricitinib), haemoglobin decreases (baricitinib and upadacitinib) and LFT elevations.[26–28] CPK increases reflect reversal of inflammation-induced inhibition of myoblast differentiation[29] and serum creatinine increases are generally idiosyncratic and reversible with discontinuation of therapy.

Table 2 Comparison of JAK/STAT inhibitor safety profiles: incidence per 100 patient years (PYs) exposure in RA

	Tofacitinib[58] JAK 3/1/2, phases II and III 5 mg and 10 mg, n=7061	**Baricitinib[59] JAK 1/2, phase III 2 mg and 4 mg, n=3770**	**Upadacitinib[60 61] JAK 1/2, phase III 15 mg, n=2629**	**Filgotinib[62 63] JAK 1, phases I–III 100 mg and 200 mg, n=3691**
PYs/median follow-up	22 874/3.1 years	13 148/4.2 years	4566/1.7 years	6081/1.6 years
SIEs	2.5	2.7	3.2	1.8
OIs	0.4	0.5	0.7	0.1
Tb	0.2	0.2	2.3	<0.1
Herpes zoster: non-serious and serious	3.6	3.0	3.4	1.6
Malignancy (excluding NMSC)	0.8	0.9	0.9	0.5
Lymphoma	0.05	0.06	NR	NR
NMSC	0.6	0.3	0.3	0.2
MACE	0.4	0.5	0.5	0.6
DVT/PE	0.3	0.5	0.5	0.15
GI perforations	0.1	0.04	0.05	<0.1

DVT/PE, deep vein thrombosis/pulmonary embolism; MACE, major cardiovascular event; NMSC, non-melanoma skin cancers; NR, not reported; OIs, opportunistic infections; RA, rheumatoid arthritis; SIEs, serious infections; Tb, Tuberculosis.

At the time of tofacitinib approval in the USA, a comparison of serious infections (SIEs) to the bDMARDs in RCTs and LTE in RA indicated a similar or lower incidence with the JAKi: 2.93/100 patient years (PYs) exposure compared with the TNFis, combined: 4.90; 5.45 with tocilizumab; 3.72 with rituximab and similar to abatacept: 3.04/100 PYs.[30] This is similar to the incidence of SIEs of 3.0/100 PYs in the baricitinib RCTs and LTE.[31] In a recently published multidatabase cohort study in the USA, including Medicare, Optum and IBM MarketScan, the adjusted HRs for hospital admissions due to SIEs in patients with RA with tofacitinib was compared with seven bDMARDs and was generally higher than etanercept, abatacept and golimumab, similar to adalimumab and certolizumab and lower than infliximab.[32]

In this same study, the incidence of herpes zoster infections was uniformly higher with tofacitinib than the comparator bDMARDs. In the German RABBIT registry of 12 470 patients with RA enrolled between 2007 and 2019 with ≥1 follow-up of the incidence/100 PYs was 2.49 with JAKis, statistically greater than with csDMARDs: 0.58/100 PYs.[33] Across all RCTs in RA, the incidence of herpes zoster increased with increasing age, higher dose groups and in Asian populations, especially Japan and Korea. Recently published GWAS data identified population-specific genetic links associated with increased herpes zoster risk.[34] The incidence of herpes zoster infections with tofacitinib was 3.6/100 PYs and increased with all doses of glucocorticoids from >0 mg to ≥7.5 mg four times a day.[35 36] The incidence with baricitinib was 3.3/100 PYs[29] and with upadacitinib was 3.4/100 PYs,[37] without association with glucocorticoid use but increased in those with prior zoster infections. The incidence with filgotinib is lower: 1.6/100 PYs. Although the FINCH-2 RCT was conducted in Japan, the filgotinib clinical development programme in RA was smaller and more limited in overall exposure than the other approved JAKis (table 2). The majority of herpes zoster infections involved single dermatomes and were not disseminated or considered serious adverse events. A preliminary report of vaccination with the recombinant adjuvanted Shingrix vaccine from Skane Hospital, Lund, Sweden, indicated it to be well tolerated in those receiving JAKis with positive antibody responses in 30/40 (75%) compared with 100% (n=20) controls.[38] These data are promising, especially as the live attenuated Zostavax is no longer available in the USA and there remains concern for use of such live vaccines in patients receiving immunosuppressive medications.

An increased incidence of VTEs with JAKis was first noted in the placebo-controlled portion of the baricitinib phase III RCTs in RA in patients receiving 4 mg: 1.3/100 PYs yet none with the 2 mg dose.[39] Including the extension studies, the overall incidence was 0.3/100 PYs. The incidence of DVTs/PEs is known to be increased in RA, estimated in the range of 0.3–0.8/100 PYs in patients receiving DMARDs and bDMARDs.[40–42] A recent study in the Swedish register linked this increase with disease activity: approximately twice the incidence in patients with high disease activity than those in remission.[43] A signal for VTEs emerged in the phase II upadacitinib RA RCTs, but in phase III, the incidence was similar to those in MTX and adalimumab treatment groups. There was not an increased incidence of VTEs evident in the large RA clinical development programme with tofacitinib: incidence: 0.3/100 PYs with both doses (table 2). Adjusted Kaplan-Meier plots did not reveal a significant difference between tofacitinib (5.6% and 5.8%) and the TNFis in 34 074 and 17 086 patients with RA, respectively, in the Truven and Medicare databases in the USA between 2013 and 2018.[44] A signal emerged with the 10 mg dose in the post approval cardiovascular (CV) safety study comparing tofacitinib to either adalimumab or etanercept. This led to FDA and EMA warnings regarding the use of the 10mg dose, and boxed warnings were added to the labels of the three approved JAKis in the USA in July and August 2019.[45 46] A recent analyses of patients with underlying CV risks receiving the 10mg tofacitinib dose in the RA RCTs revealed an incidence ratio for PEs of 0.24 (0.13–0.41) and for those in the CV safety trial of 0.54 (0.32–0.87).[47] The majority of patients reported with VTEs have had a prior event, and the use of glucocorticoids, NSAIDs and COX-2s are known to increase the risk for VTEs and arterial thromboembolic events (ATEs). However, no plausible mechanistic explanation has been identified for VTEs or ATEs as a 'class effect' of JAKi administration. Nonetheless, caution and anticoagulation should be considered with their use.

Part of the question is why the JAKis have been so rapidly and enthusiastically adopted in rheumatology, whereas they have been met with more caution, even concern, in dermatology despite dramatic results in alopecia areata, vitiligo and atopic dermatitis, similarly in psoriasis but without regulatory approval. Certainly, VTEs are a concern but such events have rarely, if ever, been reported in dermatologic conditions. Perhaps, part of the difference is that rheumatologists are familiar with and accustomed to treating systemic diseases, as well as the multiple comorbidities that occur frequently in our patients.

Another concern is pregnancy. Long-term experience and specific studies in pregnant and lactating women have given us confidence in the use of TNFis. Much more limited data are available with the JAKis, specifically tofacitinib. Two series have been published based on the databases for the RA and psoriasis trials and another in ulcerative colitis.[48 49] In the first series of 47 pregnancies, there was one congenital pulmonary valve stenosis, seven spontaneous abortions and eight medical terminations; healthy newborns were reported in 25 pregnancies. Of 44 paternal exposures, 5 spontaneous abortions and 23 healthy newborns were reported. In ulcerative colitis of 11 pregnancies and 14 paternal exposures, no congenital malformations were reported, 2 spontaneous abortions, 2 medical terminations and 15 healthy newborns. In contrast, preclinical reproductive toxicology studies in

rats and dogs with the 200 mg dose of filgotinib were associated with decreased sperm counts and motility. Specific trials in men with inflammatory bowel disease and RA to demonstrate reversibility of any observed sperm abnormalities have not yet been completed. However, following a complete response letter from FDA, Gilead has withdrawn its new drug application in the USA. This was not an apparent concern for either EMA or Japanese regulators where filgotinib was approved in September 2020.

Regulatory requirements prohibit and no current therapeutic guidelines recommend use of the JAKis in the csDMARD-naive population, despite their strong efficacy and PRO data. This may in part be due to cost restrictions in both the USA and EU. Despite these agents being far less expensive to manufacture than bDMARDs, even biosimilars, access to their use is often determined by insurance and other requirements in the USA, and limited in the EU by individual governmental restrictions and tendering systems. Given their tolerability, convenience and short pharmacokinetic and pharmacodynamic half-lives, shorter than any other therapeutic agents in rheumatology, JAKis would appear to be an obvious choice.

The question remains when will rheumatologists be ready to change their longstanding therapeutic practice? Is it because we lack long-term safety data from registries, with exception of tofacitinib which was introduced in the USA in 2012? And will long-term efficacy and improved adherence counteract the increased costs or will we be forced to wait until the first agent of this class becomes generic?

In conclusion, the JAK Inhibitor class is an exciting development for rheumatology and a broad variety of autoimmune diseases. Based on phase III RCTs in RA, responses are better in earlier disease duration, less treatment experienced patients, so they should be used early. They have well-established benefits in RA, with head-to-head comparisons against adalimumab indicating equivalent or superior efficacy and all are superior to MTX in MTX-naive patients. They are convenient, easy to travel with, without requiring injections. With half-lives that range in hours, adverse events can often resolve over a short time frame; even their pharmacodynamic effects have shorter duration than TNFis.[50] Risks with JAKi use have been identified: there is a need for recombinant attenuated antivaricella zoster vaccination and careful history and attention to risk factors for VTEs and ATEs, surveillance for SIEs and malignancies. Despite differing cytokine signalling selectivities, they share similar clinical efficacy and safety profiles. There appears to be ample evidence for JAKis to be considered as substantive alternatives to TNFis.

ADDENDUM TO rmdopen-2021–001565.R1

Since this manuscript was revised and accepted for publication, a recent press release summarised the results of the tofacitinib CV safety study, ORAL Surveillance (A3921133; NCT02092467) in patients with RA and ≥2 CV risk factors.[51] The primary endpoint of non-inferiority of tofacitinib to TNFis for incidence of major CV events (MACEs) and malignancies was not met, with an increased HR of 1.33 for MACEs and 1.48 for malignancies, excluding non-melanoma skin cancers, with both 5 mg and 10 mg doses. These data raise concerns, as a similar increased incidence of DVTs/PEs with tofacitinib has emerged in this same population as well as those with underlying CV risk factors in the RCTs. Possible explanations may include that this specific population shares similar risk factors for the CV events as well as malignancies. They could also include longer disease duration and potentially longer periods of time with inadequate disease control. But the fact that we do not see this to be true with TNFis is troubling. A plausible mechanistic explanation for such differences between JAKis and TNFis is lacking—but it is difficult to argue with evidence.

More data will become available over the next several months which may help us make better informed clinical decisions about which class of therapies to use in which patient populations with RA. In the meantime, we are already aware that we should carefully consider the use of JAKis in those patients with underlying CV risk factors in terms of PEs/DVTs, and now similarly for MACEs and malignancies. And these data underscore the importance of the long-term clinical experience we have with the use of TNFis—over 22 years.

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REFERENCES

1 Jones H, Strand V, Schulze-Koops H. Sex differences in the efficacy and safety of tofacitinib in RA: a post hoc analysis of phase 3 and long-term extension trials ACR 2020.
2 McInnes IB, Byers NL, Higgs RE, *et al*. Comparison of baricitinib, upadacitinib, and tofacitinib mediated regulation of cytokine signaling in human leukocyte subpopulations. *Arthritis Res Ther* 2019;21:183.
3 Strand V, Kremer JM, Gruben D, *et al*. Tofacitinib in combination with conventional Disease-Modifying antirheumatic drugs in patients with active rheumatoid arthritis: patient-reported outcomes from a phase III randomized controlled trial. *Arthritis Care Res* 2017;69:592–8.
4 Strand V, Wallenstein G, Kanik KS. Effects of tofacitinib monotherapy on patient-reported outcomes in a randomised phase 3 study of active rheumatoid arthritis. *Arth Res Therapy* 2015;17:307.
5 Strand V, Pope J, Tundia N, *et al*. Upadacitinib improves patient-reported outcomes in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying

antirheumatic drugs: results from SELECT-NEXT. *Arthritis Res Ther* 2019;21:272.
6 Keystone EC, Taylor PC, Tanaka Y, *et al*. Patient-reported outcomes from a phase 3 study of baricitinib versus placebo or adalimumab in rheumatoid arthritis: secondary analyses from the RA-BEAM study. *Ann Rheum Dis* 2017;76:1853–61.
7 Strand V, van Vollenhoven RF, Lee EB, *et al*. Tofacitinib or adalimumab versus placebo: patient-reported outcomes from a phase 3 study of active rheumatoid arthritis. *Rheumatology* 2016;55:1031–41.
8 Strand V, Tundia N, Bergman M. Upadacitinib improves patient-reported outcomes versus placebo or adalimumab in patients with rheumatoid arthritis: results from select-compare. *Rheumatol*.
9 Strand V, Burmester GR, Zerbini CAF, *et al*. Tofacitinib with methotrexate in third-line treatment of patients with active rheumatoid arthritis: patient-reported outcomes from a phase III trial. *Arthritis Care Res* 2015;67:475–83.
10 Smolen JS, Kremer JM, Gaich CL, *et al*. Patient-reported outcomes from a randomised phase III study of baricitinib in patients with rheumatoid arthritis and an inadequate response to biological agents (RA-BEACON). *Ann Rheum Dis* 2017;76:694–700.
11 Strand V, Sun L, Ross Terres J, *et al*. FRI0048 number needed to treat to achieve minimum clinically significant differences in patient reported outcomes in patients treated with baricitinib. *Ann Rheum Dis* 2020;79:580–600.
12 Strand V, Schiff M, Tundia N, *et al*. Effects of upadacitinib on patient-reported outcomes: results from SELECT-BEYOND, a phase 3 randomized trial in patients with rheumatoid arthritis and inadequate responses to biologic disease-modifying antirheumatic drugs. *Arthritis Res Ther* 2019;21:263.
13 Taylor PC, Keystone EC, van der Heijde D, *et al*. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med Overseas Ed* 2017;376:652–62.
14 Fleischmann R, Pangan AL, Song I-H, *et al*. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. *Arthritis Rheumatol* 2019;71:1788–800.
15 Fleischmann R, Mysler E, Hall S, *et al*. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (oral strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. *Lancet* 2017;390:457–68.
16 Combe B, Kivitz A, Tanaka Y. Efficacy and safety of Filgotinib for patients with rheumatoid arthritis with inadequate response to methotrexate: FINCH1 primary outcome results. *Arthritis Rheumatol* 2019;71.
17 Lee EB, Fleischmann R, Hall S, *et al*. Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med* 2014;370:2377–86.
18 Schiff M, Takeuchi T, Fleischmann R, *et al*. Patient-reported outcomes of baricitinib in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. *Arthritis Res Ther* 2017;19:208.
19 van Vollenhoven R, Takeuchi T, Pangan AL, *et al*. Efficacy and safety of Upadacitinib monotherapy in Methotrexate-Naive patients with Moderately-to-Severely active rheumatoid arthritis (SELECT-EARLY): a multicenter, Multi-Country, randomized, double-blind, active Comparator-Controlled trial. *Arthritis Rheumatol* 2020;72:1607–20.
20 Westhovens R, Rigby WFC, van der Heijde D. Efficacy and safety of Filgotinib for patients with rheumatoid arthritis naïve to methotrexate therapy: FINCH3 primary outcome results. *Arthritis Rheumatol* 2019;71.
21 Strand V, Mysler E, Moots RJ. Patient-reported outcomes for tofacitinib with and without methotrexate, or adalimumab with methotrexate, in rheumatoid arthritis: a phase IIIB/IV trial. *RMD Open* 2016;2:e000308.
22 Strand V, Tundia N, Wells A, *et al*. Upadacitinib monotherapy improves patient-reported outcomes in rheumatoid arthritis: results from SELECT-EARLY and SELECT-MONOTHERAPY. *Rheumatology* 2020;00:1–13.
23 Charles-Schoeman C, Fleischmann R, Davignon J, *et al*. Potential mechanisms leading to the abnormal lipid profile in patients with rheumatoid arthritis versus healthy volunteers and reversal by tofacitinib. *Arthritis Rheumatol* 2015;67:616–25.
24 Kremer JM, Genovese MC, Keystone E, *et al*. Effects of Baricitinib on lipid, apolipoprotein, and lipoprotein particle profiles in a phase IIb study of patients with active rheumatoid arthritis. *Arthritis Rheumatol* 2017;69:943–52.
25 Charles-Shoeman C, Sornasse T, Sokolove J. THU0166 treatment with upadacitinib is associated with improvements in reverse cholesterol transport in patients with rheumatoid arthritis: correlation with changes in inflammation and HDL levels. *Ann Rheum Dis* 2019;78.
26 Kay J, Harigai M, Rancourt J, *et al*. Changes in selected haematological parameters associated with JAK1/JAK2 inhibition observed in patients with rheumatoid arthritis treated with baricitinib. *RMD Open* 2020;6:e001370.
27 Schulze-Koops H, Strand V, Nduaka C, *et al*. Analysis of haematological changes in tofacitinib-treated patients with rheumatoid arthritis across phase 3 and long-term extension studies. *Rheumatology* 2017;56:46–57.
28 Cohen SB, van Vollenhoven RF, Winthrop KL, *et al*. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the select phase III clinical programme. *Ann Rheum Dis* 2020. doi:10.1136/annrheumdis-2020-218510. [Epub ahead of print: 28 Oct 2020].
29 Queeney K, Housley W, Sokolove J. FRI0131 elucidating the mechanism underlying creatine phosphokinase upregulation with upadacitinib. *Ann Rheum Dis* 2019;78.
30 Strand V, Ahadieh S, French J, *et al*. Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. *Arthritis Res Ther* 2015;17:362.
31 Winthrop KL, Harigai M, Genovese MC, *et al*. Infections in baricitinib clinical trials for patients with active rheumatoid arthritis. *Ann Rheum Dis* 2020;79:1290–7.
32 Paver A, Desai RJN, Gautam N. Risk of admission to hospital for serious infection after initiating tofacitinib versus biologic DMARDs in patients with rheumatoid arthritis: a multi-database cohort study. *Lancet Rheumatol* 2020;2:e84–98.
33 Strangfeld A, Redeker I, Kekow J. Risk of herpes zoster in patients with rheumatoid arthritis under biological, targeted synthetic and conventional synthetic DMARD treatment. *Ann Rheum Dis* 2020;79:150.2–1.
34 Bing N, Zhou H, Chen X. Contribution of a European-Prevalent variant near CD83 and an East Asian prevalent variant near IL17RB to herpes zoster risk in tofacitinib treatment: results of genome-wide association study meta-analyses. *Arth Rheum* 2021.
35 Winthrop KL, Curtis JR, Lindsey S. Herpes zoster and tofacitinib. *Arthritis Rheumatol* 2017;69:1960–8.
36 Cohen SB, Tanaka Y, Mariette X, *et al*. Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. *Ann Rheum Dis* 2017;76:1253–62.
37 Winthrop KL, Nash P, Yamaoka K. Incidence and risk factors for herpes zoster in rheumatoid arthritis patients receiving Upadacitinib.. *Arthritis Rheumatol* 2020;72.
38 Kallmark H, Gullstrand B, Nagel J. Immunogenicity of adjuvanted herpes zoster subunit vaccine in rheumatoid arthritis patients treated with Janus kinase inhibitors and controls: preliminary results. *Arthritis Rheumatol* 2020.
39 Genovese MC, Smolen JS, Takeuchi T, *et al*. Safety profile of baricitinib for the treatment of rheumatoid arthritis over a median of 3 years of treatment: an updated integrated safety analysis. *Lancet Rheumatol* 2020;2:e347–57.
40 Chung W-S, Peng C-L, Lin C-L, *et al*. Rheumatoid arthritis increases the risk of deep vein thrombosis and pulmonary thromboembolism: a nationwide cohort study. *Ann Rheum Dis* 2014;73:1774–80.
41 Hoppe B, Dörner T. Coagulation and the fibrin network in rheumatic disease: a role beyond haemostasis. *Nat Rev Rheumatol* 2012;8:738–46.
42 Scott IC, Hider SL, Scott DL. Thromboembolism with Janus kinase (JAK) inhibitors for rheumatoid arthritis: how real is the risk? *Drug Saf* 2018;41:645–53.
43 Molander V, Bower H. Does the risk of venous thromboembolism vary with disease activity in rheumatoid arthritis? *Ann Rheum Dis* 2021;80:169–75.
44 Desai RJ, Pawar A, Weinblatt ME, *et al*. Comparative risk of venous thromboembolism in rheumatoid arthritis patients receiving tofacitinib versus those receiving tumor necrosis factor inhibitors: an observational cohort study. *Arthritis Rheumatol* 2019;71:892–900.
45 EMA. EMA confirms Xeljanz to be used with caution in patients at high risk of blood clots. Available: https://www.ema.europa.eu/en/news/ema-confirms-xeljanz-be-used-caution-patients-high-risk-blood-clots [Accessed 31 Dec 20].
46 FDA. Drug safety and availability. Available: https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-boxed-warning-about-increased-risk-blood-clotsand-death higher-dose-arthritis-and [Accessed 31 Dec 20].
47 Mease P, Charles-Schoeman C, Cohen S, *et al*. Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis

development programmes and from real-world data. *Ann Rheum Dis* 2020;79:1400–13.
48 Clowse MEB, Feldman SR, Isaacs JD, *et al*. Pregnancy outcomes in the tofacitinib safety databases for rheumatoid arthritis and psoriasis. *Drug Saf* 2016;39:755–62.
49 Mahadevan U, Dubinsky MC, Su C, *et al*. Outcomes of pregnancies with Maternal/Paternal exposure in the tofacitinib safety databases for ulcerative colitis. *Inflamm Bowel Dis* 2018;24:2494–500.
50 Angelini J, Talotta R, Roncato R, *et al*. JAK-Inhibitors for the treatment of rheumatoid arthritis: a focus on the present and an outlook on the future. *Biomolecules* 2020;10:1002.
51 Pfizer. Pfizer shares co-primary endpoint results from post-marketing. Available: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-shares-co-primary-endpoint-results-post-marketing[Accessed 27 Jan 21].
52 Smolen JS, Aletaha D, Gruben D, *et al*. Brief report: remission rates with tofacitinib treatment in rheumatoid arthritis: a comparison of various remission criteria. *Arthritis Rheumatol* 2017;69:728–34.
53 Dougados M, van der Heijde D, Chen Y-C, *et al*. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis* 2017;76:88–95.
54 Taylor PC, Keystone EC, van der Heijde D, *et al*. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med* 2017;376:652–62.
55 RINVOQ. Clinical remission. Available: https://www.rinvoqhcp.com/clinical-remission [Accessed 31 Dec 20].
56 Combe B, Kivitz A, Tanaka Y. Efficacy and safety of Filgotinib for patients with rheumatoid arthritis with inadequate response to methotrexate: finch 1 primary outcome results. *Arthritis Rheumatol* 2019;71.
57 Combe B, Kivitz A, Tanaka Y, *et al*. Efficacy and safety of filgotinib for patients with rheumatoid arthritis with inadequate response to methotrexate: FINCH 1 52-week results. *Ann Rheum Dis* 2020;79:320–1.
58 Cohen SB, Tanaka Y, Mariette X, *et al*. Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme. *RMD Open* 2020;6:e001395.
59 Winthrop K, Takeuchi T, Burmester G. Safety profile of Baricitinib for the treatment of rheumatoid arthritis up to 8.4 years: an updated integrated safety analysis. *Arthritis Rheumatol* 2020;72.
60 Cohen S, van Vollenhoven R, Curtis JR. Safety profile of upadacitinib up to 3 years of exposure in patients with rheumatoid arthritis. *Arth Rheumatol* 2020;72.
61 Choy E, McInnes I, Cush J. Incidence and risk of venous thromboembolic events among patients with rheumatoid arthritis enrolled in the Upadacitinib clinical trial program. *Arthritis Rheumatol* 2020;72.
62 Winthrop K, Tanaka Y, Takeuchi T. Integrated safety of Filgotinib in patients with moderately or severely active rheumatoid arthritis receiving treatment for up to 5.5 years. *Arthritis Rheumatol* 2020;72.
63 Charles-Schoeman C, Bae S-C, Chopra A. Adjudicated mace and VTe in the Filgotinib RA program: integrated analysis from phase 2 and 3 clinical trials. *Arthritis Rheumatol* 2020;72.