



Deposited via The University of Sheffield.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/179350/>

Version: Published Version

Article:

Kerschbaumer, A., Smolen, J.S., Nash, P. et al. (2020) Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors : a systematic literature research. RMD Open, 6 (3). e001374.

<https://doi.org/10.1136/rmdopen-2020-001374>

Reuse

This article is distributed under the terms of the Creative Commons Attribution-NonCommercial (CC BY-NC) licence. This licence allows you to remix, tweak, and build upon this work non-commercially, and any new works must also acknowledge the authors and be non-commercial. You don't have to license any derivative works on the same terms. More information and the full terms of the licence here:








<https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

Original research

Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a systematic literature research

Andreas Kerschbaumer ¹, Josef S Smolen,² Peter Nash ³, Thomas Doerner ⁴, Maxime Dougados,⁵ Roy Fleischmann ⁶, Klaus Geissler,⁷ Iain B McInnes ^{8,9}, Tsutomu Takeuchi,¹⁰ Michael Trauner,¹¹ Kevin Winthrop,¹² Maarten de Wit ¹³, Wolf-Henning Boehncke,¹⁴ Louise Falzon,¹⁵ Desirée van der Heijde ¹⁶

To cite: Kerschbaumer A, Smolen JS, Nash P, *et al.* Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a systematic literature research. *RMD Open* 2020;**6**: e001374. doi:10.1136/rmdopen-2020-001374

► Supplemental material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/rmdopen-2020-001374>).

Received 21 June 2020
Revised 6 August 2020
Accepted 10 August 2020



© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Andreas Kerschbaumer;
andreas.kerschbaumer@medu
niwien.ac.at

ABSTRACT

Objectives Review of efficacy and safety of Janus kinase (JAK) inhibition in immune-mediated inflammatory diseases (IMIDs).

Methods A systematic literature research (SLR) of all publications on JAK inhibitors (JAKi) treatment published until March 2019 using MEDLINE, EMBASE and the Cochrane Library. Efficacy and safety were assessed in randomised controlled trials (RCTs), integrating long-term extension periods additionally for safety evaluation.

Results 3454 abstracts were screened with 85 included in the final analysis (efficacy and RCT safety: n=72; safety only: n=13). Efficacy of RCTs investigating tofacitinib (TOFA, n=27), baricitinib (BARI, n=9), upadacitinib (UPA, n=14), filgotinib (FILGO, n=7), decernotinib (DEC, n=3) and peficitinib (PEF, n=7) was evaluated. Six head-to-head trials comparing JAKi with tumour necrosis factor inhibitors (TNFi) were included. Efficacy of JAKi was shown in rheumatoid arthritis (RA) for all agents, psoriatic arthritis (TOFA, FILGO), ankylosing spondylitis (TOFA, FILGO), systemic lupus erythematosus (BARI), chronic plaque psoriasis (TOFA, BARI, PEF), ulcerative colitis (TOFA, UPA), Crohn's disease (UPA, FILGO) and atopic dermatitis (TOFA, BARI, UPA). Safety analysis of 72 RCTs, one cohort study and 12 articles on long-term extension studies showed increased risks for infections, especially herpes zoster, serious infections and numerically higher rates of venous thromboembolic events. No increased malignancy rates or major adverse cardiac events were observed.

Conclusion JAKi provide good efficacy compared to placebo (and to TNFi in RA and Pso) across various IMIDs with an acceptable safety profile. This SLR informed the task force on points to consider for the treatment of IMIDs with JAKi with the available evidence.

INTRODUCTION

The first randomised controlled trial (RCT) investigating the inhibition of Janus kinases (JAK) via the JAK-1/2 selective agent ruxolitinib/INCB018424 (RUXO) in patients with an immune-mediated

Key messages**What is already known about this subject?**

► Numerous randomised controlled trials investigating the efficacy and safety of Janus kinase inhibitors in immune-mediated inflammatory diseases have been conducted.

What does this study add?

► JAKi were effective in reducing signs and symptoms in rheumatic diseases (rheumatoid and psoriatic arthritis, ankylosing spondylitis and systemic lupus erythematosus) as well as inflammatory bowel disease (ulcerative colitis and Crohn's disease) and immune-mediated dermatological diseases like chronic plaque psoriasis and atopic dermatitis.

► Janus kinase inhibitors showed an acceptable safety profile in the investigated populations, with an increased risk for infections (including serious infections and herpes zoster). Rare events were difficult to assess for some agents due to the limited amount of patient-exposure-years and only few registry data. However, numerically higher rates of venous thromboembolic events were seen in JAKi-treated patients in some studies.

How might this impact on clinical practice?

► This SLR was performed to inform the task force on 'Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors' with the evidence published until March 2019.

inflammatory disease (IMID), namely rheumatoid arthritis (RA), was completed in 2008; however, this study has not been published until today (ClinicalTrials.gov identifier: NCT00550043). Since then, numerous trials on JAK inhibitors (JAKi) have been conducted in various IMIDs across many disciplines, including rheumatology, dermatology and gastroenterology.¹⁻¹⁴

In 2012, tofacitinib (TOFA), a JAK-1/2/3 inhibitor, was the first agent to be approved for an IMID, namely RA, but subsequently also for treating patients with psoriatic arthritis (PsA) and ulcerative colitis (UC). While JAK inhibition via baricitinib (BARI; JAK-1/2), upadacitinib (UPA; JAK-1/2) and filgotinib (FILGO; JAK-1) also showed good efficacy in different indications, questions on how JAK selectivity influences clinical efficacy as well as the safety profile of all these agents arose and are still insufficiently answered, continue to be issues for debate and future research.¹⁵

To guide the practicing clinician on how (not when) to use JAKi in clinical practice, the consensus meeting on 'Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors' was conducted in 2019. Participants of the consensus task force were informed by this systematic literature research (SLR) on the efficacy and safety of all trials on JAKi conducted in IMIDs.

METHODS

A review protocol for this SLR was developed by the steering group in accordance with the EULAR standardised operating procedures for recommendations.¹⁶

The systematic literature search was conducted by a database expert (LF) in EMBASE, Medline and the Cochrane Library. The search included all studies published from the earliest date indexed until 12 March 2019 (last date searched). Further, the conference abstract archives of the EULAR Annual Meeting and American college of rheumatology (ACR, until 2018) were hand-searched. All search terms used are shown in the online supplemental appendix (Section 1.1.1–1.1.3). Data extraction was done by one researcher (AK) in duplicates.

The eligibility criteria for inclusion were defined as studies in adult patients (≥ 18 years) treated with JAKi with diagnosed active autoimmune disease, that is, RA, PsA, AS, systemic lupus erythematosus (SLE), Crohn's disease (CD), UC, psoriasis (PsO), atopic dermatitis (AD) or alopecia areata (AA) and alopecia universalis. Patient populations were defined for each disease separately, based on treatment history such as an insufficient response (IR) to certain previous systemic therapies. Data of full articles could be included also if published after the last date of the database search, provided at least one abstract of the respective trial had been published within the SLR's time frame.

For efficacy evaluation, only randomised, controlled, double-blind trials on systemic or topical JAKi including BARI, decernotinib (DEC), FILGO, peficitinib (PEF), RUXO, TOFA and UPA treatment were considered. A detailed list of patient populations, interventions, controls and outcomes is shown in the online supplemental appendix (section 1.4.1.1–1.4.1.4). For safety evaluation, RCTs were evaluated for signals of adverse events (AEs). In addition, cross-sectional, cohort and case-control studies were eligible.

Research questions developed by the steering group are shown in sections 1.4.2 (for efficacy) and 1.4.3 (for safety) in the online supplemental appendix.

Safety outcomes of interest were infections, malignancies, venous thromboembolic events (VTE), haematological abnormalities (anaemia, leucopenia, neutropenia, lymphopenia), MACE and laboratory abnormalities (hepatic, cholesterol, creatine kinase).

As decided by the steering group, due to expected heterogeneity of the populations investigated, no pooling of efficacy or safety results by meta-analysis was conducted.

Risk of bias (RoB) was assessed using the Cochrane Collaboration's RoB tool for RCTs, assigning each study as having low, unclear or high RoB.¹⁷

RESULTS

A total of 3454 studies were assessed in the title and abstract screening with 262 selected for full article review; 85 publications were finally evaluated in detail. [Figure 1](#) shows the study flow chart with a detailed description of the selection process. Reports on efficacy selected for inclusion are shown in [table 1](#) (detailed results of included articles are shown in online supplemental appendix tables S2.1.1–2.1.9).

Most of the articles showed a low overall RoB, with few articles considered to be of unclear risk due to insufficient reporting on random sequence generation and allocation procedures. One study was considered to have a high RoB due to dosage unblinding of participants and investigators.¹⁸ Details are shown in the online supplemental appendix (tables S2.2.1–S2.2.9).

[Figure 2](#) visualises efficacy results of different JAKi by disease, based on the achievement of primary clinical end points. Baseline characteristics (tables S2.3.1–S2.3.9) and detailed efficacy results (tables S3.1–S3.9) are shown in the online supplemental appendix.

Besides safety data of clinical trials investigated for efficacy, 13 additional reports on safety were included (details of selected articles are shown in online supplemental appendix tables S4.1.1–S4.1.8; safety outcomes are shown in online supplemental appendix tables S4.2.1–S4.2.8 and S4.3.1–S4.3.8).

Rheumatoid arthritis

In total, 39 primary reports of clinical trials on JAKi in patients with RA were included (low RoB: $n=28$; unclear RoB: $n=9$; conference abstracts: $n=3$; for details on study characteristics, RoB analyses, baseline characteristics and efficacy outcomes, see online supplemental appendix tables S2.1.1, S2.2.1, S2.3.1 and S3.1).

TOFA was effective in reducing signs and symptoms of RA as well as inhibition of radiographic damage progression. These studies were performed in methotrexate (MTX)-naïve patients,¹⁹ patients with IR to MTX,^{20 21} or conventional synthetic disease-modifying drugs (csDMARDs)^{1 22–27} or to tumour necrosis factor alpha

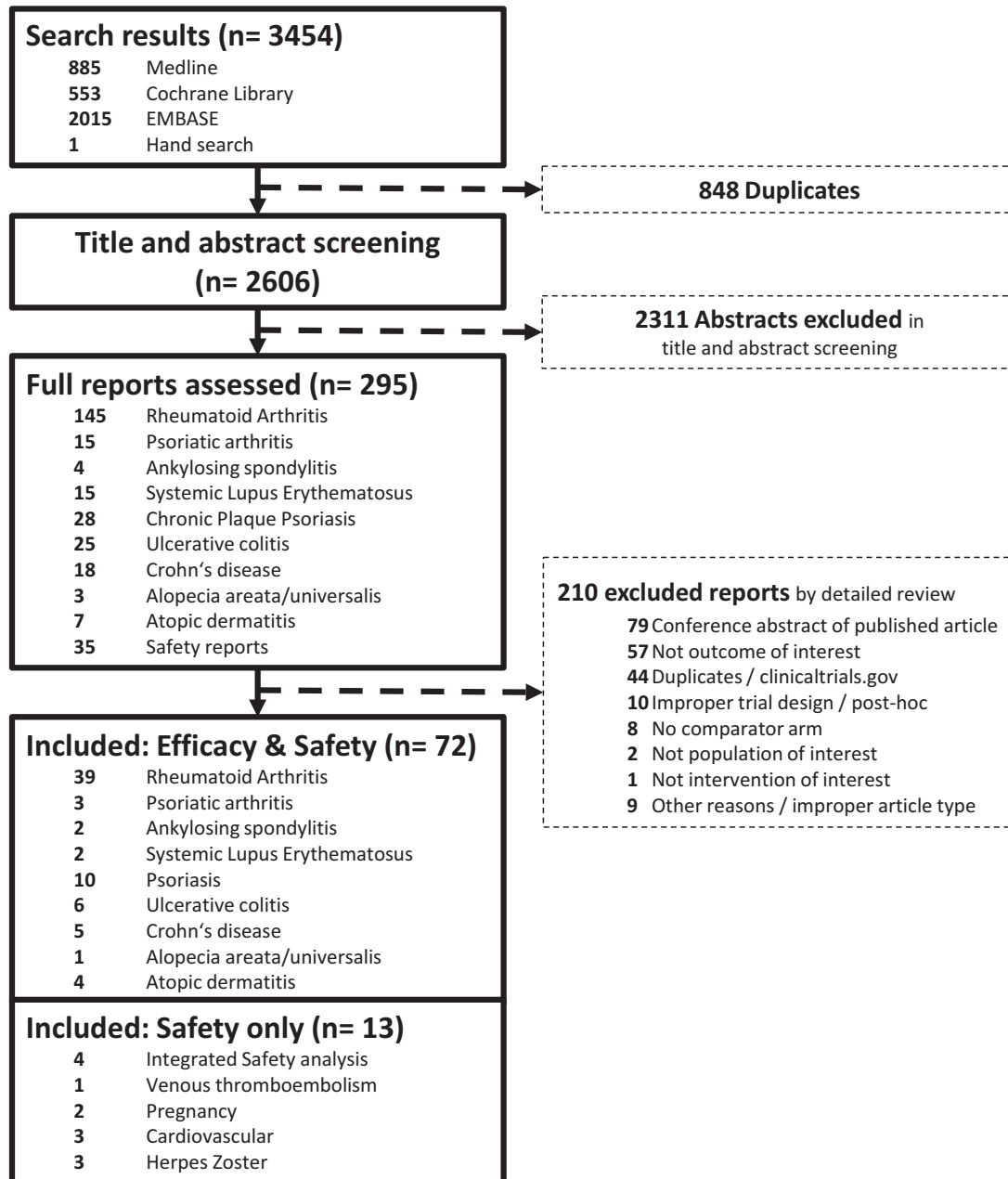


Figure 1 PRISMA flow chart for studies on JAKi efficacy and/or safety in inflammatory immune disease, published until March 2019. JAKi, Janus kinase inhibitors; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

inhibitors (TNFi) and other biological (b)DMARDs^{1 28 29}; structural outcomes were only studied in MTX-naïve and MTX-IR patients. In MTX-IR patients, van Vollenhoven *et al* showed numerically similar response rates of TOFA and adalimumab (ADA), which was used as an active comparator but not powered for non-inferiority in the ORAL Standard trial.³⁰ ORAL-Strategy, a head-to-head trial comparing TOFA 5 mg twotimes per day monotherapy and TOFA 5 mg two times per day plus MTX with ADA 40 mg every other week (EOW) plus MTX, proved non-inferiority between the combination therapy arm but not for the TOFA monotherapy arm compared with the two combination arms (table 2).³¹

Studies on BARI also revealed the efficacy of BARI 2 mg and 4 mg once daily (OD) in csDMARD-naïve,³⁶ MTX and csDMARD-IR,^{37–40} and patients previously not responding to bDMARDs, compared with placebo.² In RA-BEAM, BARI 4 mg was statistically superior clinically over placebo and ADA 40 mg EOW in MTX-IR patients (table 2).³² In a randomised tapering substudy of RA-BEYOND, Takeuchi *et al* showed that patients on BARI 4 mg OD who had achieved low disease activity according to the Clinical Disease Activity Index (CDAI, ≤10) and were subsequently randomised to reduce the BARI dose from 4 mg to 2 mg OD mostly maintained their disease state, although less so than continuing full dose

Table 1 Efficacy of Janus kinase inhibitors investigated in randomised controlled trials published until March 2019

Disease	Total	Tofacitinib (JAK 1–3)	Baricitinib (JAK 1/2)	Upadacitinib (JAK 1)	Filgotinib (JAK 1)	Decernotinib (JAK 3)	Peficitinib (JAK 1–3)	Others
Rheumatoid arthritis	39	13	6	8	4	3	5	0
Psoriatic arthritis	3	2	0	0	1	0	0	0
Ankylosing spondylitis	2	1	0	0	1	0	0	0
Systemic lupus erythematosus	2	0	1	0	0	0	0	Solcitinib (1)
Chronic plaque psoriasis	10	6	1	0	0	0	1	BMS-986 165 (1) Itacitinib (1)
Ulcerative colitis	6	2	0	3	0	0	1	0
Crohn's disease	5	2	0	2	1	0	0	0
Alopecia areata/universalis	1	0	0	0	0	0	0	PF-06651600 (1)
Atopic dermatitis	4	1	1	1	0	0	0	JTE-052 (1)
Total	72	27	9	14	7	3	7	5

JAK, Janus kinase.

Disease	Janus Kinase inhibiting agent (Target)					
	Tofacitinib (JAK 1-3)	Baricitinib (JAK 1/2)	Upadacitinib (JAK 1)	Filgotinib (JAK 1)	Decernotinib (JAK 3)	Peficitinib (JAK 1-3)
Rheumatoid arthritis	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo
Psoriatic arthritis	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo
Ankylosing spondylitis	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo
Systemic Lupus Erythematosus	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo
Chronic Plaque Psoriasis	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo
Ulcerative colitis	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	No significant difference compared to placebo
Crohn's disease	No significant difference compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo
Atopic dermatitis	topical	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo	Statistically superior compared to placebo

	Statistically superior compared to placebo
	No significant difference compared to placebo
	Not available

Figure 2 Efficacy of Janus kinase inhibiting agents across immune-mediated diseases (based on available data at end of March 2019). JAK, Janus kinase.

(CDAI \leq 10 at week 48: continued BARI 4 mg vs tapering to BARI 2 mg: 80% vs 67%; patients achieving CDAI \leq 2.8, that is, remission: BARI 4 mg vs 2 mg: 40% vs 33%); there was a numerically lower rate of non-serious infections in the tapering arm.^{41 42}

UPA was investigated in eight trials, also provided good efficacy results across various patient populations with RA (MTX-naïve, MTX-IR, csDMARD-IR, TNF-IR and bDMARD-IR) compared to placebo and both as monotherapy and when combined with MTX.^{3 37 43–50} A head-to-head comparison of UPA+MTX with ADA 40 mg EOW + MTX demonstrated superiority

(clinically and functionally) of UPA+MTX versus ADA +MTX and versus placebo + MTX (table 2).^{33 34} In SELECT-MONOTHERAPY, MTX-IR patients were either randomised to blinded UPA 15 mg OD, UPA 30 mg OD or continued MTX for 14 weeks. UPA showed statistically superior responses in clinical and functional outcomes, compared to continued MTX (ACR20 at week 14: 68%, 71% and 41% for UPA 15 mg OD, 30 mg OD and continued MTX, respectively).^{44 45}

Treatment with FILGO in MTX-IR patients showed superiority compared to placebo in four phase II RCTs.^{4 51 52} FILGO monotherapy (DARWIN 2) was

Table 2 Trials investigating Janus kinase inhibitors and tumour necrosis factor alpha inhibitors

Study	Population	Risk of bias	Treatment	n	Primary end point	P value	% of patients achieving primary end point
Rheumatoid arthritis							
van Vollenhoven 2012 (ORAL Standard) ³⁰	MTX-IR	Low	PLC+MTX (Combination group)	106	% ACR20 (week 24)	Reference	28
			TOFA 5 mg two times per day +MTX	204		<0.001	52
			TOFA 10 mg two times per day +MTX	201		<0.001	53
Fleischmann 2017 (ORAL Strategy) ³¹	MTX-IR	Low	ADA 40 mg EOW+MTX	204		<0.001	47
			TOFA 5 mg two times per day+PLC	384	Non-inferiority: % ACR50 (week 24)	NI not met -8% (98.34% CI -16 to 1)	65
			TOFA 5 mg two times per day +MTX	376		NI met 2% (98.34% CI -6 to 11)	73
Taylor 2017 (RA-BEAM) ³²	MTX-IR	Low	ADA 40 mg Q2W+MTX	386		Reference	71
			PLC+MTX	488	Superiority: % ACR20 (week 12)	-	40
			BARI 4 mg+MTX	487		0.01	70
Fleischmann 2018 (SELECT-COMPARE) ^{33 34}	MTX-IR	Low	ADA 40 mg EOW+MTX	330		Reference	61
			PLC+MTX	651	Superiority: % ACR50 (week 12)	-	15
			UPA 15 mg OD+MTX	651		<0.001	45
			ADA 40 mg EOW+MTX	327		Reference	29
Psoriatic arthritis							
Mease 2017 (OPAL Broaden) ⁵	csDMARD-IR	Low	PLC±csDMARD	105	% ACR20 (week 12) ΔHAQ (week 12)	Reference	33; -0.18
			TOFA 5 mg two times per day ±csDMARD	107		<0.01; 0.006	50; -0.35
			TOFA 10 mg two times per day ±csDMARD	104		<0.001; <0.001	61; -0.4
			ADA 40 mg EOW±csDMARD	106		NR	52; -0.38
Chronic plaque psoriasis							
Bachelez 2015 ³⁵	Candidates for systemic therapy or phototherapy +PASI >12 +PGA moderate/severe +csDMARD-IR	Low	Placebo	107	Non-inferiority: % PASI 75 (week 12) % PGA clear/almost clear (week 12)	-	6
			TOFA 5 mg two times per day	329		NI not met <0.001/<0.001	40
			TOFA 10 mg two times per day	330		NI met 0.20/0.60	64
			ETA 50 mg twice weekly	335		Reference	59

ACR, American College of Rheumatology; ADA, adalimumab; BARI, baricitinib; csDMARD, conventional synthetic disease-modifying antirheumatic drug; EOW, every other week; ETA, etanercept; ΔHAQ, changes from baseline in Health Assessment Questionnaire-Disability Index; IR, insufficient responder; MTX, methotrexate; NI, non-inferiority; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; PLC, placebo; TOFA, tofacitinib; UPA, upadacitinib.

superior to placebo after MTX washout (ACR20 at week 12: 67% vs 66% vs 73% vs 29% for FILGO 50 mg OD, 100 mg OD, 200 mg OD and placebo, respectively).^{4 51 52} FILGO in combination with MTX also showed superiority over placebo + MTX in DARWIN 1 (ACR20 at week 12: 56% vs 64% vs 69% vs 57% vs 60% vs 79% vs 44% for FILGO 50 mg OD, 100 mg OD, 200 mg OD, 25 mg two times per day, 50 mg two times per day, 100 mg two times per day and placebo, respectively).⁴ DEC (JAK-3 selective) showed superiority over placebo in three trials; however, no clear dose–response relationship exists in ACR responses.^{53–55} PEF, another pan-JAKi (JAK 1–3), was investigated in two global trials, where it failed to reveal significant efficacy (Genovese 2017: ACR20 at week 12: 22.0% vs 36.8% vs 56.3% vs 29.3%; Kivitz 2017: 43.9% vs 61.5% vs 46.4% vs 57.7% vs 44.4% for PEF 25 mg OD, 50 mg OD, 100 mg OD, 150 mg OD and placebo, respectively). But in several Japanese RA study populations (MTX-naïve, MTX-IR, csDMARD-IR), it showed significant improvement of signs and symptoms and physical function compared to placebo.^{56–62}

PsA, ankylosing spondylitis and SLE

In PsA, three trials (all with low RoB) were published (for details, see online supplemental appendix tables S2.1.2, S2.2.2, S2.3.2 and S3.2). TOFA was investigated in two phase III trials, showing efficacy not only regarding signs and symptoms of arthritis but also physical function, skin disease, dactylitis and enthesitis.^{5 63} Similar results across many outcomes (although not formally tested) in patients with csDMARD-IR PsA were observed with TOFA compared to ADA 40 mg EOW (table 2).⁵ Treatment with FILGO 200 mg OD in EQUATOR resulted in significant improvements compared to placebo regarding signs and symptoms of arthritis, PsO and enthesitis.⁶⁴

In ankylosing spondylitis, two trials in patients with IR to non-steroidal anti-inflammatory drugs were available for analysis, one on TOFA and one on FILGO (for details, see online supplemental appendix tables S2.1.3, S2.2.3, S2.3.3 and S3.3).^{6 65} In a phase II trial (unclear RoB), TOFA significantly improved clinical outcomes of spinal mobility, pain and function as well as inflammatory changes by MRI, with a clear dose–response.⁶ In phase II trial (low RoB), FILGO improved disease activity significantly more than placebo across various outcome measures.⁶⁵

Only limited data on JAKi in SLE were published (two trials, one with high RoB, one with low RoB; for details, see online supplemental appendix tables S2.1.4, S2.2.4, S2.3.4 and S3.4).^{7 18} In a phase II study, Wallace *et al* investigated BARI in patients with SLE and active skin or joint disease. Significantly more patients achieved a SLEDAI-2 K resolution of arthritis or rash at week 24 with BARI 4 mg OD (but not BARI 2 mg OD) compared to placebo treatment.⁷

Chronic plaque PsO, AD and alopecia

Ten trials on patients suffering from chronic plaque PsO were included in this SLR (for details, see online supplemental appendix tables S2.1.5, S2.2.5, S2.3.5 and S3.5), eight with low, one with unclear and one with high RoB, respectively. TOFA showed significant improvements in skin disease compared to placebo in patients who were candidates for systemic therapy or phototherapy.^{8 35 66 67} Bachelez *et al* could demonstrate non-inferiority of TOFA 10 mg two times per day compared with etanercept 50 mg twice weekly in achieving a Psoriasis Area and Severity Index (PASI) 75% response as well as clear or almost clear skin (as evaluated by the physician global assessment, PGA) at week 12 (table 2).³⁵ In a withdrawal and retreatment trial, patients with treatment response to TOFA 5 mg or 10 mg two times per day at week 24 were re-randomised to placebo or their previous TOFA dose. Moreover, 23.3% and 26.1% of the patients withdrawn from TOFA 5 mg and 10 mg two times per day, respectively, could maintain their PASI75% response (compared to 56.2% and 62.3% with ongoing TOFA 5 mg or 10 mg two times per day) after 16 weeks. Following 16 weeks of retreatment, 36.8% and 61% of the patients who relapsed after treatment withdrawal, could again achieve a PASI 75% response (compared with 63% and 73.8% of the patients continuously treated with TOFA 5 mg or 10 mg two times per day, respectively).⁶⁸ A dose-finding study investigating BARI showed BARI 8 mg OD as well as 10 mg OD (but neither 2 mg OD nor 4 mg OD) to be significantly better than placebo in achieving the primary end point (PASI75% at week 12).⁶⁹ A JAK-1 selective JAKi, itacitinib (INCB039110), showed promising results in a 28-day proof-of-concept PsO trial.⁷⁰ BMS-986165, considered as selective TYK2 inhibitor, showed better clearing of PsO than placebo at week 12.⁷¹

Topical TOFA showed greater improvements in pruritus and eczema area and severity compared to vehicle treatment in AD.⁷² Another topical pan-JAKi (JTE-052) showed rapid and significant AD improvements over vehicle treatment, with numerically similar results to open-label topical tacrolimus, but potential unblinding during the study (high RoB).⁷³

Further, systemic treatment with BARI showed promising results in improving signs, symptoms and patient-reported outcomes of AD.⁷⁴ Dose-dependent responses to UPA with significant differences compared to placebo were demonstrated in a phase II study in patients with moderate to severe AD (% change from baseline in Eczema Area and Severity Index at week 16: 39% vs 62% vs 74% vs 23% for UPA 7.5 mg OD, 15 mg OD, 30 mg OD and placebo, respectively).^{9 10}

Selective inhibition of JAK-3 via PF-06651600 and TYK2/JAK1 via PF-06700841 showed statistically superior results compared to placebo in patients with AA regarding $\geq 50\%$ improvement from baseline in severity of

alopecia tool at 24 weeks (conference abstract, no RoB analysis conducted).⁷⁵

Inflammatory bowel disease

In total, eleven reports on eight trials in inflammatory bowel disease were included, describing four trials on UC (all with low RoB) and four on CD (3 low RoB, 1 unclear RoB; for details, see online supplemental appendix tables S2.1.7, S2.1.8, S2.2.7, S2.2.8, S2.3.7, S2.3.8, S3.7 and S3.8).^{11–14 76–82}

TOFA 10 mg two times per day was effective in UC as induction therapy compared to placebo in UC, with 16.6% vs 8.2% achieving remission (defined as total Mayo score ≤ 2 , with no subscore >1 and a rectal bleeding subscore of 0) at week 8. Patients with clinical response were subsequently randomised to receive TOFA 10 mg two times per day, TOFA 5 mg two times per day or placebo with TOFA being significantly more effective than placebo therapy after 52 weeks (34.3% vs 40.6% vs 11.1% for TOFA 5 mg two times per day, TOFA 10 mg two times per day and placebo, respectively).⁷⁶ Induction therapy in patients with moderate to severe UC with UPA was investigated in a phase II trial, being more effective than placebo in inducing remission (0% vs 8.5% vs 14.3% vs 13.5% vs 19.6% for placebo, UPA 7.5 mg, 15 mg 30 mg or 45 mg OD) at week 8.^{77 78} In a phase IIb study on PEF as induction therapy in UC, the primary end point, establishment of a dose–response relationship was not met. Only PEF 150 mg showed a significant difference (nominal $p < 0.05$) in inducing remission at week 8 compared to placebo (7% vs 15.9% vs 15.9% vs 27.3% vs 15.9% for placebo, 25 mg OD, 75 mg OD, 150 mg OD or 75 mg two times per day).⁷⁹

TOFA was not effective in treating patients with active CD and insufficient response to glucocorticoids and immunomodulatory agents (including TNFi), neither for induction nor maintenance therapy in three phase II trials.^{80 81} A phase II dose-finding study on UPA showed clinical as well as endoscopic improvement in moderate-to-severe CD (clinical/endoscopic remission at week 16: 11%/0% vs 13%/10% vs 27%/8% vs 11%/8% vs vs 14%/14% vs 22%/22% for placebo, 3 mg, 6 mg, 12 mg two times per day, 24 mg OD and 24 mg two times per day, respectively).^{12 14} After 16 weeks of induction therapy, patients were re-randomised to either UPA 3 mg, 12 mg or 24 mg two times per day for maintenance therapy up until week 52. A dose–response in clinical as well as endoscopic outcomes was shown over 36 weeks of treatment in initial responders of the induction phase (clinical/endoscopic remission at week 52: 41.2%/25% vs 62.5%/25% vs 73.3%/37.5% vs 40%/10% for UPA 3 mg, 6 mg, 12 mg two times per day and 24 OD).^{13 14} JAK-1 selective treatment with FILGO 200 mg OD resulted in significantly more patients achieving clinical remission (Crohn's Disease Activity Index <150 at week 10: 47% vs 23% for FILGO 200 mg OD vs placebo). Results on endoscopic outcomes were numerically higher, although not statistically different at week 10 (50% response: 25% vs 14%,

remission: 14% vs 7% at week 10, for FILGO 200 mg OD and placebo, respectively).⁸² Detailed results of trials investigating JAKi and TNFi are shown in table 2.

Safety

All RCTs with a valid comparator (placebo or active treatment arm in the respective time period) were assessed for AEs of special interest (see online supplemental appendix tables S4.1.1–S4.1.8 for details of included reports). Numerically higher rates of serious AEs, infections, serious infections and especially herpes zoster (HZ) were identified when comparing JAKi treatment arms with placebo arms (see online supplemental appendix tables S4.2.1–S4.2.8 for detailed results). AEs of special interest are shown in online supplemental appendix tables S4.3.1–S4.3.8. Liver enzymes and creatine kinase elevations as well as grade 3 or 4 lymphopenia/leucopenia appeared more frequently during JAKi treatment.

Assessment of rare events, especially VTE (that is, deep vein thrombosis and pulmonary embolism) remained difficult to assess due to scarcity of data and a largely diverse database on the amplitude of VTE risk related to the underlying disease. One cohort study using claims databases investigated the risk of venous thromboembolism in biological and JAKi-naïve patients with RA (n=50 865) receiving TOFA versus patients receiving TNFi and found a numerically higher, however, statistically nonsignificant VTE risk (pooled propensity score-adjusted HR: 1.33; 95% CI 0.78 to 2.24).⁸³

In some RCTs, compared to placebo, numerically higher rates of DVT/PE were seen in JAKi-treated patients, suggesting an increased risk for venous thromboembolism. However, reports of head-to-head studies did not reveal a clear signal regarding VTE risk when comparing TNFi and JAKi treatment arms during the controlled period (table 3). While the individual reports did not allow to discern major differences between JAKi and placebo or active treatment arms regarding VTEs and PEs, the regulators have published important information after the time point of this SLR. For completeness, we refer to the Food and Drug Administration report revealing more VTE/PE for BARI at 4 mg,⁸⁴ and to the EMA report on a still ongoing trial of TOFA versus anti-TNFs in patients with RA with cardiovascular risk factors where significantly more VTE/PE and deaths were seen with TOFA 10 mg two times per day but numerically also for TOFA 5 mg.^{85 86} These important information also led to black box warnings in the package inserts of marketed JAKi and more long-term data will be needed, as also meanwhile partly published for some of the drugs.^{87–90}

No safety signal could be identified regarding major cardiac adverse events (MACE), malignancies excluding non-melanoma skin cancer. Table 3 shows AEs of special interest in trials comparing JAKi next to TNFi and placebo treatment.

Additionally, 12 reports on integrated safety analyses of RCTs+long-term extension trials (LTEs) were included in the analysis. TOFA RCTs (until March 2015) comprising

Table 3 Adverse events of special interest in randomised controlled trials investigating Janus kinase inhibitors and tumour necrosis factor alpha inhibitors

Study	Population	Risk of bias	Treatment	n	Time point (weeks)	Serious adverse events (%)	Serious infections (%)	Herpes zoster (%)	Tuberculosis (%)	Deep vein thrombosis (%)	Pulmonary embolism (%)	Malignancy, excluding NMSC (%)	Non-melanoma skin cancer (%)	MACE (%)	
Rheumatoid arthritis															
van Vollenhoven 2012 (ORAL Standard) ³⁰	MTX-IR	Low	PLC+MTX (Combination group)	106	24	1.9	0.9	0	0	0				0	
			TOFA 5 mg two times per day +MTX	204		5.9	1.5	0	0	0					0
			TOFA 10 mg two times per day +MTX	201		5.0	2.0	3.0	0	0.5					0
Fleischmann 2017 (ORAL Strategy) ³¹	MTX-IR	Low	ADA 40 mg EOW +MTX	204		2.5	0	0	0	0				0.5	
			TOFA 5 mg two times per day +PLC	384	24	9	2	1	0		0.26	<1	1	0	
			TOFA 5 mg two times per day +MTX	376		7	3	2	1		0	0	0	0	
Taylor 2017 (RA-BEAM) ³²	MTX-IR	Low	ADA 40 mg EOW +MTX	386		6	2	2	0		0.26	0	<1	1	
			PLC+MTX	488	24	5	1	<1	0	0*	0*	<1	<1	0	
			BARI 4 mg+ MTX	487		5	1	1	0	0.2*	0.2*	<1	0	<1	
Fleischmann 2018 (SELECT-COMPARE) ^{33 34}	MTX-IR	Low	ADA 40 mg EOW +MTX	330		2	<1	1	<1	0*	0*	0	0	0	
			PLC+MTX	651	26	2.9	0.8	0.5	0	0	0.2	0.3		0.5	
			UPA 15 mg OD +MTX	651		3.7	1.8	0.8	0.2	0.2	0.2	0	0.5	0	
Mease 2017 (OPAL Broaden) ⁵	csDMARD-IR	Low	ADA 40 mg EOW +MTX	327		4.3	1.5	0.3	0	0	0.9	0.3	0.3	0.6	
			PLC±csDMARD	105	12	1	0	0	0	0	0	0	0	0	
			TOFA 5 mg two times per day ±csDMARD	107		3	0	1	0	0	0	2	0	0	
Chronic plaque psoriasis			TOFA 10 mg two times per day ±csDMARD	104		1	0	0	0	0	0	0	1	0	
			ADA 40 mg EOW ±csDMARD	106		1	0	0	0	0	0	0	0	0	

Continued

Table 3 Continued

Study	Population	Risk of bias	Treatment	n	Time point (weeks)	Serious adverse events (%)	Serious infections (%)	Herpes zoster (%)	Tuberculosis (%)	Deep vein thrombosis (%)	Pulmonary embolism (%)	Malignancy, excluding NMSC (%)	Non-melanoma skin cancer (%)	MACE (%)
Bachelez 2015 ³⁵	Candidates for systemic therapy or phototherapy + PASI > 12 + PGA moderate/severe +csDMARD-IR	Low	PLC	107	12	1.9	0	0	0	0	0	0	0	0
			TOFA 5 mg two times per day	329		2.1	0.6	0.3	0	0	0.3	0	0.3	0.3
			TOFA 10 mg two times per day	330		1.5	0.6	0.6	0	0	0.3	0.3	0.3	0
			ETA 50 mg twice weekly	335		2.1	0.6	0.6	0	0	0	0	0.6	0.3

*Not reported in original report/supplement/ClinicalTrials.gov, source: FDA Briefing Document Arthritis Advisory Committee Meeting, 23 April 2018, pp. 54–55 (Table 25). ADA, adalimumab; BARI, baricitinib; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; EOW, every other week; ETA, etanercept; FDA, Food and Drug Administration; IR, insufficient responder; MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer; MTX, methotrexate; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; PLC, placebo; TOFA, tofacitinib; UPA, upadacitinib.

19 406 patient-years (PY) of treatment exposure within RA showed stable AEs over time (median exposure 3.4 years). Nasopharyngitis, upper respiratory tract infections and urinary tract infections were the most common AEs. Most common serious infections were pneumonia, HZ, urinary tract infections and cellulitis, with baseline glucocorticoid usage, age and geographic region (Asia) being significant risk factors. No increased incidence rate for malignancies excluding non-melanoma skin cancer (standardised incidence ratio: 1.0; 95% CI 0.8 to 1.1) was observed. Twenty-two gastrointestinal perforations (incidence ratio: 0.11, 95% CI 0.07 to 0.17) were reported, all in patients with concomitant non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoid therapy (NSAIDs + glucocorticoids: n=10; NSAIDs only: n=9; glucocorticoids only: n=3); 13 patients had a history of diverticulitis or diverticulosis and two a history of gastric ulcers.⁹¹ Consistent results were also observed in patients with UC and PsO who were treated with TOFA in RCTs and LTEs.^{92–93} Safety analyses on HZ events in patients with PsO and UC found patients treated with TOFA at increased risk for HZ infection, with age, Asian origin and previous biological use as risk factor as well as dose-dependent higher risks in patients treated with TOFA 10 mg two times per day versus TOFA 5 mg two times per day.^{94–96} Although higher levels of low-density lipoprotein, high-density lipoprotein and total cholesterol were observed during TOFA treatment, no signal regarding a higher risk of MACE was found in RA, PsO and UC trials.^{97–99}

Integrated safety on BARI in RA with 6637 total PY of exposure (median 2.1 years) showed a higher risk for infections including HZ; VTE (including deep vein thrombosis/pulmonary embolism) were reported with BARI 4 mg OD but not for placebo (IR 0.5/100PY, 95% CI 0.3 to 0.7) without differences between BARI 2 mg (IR 0.5/100PY) and BARI 4 mg (IR 0.6/100 PY). These were associated with age, higher BMI, history of DVT/PE and use of selective cyclooxygenase-2 inhibitors. Higher rates of non-melanoma skin cancer were identified in BARI 4 mg OD compared to BARI 2 mg OD-treated patients. Three cases of gastrointestinal perforations were reported in patients taking MTX+NSAIDs, with two patients taking glucocorticoids. Ten cases of tuberculosis (in endemic areas) were observed in BARI-treated patients. No increased risk of MACE or malignancies was identified.¹⁰⁰

Pregnancy is a contraindication for JAKi therapy, and patients were required to use contraception during the RCTs. Therefore, only very limited data (two retrospective analyses) on pregnancy outcomes were available.^{101–102} Clowse *et al* investigated pregnancy outcomes of patients treated with TOFA in RA (31 maternal cases: TOFA monotherapy n=18, TOFA+MTX n=13; 3 paternal cases) and PsO (16 maternal cases, 41 paternal cases). Similar frequencies of healthy newborns (n=25), no fetal death, seven spontaneous abortions, eight medical terminations and one congenital malformation (pulmonary valve

stenosis) were reported until April 2014. These frequencies were consistent with background risks in the general population as well as in patients with RA or PsO, although confounded through concomitant MTX therapy in some patients with RA.¹⁰¹ Further analysis on pregnancies in UC, RA, PsO and PsA RCTs (up to March 2017) reported results in line with the previous report with pregnancy AEs during TOFA treatment appearing similar to those in the general population.¹⁰²

DISCUSSION

We conducted this SLR to inform the task force on points to consider for the treatment of IMIDs with JAKi with data of all reports and conference abstracts published until March 2019.

Efficacy of JAK inhibition has been shown for several agents being either pan-JAKi (TOFA, PEF) as well as JAK-selective (BARI, UPA, FILGO, DEC) compounds. With TOFA being the first and therefore most extensively studied agent, the JAKi approved to date demonstrating good efficacy in various indications. FILGO recently received a positive opinion by the European Medicines Agency, recommending the granting of a marketing authorisation for treatment of RA. However, none of the available JAKi was approved for PsO until now, as efficacy data were especially promising in higher doses, but these were not approved due to regulatory safety concerns. The JAKi approved up until the date of submission of this manuscript (TOFA, BARI, UPA) appeared to demonstrate a similar safety profile with an increased risk of infections (particularly HZ) and a potential risk of VTE. Although overall rare, VTE were observed in patients at risk for thrombosis, subsequently leading to warnings issued by the regulators. However, large registry data and studies of at-risk patients with sufficiently large cohort and comparator arms for safety analyses are still lacking.

There are several limitations of this SLR: (1) only one researcher (AK) conducted the title and abstract screening, data extraction and RoB analysis; (2) we only reported data narratively due to the heterogeneity of data; (3) safety analyses were completely based on RCTs and their LTEs, limiting the interpretability due to selection bias of clinical trial patient populations, which are only partly comparable to the general population; (4) RoB is difficult to assess in conference abstracts (and was therefore not assessed). Possibly, data of conference abstracts of trials with poor study design and/or inconsistent or incomplete results may therefore never get published in peer-reviewed journals. However, in advance of the meeting, critical questions regarding the SLR could be discussed with members of the task force with long-standing experience in clinical trials of JAKi, including efficacy and safety analyses, and rechecked in the literature when needed.

This SLR formed the basis for the formulation of the points to consider for the treatment of IMIDs with JAKi

and for the definition of the levels of evidence and strengths of recommendations of each item.¹⁰³

Author affiliations

- ¹Abteilung Für Rheumatologie, Medizinische Universität Wien Universitätsklinik Für Innere Medizin III, Wien, Austria
- ²Medicine 3, Division of Rheumatology, Medizinische Universität Wien, Wien, Austria
- ³Griffith University School of Medicine, Gold Coast, Australia
- ⁴Rheumatology, Charité Medical Faculty Berlin, Berlin, Germany
- ⁵Hopital Cochin, Rheumatology, Université Paris Descartes Faculté De Médecine Site Cochin, Paris, France
- ⁶Metroplex Clinical Research Center, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, USA
- ⁷Sigmund Freud Private University Vienna, Wien, Austria
- ⁸Institute of Infection, Immunity & Inflammation, University of Glasgow, Glasgow, UK
- ⁹University of Glasgow, Glasgow, UK
- ¹⁰Rheumatology, Keio Univ, School of Medicine, Tokyo, Japan
- ¹¹Abteilung Für Gastroenterologie, Medizinische Universität Wien Universitätsklinik Für Innere Medizin III, Wien, Austria
- ¹²Oregon Health & Science University, Portland, Oregon, USA
- ¹³Patient Research Partner, EULAR, Zaltbommel, Netherlands
- ¹⁴Division of Dermatology and Venereology, Geneva University Hospitals, Geneva, Switzerland
- ¹⁵Center for Personalized Health, Feinstein Institutes for Medical Research, Northwell Health, Manhasset, New York, USA
- ¹⁶Rheumatology, LUMC, Leiden, Netherlands

Contributors All authors contributed and finally approved the current manuscript.

Funding This study was supported by grants from AbbVie and Lilly. The companies had no influence on the selection of participants, were not present at any of the meetings and had no influence on the contents of the present paper.

Competing interests AK: Speakers bureau: Bristol-Myers Squibb, Celgene, Eli Lilly, Merck Sharp and Dohme, Novartis, Pfizer; non-financial support: Gilead. JSS: Amgen, AbbVie, AstraZeneca, Astro, BMS, Celgene, Glaxo, ILTOO, Janssen, Merck-Serono, MSD, Novartis-Sandoz, Pfizer, Roche-Chugai, Samsung, UCB. PN: AbbVie, BMS, UCB, Lilly, Gilead/Galapagos, Pfizer, GSK, Roche, Sanofi, Janssen, MSD, Novartis, Boehringer-Ingelheim, Celgene, Samsung. TD: AbbVie, BMS, Celgene, Eli Lilly, Janssen, EMD Merck-Serono, Galapagos, Gilead, Novartis, Roche, Samsung, UCB. MD: AbbVie, Biogen, Celgene, Janssen, Lilly, Novartis, Merck, Pfizer, Sanofi-Aventis, UCB. RF: Consultant: AbbVie, Acea, Akros, Amgen BMS, Celltrion, Gilead, GSK, Jansen, Eli Lilly, Novartis, Pfizer, Samsung, Sanofi-Aventis, Tahio, UCB; Data Safety Monitoring Boards EMDSerano, Celltrion; Clinical Trial Grants: AbbVie, Acea, Akros, Amgen, AstraZeneca, BMS, Gilead, GSK, Janssen, Eli Lilly, Novartis, Pfizer, Regeneron, Sanofi-Aventis, UCB. KG has received consultancy and lecture fees from Novartis, Pfizer and Roche and investigational grants from Roche. IBM has received research funding or honoraria from AbbVie, AstraZeneca, Celgene, GSK, Lilly, Boehringer, Pfizer, Janssen, Novartis, UCB, BMS, Sanofi. TT: AbbVie GK, Astellas, Asahi Kasei, Chugai, Daiichi Sankyo, Eisai, Mitsubishi Tanabe, Pfizer Japan, Nippon Kayaku and Takeda. MT: speaker fees from Bristol-Myers Squibb (BMS), Falk Foundation, Gilead, Intercept and Merck Sharp & Dohme (MSD); advisory board fees from Albiro, Boehringer Ingelheim, BiomX, Falk Pharma GmbH, GENFIT, Gilead, Intercept, MSD, Novartis, Phenex, and Regulus; travel grants from AbbVie, Falk, Gilead, and Intercept; and research grants from Albiro, CymaBay, Falk, Gilead, Intercept, MSD, and Takeda. He is also coinventor of patents on the medical use of norUDCA filed by the Medical University of Graz. KW: Research grants from BMS, Pfizer; Consulting fees: AbbVie, BMS, Eli Lilly, Galapagos, Gilead, Pfizer, UCB, Regeneron, GSK, and Roche; MdW has received honoraria for consultancies and speaking through Stichting Tools from AbbVie, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, Roche. W-HB has received a research grant from Pfizer and honoraria for advice from AbbVie, Alimirall, BMS, Celgene, Janssen, Leo, Lilly, Novartis and UCB. LF: Nothing to declare. DvdH: Consulting fees: AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Cyxone, Daiichi, Eisai, Eli Lilly, Galapagos, Gilead, GSK, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, UCB Pharma, Director of Imaging Rheumatology BV.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Andreas Kerschbaumer <http://orcid.org/0000-0002-6685-8873>

Peter Nash <http://orcid.org/0000-0002-2571-788X>

Thomas Doerner <http://orcid.org/0000-0002-6478-7725>

Roy Fleischmann <http://orcid.org/0000-0002-6630-1477>

Iain B McInnes <http://orcid.org/0000-0003-4449-8501>

Maarten de Wit <http://orcid.org/0000-0002-8428-6354>

Desirée van der Heijde <http://orcid.org/0000-0002-5781-158X>

REFERENCES

- Kremer JM, Bloom BJ, Breedveld FC, *et al*. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. *Arthritis Rheum* 2009;60:1895–905.
- Genovese MC, Kremer J, Zamani O, *et al*. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med* 2016;374:1243–52.
- Genovese MC, Smolen JS, Weinblatt ME, *et al*. Efficacy and safety of ABT-494, a selective JAK-1 inhibitor, in a phase IIb study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Rheumatol* 2016;68:2857–66.
- Westhovens R, Taylor PC, Alten R, *et al*. Filgotinib (GLPG0634/GS-6034), an oral JAK1 selective inhibitor, is effective in combination with methotrexate (MTX) in patients with active rheumatoid arthritis and insufficient response to MTX: results from a randomised, dose-finding study (DARWIN 1). *Ann Rheum Dis* 2017;76:998–1008.
- Mease P, Hall S, FitzGerald O, *et al*. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. *N Engl J Med* 2017;377:1537–50.
- van der Heijde D, Deodhar A, Wei JC, *et al*. Tofacitinib in patients with ankylosing spondylitis: a phase II, 16-week, randomised, placebo-controlled, dose-ranging study. *Ann Rheum Dis* 2017;76:1340–7.
- Wallace DJ, Furie RA, Tanaka Y, *et al*. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet* 2018;392:222–31.
- Papp KA, Menter A, Strober B, *et al*. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a phase 2b randomized placebo-controlled dose-ranging study. *Br J Dermatol* 2012;167:668–77.
- De Bruin-Weller MS, Guttman-Yassky E, Forman SB, *et al*. Effects of upadacitinib on atopic dermatitis signs, symptoms and patient-reported outcomes from a phase IIb randomized, placebo-controlled trial. *Br J Dermatol* 2018;179:e13.
- Guttman-Yassky E, Thaci D, Pangan AL, *et al*. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2020;145:877–84.
- Sandborn WJ, Ghosh S, Panes J, *et al*. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. *N Engl J Med* 2012;367:616–24.
- Sandborn WJ, Feagan B, Panes J, *et al*. Safety and efficacy of upadacitinib (ABT-494), an oral JAK1 inhibitor, as induction therapy in patients with Crohn's disease: results from celest. *United Eur Gastroenterol J* 2017;5:A3–A4.
- Panes J, Sandborn WJ, Loftus EV, *et al*. Efficacy and safety of upadacitinib maintenance treatment for moderate to severe Crohn's disease: results from the CELEST study. *J Crohn's Colitis* 2018;12:S238–S239.
- Sandborn WJ, Feagan BG, Loftus EV Jr., *et al*. Efficacy and safety of upadacitinib in a randomized trial of patients with Crohn's disease. *Gastroenterology* 2020.
- Solimani F, Meier K, Ghoreschi K. Emerging topical and systemic JAK inhibitors in dermatology. *Front Immunol* 2019;10:2847.
- van der Heijde D, Aletaha D, Carmona L, *et al*. 2014 update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8–13.
- Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- Kahl L, Patel J, Layton M, *et al*. Safety, tolerability, efficacy and pharmacodynamics of the selective JAK1 inhibitor GSK2586184 in patients with systemic lupus erythematosus. *Lupus* 2016;25:1420–30.
- Lee EB, Fleischmann R, Hall S, *et al*. Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med* 2014;370:2377–86.
- van der Heijde D, Tanaka Y, Fleischmann R, *et al*. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis Rheum* 2013;65:559–70.
- van der Heijde D, Strand V, Tanaka Y, *et al*. Tofacitinib in combination with methotrexate in patients with rheumatoid arthritis: clinical efficacy, radiographic and safety outcomes from the 24-month phase 3 ORAL scan study. *Arthritis Rheumatol* 2019;22:22.
- Tanaka Y, Suzuki M, Nakamura H, *et al*. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Care Res (Hoboken)* 2011;63:1150–8.
- Fleischmann R, Cutolo M, Genovese MC, *et al*. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. *Arthritis Rheum* 2012;64:617–29.
- Kremer JM, Cohen S, Wilkinson BE, *et al*. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. *Arthritis Rheum* 2012;64:970–81.
- Kremer J, Li ZG, Hall S, *et al*. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2013;159:253–61.
- Tanaka Y, Takeuchi T, Yamanaka H, *et al*. Efficacy and safety of tofacitinib as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study. *Mod Rheumatol* 2015;25:514–21.
- Tanaka Y, Sugiyama N, Toyozumi S, *et al*. Modified- versus immediate-release tofacitinib in Japanese rheumatoid arthritis patients: a randomized, phase III, non-inferiority study. *Rheumatology (Oxford)* 2019;58:70–9.
- Burmester GR, Blanco R, Charles-Schoeman C, *et al*. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet* 2013;381:451–60.
- Fleischmann R, Kremer J, Cush J, *et al*. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med* 2012;367:495–507.
- van Vollenhoven RF, Fleischmann R, Cohen S, *et al*. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med* 2012;367:508–19.
- 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.
- 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.
- Fleischmann R, Pangan AL, Mysler E, *et al*. A phase 3, randomized, double-blind study comparing upadacitinib to placebo and to adalimumab, in patients with active rheumatoid arthritis with inadequate response to methotrexate. 2018 ACR/ARHP Annual Meeting Chicago, USA; 2018: Arthritis & Rheumatology; 2018.
- Fleischmann R, Pangan AL, Song IH, *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.
- 35 Bachelez H, van de Kerkhof PC, Strohal R, *et al.* Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. *Lancet* 2015;386:552–61.
 - 36 Fleischmann R, Schiff M, van der Heijde D, *et al.* Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. *Arthritis Rheumatol* 2017;69:506–17.
 - 37 Tanaka Y, Emoto K, Cai Z, *et al.* Efficacy and safety of baricitinib in Japanese patients with active rheumatoid arthritis receiving background methotrexate therapy: a 12-week, double-blind, randomized placebo-controlled study. *J Rheumatol* 2016;43:504–11.
 - 38 Dougados M, van der Heijde D, Chen YC, *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.
 - 39 Hu J, Bao C, Li X, *et al.* Efficacy and safety of baricitinib in MTX-IR patients with rheumatoid arthritis: 52 week results from a phase 3 study (RA-balance). Annals of the Rheumatic Diseases Conference: annual European congress of rheumatology, EULAR 2018 Netherlands. 2018; 77 (Supplement2): 969–970
 - 40 Yue Y, Hu J, Bao C, *et al.* Patient-reported outcomes from a phase 3 study (RA-BALANCE) of baricitinib versus placebo in rheumatoid arthritis. International Journal of Rheumatic Diseases Conference: 20th Asia Pacific League of Associations for Rheumatology Congress, APLAR 2018 Taiwan (republic of china). 2018; 21 (Supplement1): 40.
 - 41 Takeuchi T, Genovese MC, Haraoui B, *et al.* Dose reduction of baricitinib in patients with rheumatoid arthritis achieving sustained disease control: results of a prospective study. *Ann Rheum Dis* 2018.
 - 42 Takeuchi T, Genovese MC, Haraoui B, *et al.* Dose reduction of baricitinib in patients with rheumatoid arthritis achieving sustained disease control: results of a prospective study. *Ann Rheum Dis* 2019;78:171–8.
 - 43 van Vollenhoven R, Takeuchi T, Pangan AL, *et al.* A phase 3, randomized, controlled trial comparing upadacitinib monotherapy to MTX monotherapy in MTX-naïve patients with active rheumatoid arthritis - ACR meeting abstracts. 2018 ACR/ARHP Annual Meeting Chicago, USA; 2018: Arthritis & Rheumatology; 2018.
 - 44 Smolen J, Cohen S, Emery P, *et al.* Upadacitinib as monotherapy: a phase 3 randomised controlled double-blind study in patients with active rheumatoid arthritis and inadequate response to methotrexate. Annals of the rheumatic diseases Conference: annual European congress of rheumatology, EULAR 2018, Netherlands. 2018; 77(Supplement2): 67–68.
 - 45 Smolen JS, Pangan AL, Emery P, *et al.* Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. *Lancet* 2019;393:2303–11.
 - 46 Burmester GR, Kremer JM, Van den Bosch F, *et al.* Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2018;391:2503–12.
 - 47 Tanaka Y, Takeuchi T, Yamaoka K, *et al.* A phase 2b/3 randomised, placebo-controlled, double-blind study of upadacitinib, a selective jak1 inhibitor, in Japanese patients with active rheumatoid arthritis and inadequate response to conventional synthetic DMARDs. Annals of the rheumatic diseases Conference: annual European congress of rheumatology, EULAR 2018, Netherlands. 2018; 77 (Supplement2): 991–992.
 - 48 Kameda H, Takeuchi T, Yamaoka K, *et al.* Efficacy and safety of upadacitinib in Japanese patients with rheumatoid arthritis (SELECT-SUNRISE): a placebo-controlled phase IIb/III study. *Rheumatology (Oxford)* 2020.
 - 49 Kremer JM, Emery P, Camp HS, *et al.* A phase IIb study of ABT-494, a selective JAK-1 inhibitor, in patients with rheumatoid arthritis and an inadequate response to anti: tumor necrosis factor therapy. *Arthritis Rheumatol* 2016;68:2867–77.
 - 50 Genovese MC, Fleischmann R, Combe B, *et al.* Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. *Lancet* 2018;391:2513–24.
 - 51 Kavanaugh A, Kremer J, Ponce L, *et al.* Filgotinib (GLPG0634/GS-6034), an oral selective JAK1 inhibitor, is effective as monotherapy in patients with active rheumatoid arthritis: results from a randomised, dose-finding study (DARWIN 2). *Ann Rheum Dis* 2017;76:1009–19.
 - 52 Vanhoutte F, Mazur M, Voloshyn O, *et al.* Efficacy, safety, pharmacokinetics, and pharmacodynamics of filgotinib, a selective JAK-1 inhibitor, after short-term treatment of rheumatoid arthritis: results of two randomized phase IIA trials. *Arthritis Rheumatol* 2017;69:1949–59.
 - 53 Fleischmann RM, Damjanov NS, Kivitz AJ, *et al.* A randomized, double-blind, placebo-controlled, twelve-week, dose-ranging study of decernotinib, an oral selective JAK-3 inhibitor, as monotherapy in patients with active rheumatoid arthritis. *Arthritis Rheumatol* 2015;67:334–43.
 - 54 Genovese MC, van Vollenhoven RF, Pacheco-Tena C, *et al.* VX-509 (Decernotinib), an oral selective JAK-3 inhibitor, in combination with methotrexate in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2016;68:46–55.
 - 55 Genovese MC, Yang F, Ostergaard M, *et al.* Efficacy of VX-509 (decernotinib) in combination with a disease-modifying antirheumatic drug in patients with rheumatoid arthritis: clinical and MRI findings. *Ann Rheum Dis* 2016;75:1979–83.
 - 56 Takeuchi T, Tanaka Y, Iwasaki M, *et al.* Efficacy and safety of the oral Janus kinase inhibitor peficitinib (ASP015K) monotherapy in patients with moderate to severe rheumatoid arthritis in Japan: a 12-week, randomised, double-blind, placebo-controlled phase IIb study. *Ann Rheum Dis* 2016;75:1057–64.
 - 57 Genovese MC, Greenwald M, Coddling C, *et al.* Peficitinib, a JAK inhibitor, in combination with limited conventional synthetic disease-modifying antirheumatic drugs in the treatment of moderate-to-severe rheumatoid arthritis. *Arthritis Rheumatol* 2017;69:932–42.
 - 58 Kivitz AJ, Gutierrez-Urena SR, Poiley J, *et al.* Peficitinib, a JAK inhibitor, in the treatment of moderate-to-severe rheumatoid arthritis in patients with an inadequate response to methotrexate. *Arthritis Rheumatol* 2017;69:709–19.
 - 59 Tanaka Y, Takeuchi T, Tanaka S, *et al.* Efficacy and safety of the novel oral janus kinase (JAK) inhibitor, peficitinib (ASP015K), in a phase 3, double-blind, placebo-controlled, randomized study of patients with RA who had an inadequate response to DMARDs. 2018 ACR/ARHP Annual Meeting Chicago, USA; 2018: Arthritis & Rheumatology; 2018.
 - 60 Tanaka Y, Takeuchi T, Tanaka S, *et al.* Efficacy and safety of peficitinib (ASP015K) in patients with rheumatoid arthritis and an inadequate response to conventional DMARDs: a randomised, double-blind, placebo-controlled phase III trial (RAJ3). *Ann Rheum Dis* 2019;78:1320–32.
 - 61 Takeuchi T, Tanaka Y, Tanaka S, *et al.* Efficacy and safety of the novel oral Janus kinase (JAK) inhibitor, peficitinib (ASP015K), in a phase 3, double-blind, placebo-controlled, randomized study of patients with RA who had an inadequate response to methotrexate. 2018 ACR/ARHP Annual Meeting Chicago, USA; 2018: Arthritis & Rheumatology; 2018.
 - 62 Takeuchi T, Tanaka Y, Tanaka S, *et al.* Efficacy and safety of peficitinib (ASP015K) in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III randomised, double-blind, placebo-controlled trial (RAJ4) in Japan. *Ann Rheum Dis* 2019;78:1305–19.
 - 63 Gladman D, Rigby W, Azevedo VF, *et al.* Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. *N Engl J Med* 2017;377:1525–36.
 - 64 Mease P, Coates LC, Helliwell PS, *et al.* Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial. *Lancet* 2018;392:2367–77.
 - 65 van der Heijde D, Baraliakos X, Gensler LS, *et al.* Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis (TORTUGA): results from a randomised, placebo-controlled, phase 2 trial. *Lancet* 2018;392:2378–87.
 - 66 Papp KA, Menter MA, Abe M, *et al.* Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two randomized, placebo-controlled, phase III trials. *Br J Dermatol* 2015;173:949–61.
 - 67 Zhang J, Tsai TF, Lee MG, *et al.* The efficacy and safety of tofacitinib in Asian patients with moderate to severe chronic plaque psoriasis: a phase 3, randomized, double-blind, placebo-controlled study. *J Dermatol Sci* 2017;88:36–45.
 - 68 Bissonnette R, Iversen L, Sofen H, *et al.* Tofacitinib withdrawal and retreatment in moderate-to-severe chronic plaque psoriasis: a randomized controlled trial. *Br J Dermatol* 2015;172:1395–406.
 - 69 Papp KA, Menter MA, Raman M, *et al.* A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis. *Br J Dermatol* 2016;174:1266–76.

- 70 Bissonnette R, Luchi M, Fidelus-Gort R, *et al.* A randomized, double-blind, placebo-controlled, dose-escalation study of the safety and efficacy of INCB039110, an oral Janus kinase 1 inhibitor, in patients with stable, chronic plaque psoriasis. *J Dermatological Treat* 2016;27:332–8.
- 71 Papp K, Gordon K, Thaci D, *et al.* Phase 2 trial of selective tyrosine kinase 2 inhibition in psoriasis. *N Engl J Med* 2018;379:1313–21.
- 72 Bissonnette R, Papp KA, Poulin Y, *et al.* Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. *Br J Dermatol* 2016;175:902–11.
- 73 Nakagawa H, Nemoto O, Igarashi A, *et al.* Efficacy and safety of topical JTE-052, a Janus kinase inhibitor, in Japanese adult patients with moderate-to-severe atopic dermatitis: a phase II, multicentre, randomized, vehicle-controlled clinical study. *Br J Dermatol* 2018;178:424–32.
- 74 Guttman-Yassky E, Silverberg JI, Nemoto O, *et al.* Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. *J Am Acad Dermatol* 2018;1:1.
- 75 Guttman-Yassky E, Page K, Pavel AB, *et al.* Selective oral JAK3 and TYK2/JAK1 kinase inhibitors both demonstrate significant hair-growth compared to placebo and improvement of hair-associated keratins in patients with moderate-to-severe alopecia areata. *Exp Dermatol* 2018;27:52–3.
- 76 Sandborn WJ, Su C, Sands BE, *et al.* Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2017;376:1723–36.
- 77 Sandborn WJ, Ghosh S, Panés J, *et al.* Efficacy and safety of upadacitinib as an induction therapy for patients with moderately-to-severely active ulcerative colitis: data from the phase 2b study u-achieve. *United Eur Gastroenterol J* 2018;6:A74–A75.
- 78 Sandborn WJ, Ghosh S, Panes J, *et al.* Efficacy of upadacitinib in a randomized trial of patients with active ulcerative colitis. *Gastroenterology* 2020.
- 79 Sands BE, Sandborn WJ, Feagan BG, *et al.* Peficitinib, an oral Janus kinase inhibitor, in moderate-to-severe ulcerative colitis: results from a randomised, phase 2 study. *J Crohns Colitis* 2018;12:1158–69.
- 80 Sandborn WJ, Ghosh S, Panes J, *et al.* A phase 2 study of tofacitinib, an oral Janus kinase inhibitor, in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2014;12:1485–1493.e1482.
- 81 Panes J, Sandborn WJ, Schreiber S, *et al.* Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. *Gut* 2017;16:16.
- 82 Vermeire S, Schreiber S, Petryka R, *et al.* Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial. *Lancet* 2017;389:266–75.
- 83 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.
- 84 FDA briefing document arthritis advisory committee meeting April 23, 2018. 2019. Available <https://www.fda.gov/media/112372/download> (accessed 24 May 2020)
- 85 EMA confirms Xeljanz to be used with caution in patients at high risk of blood clots. 2019. Available <https://www.ema.europa.eu/en/news/ema-confirms-xeljanz-be-used-caution-patients-high-risk-blood-clots> (accessed 24 May 2020)
- 86 Safety study of tofacitinib versus tumor necrosis factor (TNF) inhibitor in subjects with rheumatoid arthritis. 2020. Available <https://clinicaltrials.gov/ct2/show/NCT02092467> (accessed 24 May 2020)
- 87 Highlights of prescribing information - Xeljanz (tofacitinib). 2019. Available https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203214s0181bl.pdf (accessed 24 May 2020)
- 88 Summary of product characteristics - Xeljanz (tofacitinib). 2020 (cited 24 May 2020); Available https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf
- 89 Summary of product characteristics - Olumiant (baricitinib). 2019 (cited 24 May 2020); Available https://www.ema.europa.eu/en/documents/product-information/olumiant-epar-product-information_en.pdf
- 90 Highlights of prescribing information - Olumiant (baricitinib). 2019. Available https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207924s0001bl.pdf (accessed 24 May 2020)
- 91 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.
- 92 Sandborn WJ, Panes J, D'Haens GR, *et al.* Safety of tofacitinib for treatment of ulcerative colitis, based on 4.4 years of data from global clinical trials. *Clin Gastroenterol Hepatol* 2018;23:23.
- 93 Strober BE, Gottlieb AB, van de Kerkhof PCM, *et al.* Benefit-risk profile of tofacitinib in patients with moderate-to-severe chronic plaque psoriasis: pooled analysis across six clinical trials. *Br J Dermatol* 2019;180:67–75.
- 94 Winthrop KL, Lebowitz M, Cohen AD, *et al.* Herpes zoster in psoriasis patients treated with tofacitinib. *J Am Acad Dermatol* 2017;77:302–9.
- 95 Winthrop KL, Melmed GY, Vermeire S, *et al.* Herpes zoster infection in patients with ulcerative colitis receiving tofacitinib. American journal of gastroenterology conference: 82nd annual scientific meeting of the American College of Gastroenterology United states. 2017; 112 (Supplement 1):S327–S328.
- 96 Winthrop KL, Melmed GY, Vermeire S, *et al.* Herpes zoster infection in patients with ulcerative colitis receiving tofacitinib. Journal of Crohn's and Colitis Conference: 13th congress of European Crohn's and Colitis Organisation, ECCO 2018 Austria. 2018; 12 (Supplement 1): S364.
- 97 Charles-Schoeman C, Wicker P, Gonzalez-Gay MA, *et al.* Cardiovascular safety findings in patients with rheumatoid arthritis treated with tofacitinib, an oral Janus kinase inhibitor. *Semin Arthritis Rheum* 2016;46:261–71.
- 98 Wu JJ, Strober BE, Hansen PR, *et al.* Effects of tofacitinib on cardiovascular risk factors and cardiovascular outcomes based on phase III and long-term extension data in patients with plaque psoriasis. *J Am Acad Dermatol* 2016;75:897–905.
- 99 Sands BE, Taub PR, Feagan BG, *et al.* The effect of tofacitinib on serum lipids and cardiovascular safety in patients with ulcerative colitis: results from the tofacitinib ulcerative colitis clinical programme. *J Crohn's Colitis* 2018;12:S023.
- 100 Smolen JS, Genovese MC, Takeuchi T, *et al.* Safety profile of baricitinib in patients with active rheumatoid arthritis with over 2 years median time in treatment. *J Rheumatol* 2019;46:7–18.
- 101 Clowse ME, Feldman SR, Isaacs JD, *et al.* Pregnancy outcomes in the tofacitinib safety databases for rheumatoid arthritis and psoriasis. *Drug Saf* 2016;39:755–62.
- 102 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.
- 103 Nash P, Kerschbaumer A, Dörner T, *et al.* Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement. *Ann Rheum Dis* 2020.