Venous Thromboembolism Risk With JAK Inhibitors: A Meta-Analysis

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Objective. JAK inhibitor therapies are effective treatment options for immune-mediated inflammatory diseases (IMIDs), but their use has been limited by venous thromboembolism (VTE) risk warnings from licensing authorities. We undertook this study to evaluate the VTE risk of JAK inhibitors in patients with IMIDs.

Methods. Systematic searches of Medline and Embase databases from inception to September 30, 2020 were conducted. Phase II and phase III double-blind, randomized controlled trials (RCTs) of JAK inhibitors at licensed doses were included in our analyses. RCTs with no placebo arm, long-term extension studies, post hoc analyses, and pooled analyses were excluded. Three researchers independently extracted data on exposure to JAK inhibitors or placebo and VTE events (e.g., pulmonary embolism [PE] and deep vein thrombosis [DVT]) and assessed study quality.

Results. A total of 42 studies were included, from an initial search that yielded 619. There were 6,542 JAK inhibitor patient exposure years (PEYs) compared to 1,578 placebo PEYs. There were 15 VTE events in the JAK inhibitor group and 4 in the placebo group. The pooled incidence rate ratios (IRRs) of VTE, PE, and DVT in patients receiving JAK inhibitors were 0.68 (95% confidence interval [95% CI] 0.36–1.29), 0.44 (95% CI 0.28–0.70), and 0.59 (95% CI 0.31–1.15), respectively.

Conclusion. This meta-analysis of RCT data defines the VTE risk with JAK inhibitors as a class in IMID patients. The pooled IRRs do not provide evidence that support the current warnings of VTE risk for JAK inhibitors. These findings will aid continued development of clinical guidelines for the use of JAK inhibitors in IMIDs.

INTRODUCTION

The introduction of biologic therapies in the early 2000s led to a phase change in the management of immune-mediated inflammatory diseases (IMIDs) including inflammatory arthropathies, psoriasis, and inflammatory bowel disease. More recently, small molecule inhibitors have been added to the growing list of therapeutic methods (1). The JAK/STAT pathway is a key modulator of the inflammatory response (2). To date, 4 JAK inhibitors have been licensed for the treatment of rheumatoid arthritis (RA) and/or psoriatic arthritis (PsA) in North America and/or Europe: tofacitinib (RA, PsA), baricitinib (RA), upadacitinib (RA), and filgotinib (RA). Licensing for other IMID indications will likely follow.

Concerns have been raised regarding the risk of venous thromboembolism (VTE) with JAK inhibitor therapy. In 2017, the Food and Drug Administration (FDA) added a black box warning to the Summary of Product Characteristics (SPC) for baricitinib, stating that it should be used with caution in patients at increased risk for VTE (3). This was followed by a similar warning from the FDA and the European Medicines Agency (EMA) in 2019 for tofacitinib 10 mg prescribed twice daily for the treatment of ulcerative colitis (UC). It was recommended that clinicians avoid prescribing these medications to patients at a higher risk for VTE (4,5). These warnings were based upon a small number of randomized controlled trials (RCTs). Given the rarity of VTEs, individual trials had insufficient power to confirm or exclude a significant difference in risk (6).

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Previous studies have demonstrated an increased risk of VTE events in patients with an IMID diagnosis (7), with a biologic explanation that the inflammatory burden creates a prothrombotic state. Consequently, controlling inflammation with effective IMID treatment could reduce VTE risk. JAK inhibitors may be a special case, as this class of therapy modulates the JAK2 receptor, which is involved in myelopoiesis and the production of platelets (8). Transient increases in platelet counts have been observed following JAK inhibitor therapy initiation, although these were not predictive of VTE (9). There remains considerable uncertainty about any link between JAK inhibitor therapy and VTE events.

Clarification of VTE risk with JAK inhibitor therapy is crucial to informing physicians who are considering this strategy, given that these drugs offer to patients clinically meaningful improvements in disease activity. Accordingly, we set out to evaluate the link between JAK inhibitor therapy and VTE events.

METHODS

Databases and search strategy. We performed a systematic search of studies in humans up to November 30, 2019, with no specified start date. The following search was performed using the Medline and Embase databases: “tofacitinib or baricitinib or upadacitinib or filgotinib” and “rheumatoid or psoriatic using the Medline and Embase databases: “tofacitinib or baricitinib or upadacitinib or filgotinib” and “rheumatoid or psoriatic arthritis or psoriasis or ankylosing spondylitis or axial spondyloarthritis or ulcerative colitis or crohns.” The search was limited by the following constraints: RCTs, English language, and human study participants. The initial search was conducted by 2 researchers (MY and AM) with verification from a third (MA). The study was registered with an international prospective register of systematic reviews (Prospero 2020 CRD42020161645).

Eligibility criteria. Eligible studies were original reports of phase II and phase III RCTs of JAK inhibitor therapy, with a placebo comparator arm. Studies were excluded if they were not double-blind. Long-term extension (LTE) studies, post hoc analyses, and pooled analyses were excluded after checking to ensure that the original reports had been included in the search. Conference abstracts, case reports, letters to the editor, review articles, case-control studies, and cohort studies were all excluded. Doses of JAK inhibitors (tofacitinib 5 mg and 10 mg twice daily, baricitinib 2 mg and 4 mg once daily, upadacitinib 15 mg once daily) that were licensed when the literature search was performed (September 2020) were considered. Doses of filgotinib (200 mg and 100 mg) were also included, having just received marketing authorization from the European Commission for the treatment of RA.

Study selection. Two researchers independently screened study titles and abstracts and selected eligible studies. Disagreement was discussed, with a third researcher resolving any differences over a study’s inclusion. Data were extracted from eligible studies into a data collection table by 3 researchers. Studies that were subsequently found to be ineligible after a full transcript review were excluded. National clinical trial numbers of included studies were compared to ensure that there was no duplication.

Data extraction. The following information was extracted from each study: citation details, author list, study design, underlying condition, study duration, study location, number of patients, inclusion/exclusion criteria, drug doses, patient characteristics, adverse events (AEs), and serious AEs (SAEs). Deep vein thrombosis (DVT) and pulmonary embolism (PE) were considered VTE events. Details about these events were extracted from full-text articles, supplementary materials, and appendices. To ensure that all VTE events were identified, an additional review of the tabular summary of original RCT data in the ClinicalTrials.gov database was performed. All data included in the meta-analysis were checked by 3 independent researchers.

Assessment of bias. Each study undergoing data extraction was assessed for quality using the Cochrane risk-of-bias tool (10).

Statistical analysis. Analyses were performed using Stata 16 software. Patient exposure years (PEYs) were calculated using sample size and study duration for the treatment and placebo groups, assuming a per-protocol model. Per-protocol analyses are generally considered more appropriate for safety outcomes.

Crude incidence rates of PE, DVT, and overall VTE events were calculated for each study. Overall VTE event numbers were calculated as a sum of PE and DVT events. In RCTs, reported PEs are coded as SAES; therefore, complete reporting was assumed. DVTs may be coded as an AE or SAE. Most RCTs have an AE reporting threshold. This can lead to VTE events not being reported. For example, in an RCT with an AE reporting threshold of 5%, where 2 DVT events occurred in 100 patients receiving a study drug, these would not be included in the trial findings on ClinicalTrials.gov.

For the primary analyses of VTE and DVT event rates, only studies with an explicit publication of VTE/DVT event rates were included. To address the reporting threshold issue, the impact of VTE reporting uncertainty was explored with 2 sensitivity analyses. In the first analysis, it was assumed that 0 DVT events had occurred when the number of events was not explicitly reported due to falling below the threshold. In the second analysis, it was assumed that the maximum number of DVTs could have occurred and remained under the reporting threshold in the treatment arm only. A further sensitivity analysis was conducted to identify differences between diagnostic groups.

The pooled relative risk of VTE with JAK inhibitor therapy versus placebo was estimated with incidence rate ratios (IRRs) and 95% confidence intervals (95% CIs), using the Mantel-Haenszel
random-effects method for binary data. Estimates are graphically displayed in forest plots.

RESULTS

Study screening. The electronic database search identified 619 articles. Following a title and abstract review, 513 articles were excluded for not meeting eligibility criteria. A total of 106 articles underwent a full-text review. This led to a further 64 articles being excluded for not meeting eligibility criteria, leaving a total of 42 eligible articles. The systematic literature review flow diagram is detailed in Figure 1.

Study characteristics. A total of 42 studies were included in this meta-analysis, of which 20 were phase II and 20 were phase III RCTs. Two studies were described as phase II/III. Articles were published from 2009 to 2020, with 12,207 patients receiving JAK inhibitor therapy and 5,062 receiving a placebo. Twenty-nine studies were RCTs of patients with inflammatory arthropathies (RA, PsA, ankylosing spondylitis), 6 focused on inflammatory bowel disease (UC, Crohn's disease), and 7 focused on psoriasis. Of the 42 studies, 31 (74%) included patients with previous or current exposure to other immunosuppressive therapies. Details about all included RCTs can be found in Table 1. AE reporting thresholds ranged from 0% to 5%.

Risk of bias. Risk of bias for this sample of studies was typically low. Forty studies (95%) were randomized and double-blind (with regard to participants and assessors), with 33 studies (79%) considered to have an overall low risk of bias. Further details on individual study bias assessment can be found in Supplementary Table 1 (available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.41580/abstract).

Meta-analysis. A total of 15 VTE events (10 PEs, 5 DVTs) were reported in patients receiving JAK inhibitor therapy over 6,542 PEYs, equivalent to a rate of 0.23 per 100 PEYs (95% CI 0.12–0.38). In comparison, we observed a rate of 4 VTE events (2 PEs, 2 DVTs) in patients receiving placebo over 1,578 PEYs, equivalent to a rate of 0.25 per 100 PEYs (95% CI 0.07–0.73).

The pooled IRRs of VTE, PE, and DVT events in patients receiving JAK inhibitors were 0.68 (95% CI 0.36–1.29), 0.44 (95% CI 0.25–0.73), and 0.44 (95% CI 0.25–0.73), respectively.

Figure 1. Flow diagram of the systematic search.
| Author, year, study name (ref.) | Study location | Dose included in analyses, mg | Phase of study | Disease | No. of subjects receiving JAK inhibitors | No. of subjects receiving placebo | Age, mean ± SD years |
|--------------------------------|----------------|-------------------------------|----------------|---------|------------------------------------------|---------------------------------|------------------------|
| Tofacitinib                    |                |                               |                |         |                                          |                                 |                        |
| Gladman et al, 2017, OPAL Beyond (11) | Worldwide | 5, 10                          | III            | PsA     | 263                                       | 131                             | 50 ± 12                |
| Sandborn et al, 2012 (12)      | Worldwide | 10                             | II             | UC      | 33                                         | 48                              | 43.2 ± 12.8†           |
| Tanaka et al, 2015 (13)        | Japan         | 5, 10                          | II             | RA      | 105                                        | 53                              | 52.6 ± 10.9†           |
| Sandborn et al, 2014 (14)      | Worldwide | 5                              | II             | CD      | 20                                         | 34                              | 37 ± 12                |
| Panes et al, 2017 (15)         | Worldwide | 5, 10                          | II             | CD      | 172                                        | 92                              | 39 ± 12                |
| Sandborn et al, 2017, OCTAVE Induction 1 (16) | Worldwide | 10                             | III            | UC      | 476                                        | 122                             | 41.3 ± 14.1†           |
| Sandborn et al, 2017, OCTAVE Induction 2 (16) | Worldwide | 10                             | III            | UC      | 429                                        | 112                             | 41.1 ± 13.5†           |
| Bechelez et al, 2015 (17)      | Worldwide | 5, 10                          | III            | Psoriasis | 662                                       | 108                             | 44 ± 12                |
| Papp et al, 2015, OPT Pivotal 1 (18) | Worldwide | 5, 10                          | III            | Psoriasis | 723                                       | 177                             | 45 ± 13                |
| Papp et al, 2015, OPT Pivotal 2 (18) | Worldwide | 5, 10                          | III            | Psoriasis | 763                                       | 196                             | 45 ± 13                |
| Van Vollenhoven et al, 2012 (19) | Worldwide | 5, 10                          | III            | RA      | 513                                        | 108                             | 53 ± 12                |
| Van der Heijde et al, 2019, ORAL Scan (20) | Worldwide | 5, 10                          | III            | RA      | 797                                        | 160                             | 53 ± 12                |
| Kremer et al, 2009 (21)        | Worldwide | 5                              | II             | RA      | 61                                         | 65                              | 51 ± 12                |
| Mease et al, 2017, OPAL Broaden (22) | Worldwide | 5, 10                          | III            | PsA     | 316                                        | 105                             | 48 ± 12                |
| Zhang et al, 2017 (23)         | Asia          | 5, 10                          | III            | Psoriasis | 178                                       | 88                              | 41 ± 12                |
| Winthrop et al, 2017 (24)      | US            | 5                              | II             | RA      | 55                                         | 57                              | 62 ± 8                 |
| Van der Heijde et al, 2017 (25) | Worldwide | 5, 10                          | III            | AS      | 104                                        | 51                              | 42 ± 12                |
| Burmester et al, 2013 (26)     | Worldwide | 5, 10                          | III            | RA      | 267                                        | 132                             | 55.0 ± 11.3            |
| Kremer et al, 2013 (27)        | Worldwide | 5, 10                          | III            | RA      | 633                                        | 159                             | 52.3 ± 11.6            |
| Papp et al, 2012 (28)          | US, Canada    | 5                              | IIb            | Psoriasis | 147                                       | 50                              | 44 ± 12.6†             |
| Fleischmann et al, 2012 (29)   | Worldwide | 5, 10                          | IIb            | RA      | 272                                        | 59                              | 53.3 ± 12.6            |
| Kremer et al, 2012 (30)        | Worldwide | 5, 10                          | IIb            | RA      | 438                                        | 69                              | 52 ± 12.8†             |
| Fleischmann et al, 2012 (31)   | Worldwide | 5, 10                          | III            | RA      | 488                                        | 122                             | 51.8 ± 11.8            |
| Tanaka et al, 2011 (32)        | Japan         | 5, 10                          | II             | RA      | 108                                        | 28                              | 51.3 ± 10.7            |
| Krueger et al, 2016 (33)       | US            | 10                             | II             | Psoriasis | 9                                         | 3                              | 45.6 ± 13.3            |
| Baricitinib                    |                |                               |                |         |                                          |                                 |                        |
| Keystone et al, 2015 (34)      | Worldwide | 2.4                            | IIb            | RA      | 203                                        | 98                              | 51.2 ± 11.71           |
| Taylor et al, 2017, RA-BEAM (35) | Worldwide | 4                              | III            | RA      | 487                                        | 488                             | 53.3 ± 12.1            |
| Papp et al, 2016 (36)          | US, Canada, Japan | 2.4                          | IIb            | Psoriasis | 237                                       | 34                              | 47.3 ± 13.3            |
| Tanaka et al, 2016 (37)        | Japan         | 2.4                            | IIb            | RA      | 96                                         | 49                              | 53.6 ± 11.8            |
| Genovese et al, 2016, RA-BEACON (38) | Worldwide | 2.4                            | III            | RA      | 351                                        | 176                             | 55.7 ± 11.0            |
| Dougados et al, 2017, RA-BUILD (39) | Worldwide | 2.4                            | III            | RA      | 456                                        | 228                             | 51.8 ± 12.3            |

(Continued)
### Table 1. (Cont’d)

| Author, year, study name (ref.) | Study location | Dose included in analyses, mg | Phase of study | Disease | No. of subjects receiving JAK inhibitors | No. of subjects receiving placebo | Age, mean ± SD years |
|---------------------------------|----------------|-------------------------------|----------------|---------|-----------------------------------------|-------------------------------|---------------------|
| Van der Heijde et al, 2019, SELECT-AXIS 1 (40) | Worldwide | 15 | II/III | AS | 93 | 94 | 47 ± 12.8† |
| Fleischmann et al, 2019, SELECT-COMPARE (41) | Worldwide | 15 | III | RA | 651 | 651 | 53.9 ± 12.07 |
| Genovese et al, 2018, SELECT-BEYOND (42) | Worldwide | 15 | III | RA | 329 | 169 | 57.1 ± 11.42 |
| Burmester et al, 2018, SELECT-NEXT (43) | Worldwide | 15 | III | RA | 440 | 221 | 55.7 ± 11.65 |
| Sandborn et al, 2020, U-ACHIEVE (44) | Worldwide | 15 | IIb | UC | 49 | 46 | 47 (range 22–71) |
| Kameda et al, 2020, SELECT-SUNRISE (45) | Japan | 15 | IIb/III | RA | 49 | 49 | 56.0 ± 12.5 |
| Westhovens et al, 2017, DARWIN 1 (46) | Worldwide | 100, 200 | IIb | RA | 171 | 86 | 52 ± 1.4† |
| Kavanaugh et al, 2017 DARWIN 2 (47) | Worldwide | 100, 200 | II | RA | 139 | 72 | 53 ± 1.4† |
| Genovese et al, 2019, FINCH 2 (48) | Worldwide | 100, 200 | III | RA | 301 | 148 | 55 ± 1.9‡ |
| Mease et al, 2018, EQUATOR (49) | Worldwide | 200 | II | PsA | 65 | 66 | 49 ± 12.2 |
| Van der Heijde et al, 2018, TORTUGA (50) | Worldwide | 200 | II | AS | 58 | 58 | 41 ± 11.6† |

* RCTs = randomized controlled trials; PsA = psoriatic arthritis; UC = ulcerative colitis; RA = rheumatoid arthritis; CD = Crohn’s disease; AS = ankylosing spondylitis.
† For treatment group.
‡ For most populous region.
CI 0.28–0.70), and 0.59 (95% CI 0.31–1.15), respectively. Further details about the individual studies can be found in Figures 2–4.

Sensitivity analyses explored the impact of missing data due to reporting thresholds. If it was assumed that there were no events for which no information on DVT was reported, the odds ratio was 0.42 (95% CI 0.26–0.65). Conversely, if it was assumed that the maximum number of DVTs occurred in the treatment arm (while remaining below the reporting threshold), the odds ratio increased to 1.34 (95% CI 0.91–1.97). Additional details are shown in Supplementary Figures 1 and 2 (on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.41580/abstract). Repeat analyses stratified by diagnosis did not identify any differences from the overall analysis.

**DISCUSSION**

This meta-analysis defines the risk of VTE with JAK inhibitor therapy in IMID patients across a large number of RCTs. Overall, the pooled-effect estimates confirm that VTE risk is unlikely to be substantially increased in those receiving JAK inhibitors compared to those receiving placebo. However, given the low event rates, and thus less precise data, a true effect involving a small increase in risk cannot be ruled out, nor can small-to-large protective effects.

Currently, a product warning is in place for JAK inhibitors regarding VTE risk (3–5). For baricitinib, this was based on regulatory review of RCTs and an LTE study, which identified an imbalance in the number of events in JAK inhibitor therapy arms (51), whereas for tofacitinib, it was based upon interim findings from an as-yet-unpublished LTE (52). Our findings do not confirm this association.

The likely explanation for the discrepancy in findings is the exclusion of LTEs from our meta-analysis and the pooling of results across different JAK inhibitor therapies. We intentionally excluded LTE studies as they are open-label trials with no placebo arm. This widens the discrepancy between placebo and treatment arm PEYs, which is relevant due to the rarity of VTE as an outcome. Even with LTE study data excluded, our meta-analysis provided 4,780 more PEYs in treatment arms compared to placebo. Adding LTE study data amplifies this difference substantially.

It is important to consider the context within which the excess VTE risk has been observed. The mechanism by which JAK inhibitors could lead to an altered VTE risk is difficult to reconcile biologically. IMIDs confer an increased risk of VTE, a relationship that is associated with disease severity (53). Controlling the inflammatory burden should theoretically offset any excess VTE risk attributable to the disease. In polycythemia rubra vera, a condition associated with significantly increased rates of VTE, ruxolitinib (a JAK2 inhibitor) was associated with a reduced VTE rate, according to a recent meta-analysis (54).

However, it may be that there are 2 effects present, operating in different directions. The JAK signaling pathways encompass a series of homodimer and heterodimer transmembrane receptors that have a broad range of activating ligands and downstream
signaling effects. From a hematopoiesis perspective, blocking JAK2 in particular could be expected to suppress platelet growth by the inhibition of thrombopoietin signaling (55). Paradoxically, platelet counts transiently increase in the first weeks of baricitinib treatment (9).

A further consideration is that we are assuming that the mechanistic explanation for a link between JAK inhibitor therapy and VTE risk would be mediated by the JAK/STAT signaling pathway. In the era of biologic therapies, where target specificity is perfect, this would be a reasonable assumption. In contrast, the modulation of the JAK pathway uses small-molecule inhibitors, and it is possible that there are off-target effects on other signaling pathways that are as yet unknown.

An important additional study that examines the long-term safety of tofacitinib in patients at increased risk for cardiovascular disease is ongoing. Interim analysis of the data resulted in an FDA and EMA advisory warning regarding the use of tofacitinib at a higher dose (10 mg twice daily) because of an increased risk of infection and VTE (52). Caveats about this research include that there is selection bias toward high-risk patients, and the dose tested is greater than the licensed dose for some indications, including RA. This study is powered based on an event-driven sample size (i.e., the study will terminate only after a predetermined number of people have experienced the primary end point, as opposed to studies that have fixed sample sizes for a predefined follow-up period). When the full study is published, it will provide important additional information pertaining to the risk of VTE with JAK inhibitor therapy. Future registry data will also be critical.

The present study is the most extensive meta-analysis, to date, of VTE risk with JAK inhibitor therapy, spanning licensed doses across multiple IMIDs. A further strength of this work was the ability to identify granular data on both AEs and SAEs from all studies in ClinicalTrials.gov, providing confidence in event ascertainment.
There were limitations to our study, as well. The studies included in this meta-analysis are RCTs with tight inclusion/exclusion criteria that limit the external validity of findings. Patients at the highest risk for VTE, such as older patients and those with multiple morbidities, may be underrepresented in the RCTs, so the extrapolation of findings among these populations must be done cautiously. This could explain the lower rate of VTEs in the placebo group (0.25 per 100 PEYs) compared to that reported in IMID observational studies (0.35 per 100 PEYs) (56).

Our analyses used aggregate data, and it was not possible to adopt a full survival model approach using individual patient-level data and time to event analyses, which would have added power and potentially allowed for additional subanalyses exploring differences between drugs and doses.

Reports from a number of studies did not explicitly show event rates for DVT. We modeled this in sensitivity analyses, by comparing the 0-event rate and the maximum-event rate that would have remained under the reporting threshold on ClinicalTrials.gov. The former offers the most conservative estimate of risk, suggesting that JAK inhibitor therapy reduces DVT risk by >60%, and the latter offers the most punitive estimate, suggesting a 30% increase in DVT risk with JAK inhibitors. These estimates are extreme, with the true value likely lying between the two. The width between these estimates (IRR 0.42 and IRR 1.34, respectively) highlights the importance of RCTs publishing full data sets with no reporting threshold for AEs. It is important to acknowledge uncertainty, particularly when considering earlier RCTs published prior to the scientific community’s awareness of a possible link between JAK inhibitors and VTE.

The RCTs included have relatively short durations of follow-up, with a notably shorter exposure window for patients receiving placebo compared to those receiving JAK inhibitors, as illustrated by the total PEYs: 1,578 versus 6,542. In pharmacovigilance studies, AEs and SAEs typically follow an exponential decay distribution, with event frequencies higher shortly after drug initiation. Occasionally, events do not follow this pattern and increase in frequency with cumulative drug exposure. As we do not know the time-varying nature of VTE risk, it is possible—if there is a cumulative effect with JAK inhibitor therapy—that we would not have observed this.

Our analyses were unable to include consideration for concomitant medication, such as glucocorticoids. There is an established risk between glucocorticoid therapy and VTE risk (57), and it is possible that there are associations between glucocorticoids and other AEs, as has been described with infections (58). We did not have access to patient-level data (including markers of disease activity and individual treatment modifications) and could not adjust for these in our analyses. It is plausible that patients receiving placebo had higher disease activity and ongoing active inflammation, increasing their VTE risk compared to patients receiving JAK inhibitors.

The data presented here do not provide evidence in support of the current warnings of VTE risk for typical trial patients offered JAK inhibitors. These findings will aid in the continued development of clinical guidelines for the use of JAK inhibitor therapies in IMIDs. VTE represents only one aspect of the safety profile of this class of

Figure 4. Forest plot of deep vein thrombosis events. See Figure 2 for definitions. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.41580/abstract.
therapy, and these results should be considered in the wider context of the risk and benefit of JAK inhibitors in different therapeutic areas.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Yates had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Yates, Mootoo, Cope, Norton, Galloway.

Acquisition of data. Yates, Mootoo, Adas, Rampes, Patel, Oureshi.

Analysis and interpretation of data. Yates, Adas, Bechman, Cope, Norton, Galloway.

REFERENCES

1. Bechman K, Yates M, Galloway JB. The new entries in the therapeutic armamentarium: the small molecule JAK inhibitors [review]. Pharmacol Res 2019;147:104392.

2. Renauld JC. Class II cytokine receptors and their ligands: key antiviral and inflammatory modulators [review]. Nat Rev Immunol 2003;3:667–76.

3. Olumiant (baricitinib) prescribing information. Indianapolis (IN): Lilly; 2018.

4. European Medicines Agency. EMA confirms Xeljanz to be used with caution in patients at high risk of blood clots. November 2019. URL: https://www.ema.europa.eu/en/news/ema-confirms-xeljanztocautioni n-patients-high-risk-blood-clots#:~:text=EMA%20has%20concluded%20that%20Xeljanz,%high%20risk%20of%20bloodclots.

5. 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.

6. Zöller B, Liu W, Wang W, Fidler T, Woods B, Levine RL, et al. Inhibition of JAK2 suppresses myelopoiesis and atherosclerosis in Apoe-/- mice. Cardiovasc Drugs Ther 2020;34:145–52.

7. Kremer JM, Bloom BJ, Breedveld FC, Coombs JH, Fletcher MP, Gruben D, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: results of a double-blind, placebo-controlled phase II trial of three dosage levels of CP-690,550 versus placebo [published erratum appears in Arthritis Rheum 2012;64:1487]. Arthritis Rheum 2009;60:1895–905.

8. Mease P, Hall S, FitzGerald O, van der Heijde D, Merola JF, Avila-Zapata F, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. N Engl J Med 2017;377:1537–50.

9. Zhang J, Tsai TF, Lee MG, Zheng M, Wang G, Jin H, 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;83:36–45.

10. Winthrop KL, Wouters AG, Choy EH, Soma K, Hodge JA, Nduaka CI, et al. The safety and immunogenicity of live zoster vaccination in patients with rheumatoid arthritis before starting tofacitinib: a randomized phase II trial. Arthritis Rheumatol 2017;69:1969–77.

11. Van der Heijde D, Deodhar A, Wei JC, Drescher E, Fleishaker D, Hendrikx T, 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.

12. Burmester GR, Blanco R, Schoeneman C, Wollenhaupt J, Zerbini C, Benda B, 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.

13. Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, 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.

14. Sandborn WJ, Ghosh S, Panes J, Vranic I, Wang W, Niezychowski W, et al. A phase 2 study of tofacitinib, an oral Janus kinase inhibitor, in patients with Crohn’s disease. Clin Gastroenterol Hepatol 2014;12:1485–93.

15. Panés J, Sandborn WJ, Schreiber S, Sands BE, Vermeire S, D’Haens G, et al. Tofacitinib for induction and maintenance therapy of Crohn’s disease: results of two phase Ib/2b randomised placebo-controlled trials. Gut 2017;66:1049–59.

16. Sandborn WJ, Su C, Sands BE, D’Haens GR, Vermeire S, Schreiber S, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2017;376:1723–36.

17. Bachelez H, van de Kerkhof PC, Strohal R, Kubanov A, Valenzuela F, Lee JH, 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.

18. Papp KA, Menter MA, Abe M, Elewski B, Feldman SR, Gottlieb AB, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two randomised, placebo-controlled, phase III trials. Br J Dermatol 2015;173:949–61.

19. Van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012;367:508–19.

20. Van der Heijde D, Strand V, Tanaka Y, Keystone E, Kremer J, Zerbini CA, et al. Tofacitinib in combination with methotrexate in patients with rheumatoid arthritis: clinical efficacy, radiographic, and safety outcomes from a twenty-four–month, phase III study. Arthritis Rheumatol 2019;71:878–91.
(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.

30. Kremer JM, Cohen S, Wilkinson BE, Connell CA, French JL, Gomez-Reino J, 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.

31. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med 2012;367:495–507.

32. Tanaka Y, Suzuki M, Nakamura H, Toyozumi S, Zwillsh SH, Tofacitinib Study Investigators. 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;63:1150–9.

33. Krueger J, Clark JD, Suárez-Fariñas M, Fuentes-Duculan J, Cueto I, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Ann Rheum Dis 2015;74:339–40.

34. Keystone EC, Taylor PC, Drescher E, Schlichting DE, Beattie SD, et al. A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis: a randomized phase 2 study. J Allergy Clin Immunol 2016;137:1070–90.

35. Keystone EC, Taylor PC, Drescher E, Schlichting DE, Beattie SD, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Ann Rheum Dis 2015;74:339–40.

36. Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, del Carmen Morales L, Gonzaga JR, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med 2017;376:652–62.

37. Papp KA, Menter MA, Raman M, Disch D, Schlichting DE, Baettie SD, Berclaz PY, et al. Safety and efficacy of baricitinib in 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. Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, et al. Efficacy and safety of baricitinib in Japanese patients with active rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 2017;76:998–1008.

39. Van der Heijde D, Baraliakos X, Genovese MC, Ruiz-Velasco A, Durez P, et al. Efficacy and safety of baricitinib in patients with active psoriatic arthritis (EQUATOR); results from a randomised, dose-controlled, phase 2 trial. Lancet 2018;392:2367–77.

40. Mease P, Coates LC, Hellwell PS, Stanislawchuk M, Rychlewskia-Hanczewska A, Dudek A, et al. Efficacy and safety of baricitinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR); results from a randomised, dose-controlled, phase 2 trial. Lancet 2018;392:2367–77.

41. US Food and Drug Administration. FDA briefing information for the April 23, 2018 meeting of the Arthritis Advisory Committee. URL: https://www.fda.gov/media/112372/download.

42. Pfizer. Sponsor. Safety study of tofacitinib versus tumor necrosis factor (TNF) inhibitor in subjects with rheumatoid arthritis. ClinicalTrials.gov identifier: NCT02092467; 2020.

43. Davies R, Galloway JB, Watson KD, Lunt M, Symmons DP, Hyrich KL. Venous thrombotic events are not increased in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2011;70:1831–4.

44. Sandborn WJ, Ghosh S, Panes J, Schreiber S, D’Haens G, Tanida S, et al. Efficacy of upadacitinib in a randomized trial of patients with active ulcerative colitis. Gastroenterology 2020;158:2139–49.

45. Kameda H, Takeuchi T, Yamaoka K, Oribe M, Kawano M, Zhou Y, et al. Efficacy and safety of upadacitinib in Japanese patients with rheumatoid arthritis (SELECT-SUNRISE): a placebo-controlled phase Ib/ll study. Rheumatology (Oxford) 2020;59:3303–13.

46. Westhovens R, Taylor PC, Alten R, Pavlova D, enriquez-Sosa F, Mazur M, et al. Filgotinib (GLPG0634/GS-6034), an oral selective JAK1 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.

47. Kavaugha A, Kremer J, Ponce L, Cseuz R, Reshoket OV, Stanislawchuk M, 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.

48. Genovese MC, Kallinjen K, Gottenberg JE, Mozaffarian N, Bartok B, Matzkes F, et al. Effect of filgotinib vs placebo on clinical response in patients with moderate to severe rheumatoid arthritis refractory to disease-modifying antirheumatic drug therapy: the FINCH 2 randomised clinical trial. JAMA 2019;322:315–25.