Efficacy and Safety of JAK Inhibitors for Rheumatoid Arthritis: A Meta-Analysis

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Abstract: Background: More and more trials have been conducted. We aimed to assess the efficacy and safety of different JAKinibs in RA. Methods: A systematic search of randomized controlled trials (RCTs) with JAKinib treatment in RA published in the Medline, Embase, and Cochrane databases up to May 2021 was performed. Results: 37 trials involving 15,174 patients were identified. Pooled analysis revealed that JAKinibs were associated with significant therapeutic improvement in RA patients as determined by ACR20 (RR = 2.03, 95% CI: 1.85 to 2.28) and HAQ-DI (MD = −0.31, 95% CI: −0.33 to −0.28) over placebo. Compared to placebo, JAKinib treatment was also associated with more adverse events (RR = 1.10, p < 0.001; RR = 1.29, p < 0.001; RR = 1.59, p = 0.02). Baricitinib and upadacitinib were related to more frequent adverse events (RR = 1.10; 95% CI: 1.01, 1.21; RR = 1.19; 95% CI: 1.11, 1.28) and infection (RR = 1.22; 95% CI: 1.09, 1.37; RR = 1.38; 95% CI: 1.22, 1.56), whereas only baricitinib was associated with more herpes zoster (RR = 3.15; 95% CI: 1.19, 8.33). Conclusions: JAKinibs were superior to placebo for improving signs, symptoms, and health-related quality of life in RA patients at short term, whereas the overall risk of adverse events and infections were greater with baricitinib and upadacitinib, and a higher risk of herpes zoster was only associated with baricitinib. More trials are needed to investigate the long-term safety.

Keywords: rheumatoid arthritis; JAK; inhibitors; meta-analysis; systematic review

1. Introduction

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis in adults, which is characterized by chronic synovial joint inflammation, driven by immune system dysregulation [1]. The disease has a negative effect on quality of life and imposes a substantial economic burden on patients and society [2,3].

The cornerstone of RA treatment is conventional disease-modifying drugs (csDMARDs), like methotrexate (MTX). Over the last few decades, the evolving therapeutic landscape, like monoclonal antibodies or soluble receptors blocking pro-inflammatory cytokines such as TNF or IL-6 for RA, has seen major breakthroughs. However, many biological therapies are routinely administered in combination with nonbiological DMARDs, especially methotrexate. Although the outcome for patients with RA has improved in recent years, only approximately half of patients meet the criteria for low disease activity (≤3.2 on the on a 28-joint disease activity score using the erythrocyte sedimentation rate DAS28-4 (ESR)) or remission (<2.6 on the DAS28-4 (ESR)) [4]. In addition, their own side-effect profiles limited their use in patients [5]. Therefore, the development of orally available small molecules that inhibit intracellular signaling of cytokines and growth factors is an unmet need.
Janus kinases (JAKs) are a family of non-receptor tyrosine kinases linked to the intracellular domain of many cytokine receptors [6]. JAK phosphorylates cytokine-bound receptors, which triggers the intracellular molecular signaling that eventually modulates expression of genes involved in inflammation and tissue remodeling [6–8]. Studies have demonstrated that continuous activation of JAK/signal transduction and activation of transcription (STAT) signaling in RA synovial joints could induce a high level of matrix metalloproteinase gene expression, apoptosis of chondrocytes, and most prominently, apoptosis resistance of inflammatory cells in the synovial tissue, supporting that therapeutics targeting the JAK pathway may provide symptomatic relief for RA [9].

To date, a new field of clinical trials has been investigating the blockade of JAKkinase activity for the treatment of RA. Four isoforms of JAK were identified, including JAK1, JAK2, JAK3, and TYK2. Several JAK inhibitors (JAKinibs) with differing degrees of specificity for JAKs are in clinical trial. Tofacitinib is considered a pan-JAKinib, which mainly inhibits JAK1 and JAK3. Baricitinib is selective for JAK1 and JAK2, and peficitinib for JAK1 and JAK3. Filgotinib and upadacitinib are JAK1-selective agents, whereas decernotinib is a selective JAK3 inhibitor [1,5,10]. Now, tofacitinib, baricitinib, and upadacitinib have recently been approved by the FDA for the treatment of RA [11–13]. However, differences in efficacy and safety were seen, and which drug is relatively safe and effective is unclear. To help inform this debate, we conducted a systematic review and meta-analysis of all placebo-controlled randomized trials evaluating JAKinibs for RA to determine their pooled efficacy and safety relative to placebo.

2. Methods
2.1. Literature Searches and Study Selection
PubMed, Embase, and the Cochrane CENTRAL Library were searched without language restriction from inception to 5 May 2021 using the search terms “tofacitinib” or “CP-690550” or “baricitinib” or “LY3009104” or “Olumiant” or “upadacitinib” or “decernotinib” or “VX-509” or “peficitinib” or “ASP015K” or “filgotinib” or “GLPG0634” or “JAK inhibitors” and “rheumatoid arthritis’. All of the studies identified were reviewed independently by three investigators (FW, XT and MZ). Discrepancies were resolved through consensus and consultation with a third reviewer (FML) if needed. An example of the search strategy used to identify relevant trials published in Embase is presented in Table S2.

2.2. Inclusion and Exclusion Criteria
Eligible clinical trials were as follows: (1) adult patients with a diagnosis of RA and treated with JAKinibs; (2) double-blind, randomized, placebo-controlled studies; and (3) outcomes including the American College of Rheumatology 20% (ACR 20), ACR50, ACR70, Health Assessment Questionnaire—Disability Index (HAQ-DI, in which scores range from 0 to 3, with higher scores indicating greater disability), and adverse events. Studies presenting duplicate data or no safety data were excluded. No restrictions were applied to the length of follow-up and language.

2.3. Data Extraction and Outcome Measures
Data extraction was performed in duplicate by two independent reviewers (FW, XT, and MZ) using a standardized electronic data collection form. The following variables were extracted: authors, year of publication, study type, name of the study, clinicaltrials.gov number, doses used, number of patients, duration of study periods, and outcome measures. The ACR20 response was defined as at least 20% improvement in both the tender joint count and the swollen joint count and at least 20% improvement in three of five other core set measures: patient’s assessment of pain, patient’s global assessment of disease activity, physician’s global assessment of disease activity, patient’s assessment of physical function, or acute-phase reactant value [14]. The proportion of patients experiencing any adverse events (AE), serious AE (SAE), infections, and serious infections were extracted. Additionally, we captured the number of patients with herpes zoster (HZ), upper respiratory
tract infections, thromboembolic events, MACE (major adverse cardiovascular events), and neoplasms.

2.4. Statistical Analyses

We calculated mean differences (MD) and risk ratio (RR). Study-level RRs or MDs with 95% confidence intervals (CI) were calculated in accordance with the intention-to-treat principle. Fixed-effects models were used when heterogeneity between studies was non-significant, and random-effects were used for analyses with significant heterogeneity. A p-value of less than 0.05 was considered statistically significant. For dose-ranging studies, data from all treatment doses were pooled. Heterogeneity was quantified using $I^2$ (range, 0% to 100%; $>50\%$ indicates evidence of heterogeneity) [15,16]. In addition, the quality of the included trials and the risk of bias were assessed by using elements included in the Cochrane collaboration tool for assessing risk of bias. The funnel plot was determined and was used to evaluate the publication bias in our meta-analysis [17,18]. In addition, event rates for ACR20, ACR50, ACR70, AEs, SAEs, infections, serious infections, HZ, upper respiratory tract infections, thromboembolic events, MACE, and neoplasm among all studied outcomes were calculated and the numbers needed to treat (NNTs) or the numbers needed to harm (NNH). The NNT was equal to $1/|\text{risk difference}|$ according to Cochrane Handbook for Systematic Reviews of Interventions. Review Manager (RevMan version 5.3; The Cochrane Collaboration, n, Oxford, UK) was used for statistical analysis. The Grading of Recommendations Assessment, Development and Evaluation’s (GRADE’s) official GRADEpro software tool www.gradepro.org (accessed on 5 May 2021) was used to evaluate the certainty of evidence.

3. Results

3.1. Study Characteristics

A total of 2139 manuscripts were identified (Figure 1): 568 from Medline, 779 from Embase, and 792 from The Cochrane Library. After removal of duplicates, we evaluated 1318 studies, of which 1079 were excluded based on title and abstract review. A full text assessment of the remaining 239 records was conducted. Finally, 36 studies (37 trials in total) carried out in different countries and on different ethnic backgrounds were included in this meta-analysis [19–54]. Seven trials were conducted in only one country, whereas the rest were performed in multiple countries.

A total of 37 RCTs and 15,174 participants in total were enrolled in this systematic review and meta-analysis, including 12 tofacitinib, 6 baricitinib, 6 upadacitinib, 3 decernotinib, 5 peficitinib, and 5 filgotinib. The baseline patient characteristics of trials are shown in Table 1. Duration of treatment ranged from 4 to 24 weeks. The characteristics of the included trials are summarized in Table 1. Key findings are summarized in Table 2.

### Table 1. Characteristics of included trials. Only data including placebo and the doses of interest are selected; therefore, the selected study duration is different from the original research.

| Author (Year)       | Region                     | Trial Identifier | Follow-Up | No. of Patients | Dose                                      |
|---------------------|-----------------------------|------------------|-----------|----------------|-------------------------------------------|
| Tofacitinib         |                             |                  |           |                |                                           |
| Kremer 2009 [19]    | Worldwide                   | NCT00147498      | 6 weeks   | 264            | 5, 15, 30 mg twice daily                  |
| Tanaka 2011 [20]    | Japan                       | NCT00603512      | 12 weeks  | 140            | 1, 3, 5, 10, 15 mg twice daily            |
| Vollenhoven 2012    | America and Europe          | NCT00853385      | 24 weeks  | 513            | 5, 10 mg twice daily                      |
| Fleischmann 2012[a] | Worldwide                   | NCT00550446      | 24 weeks  | 274            | 1, 3, 5, 10, 15 mg twice daily            |
| Fleischmann 2012 b | Worldwide                   | NCT00814307      | 24 weeks  | 611            | 5, 10 mg twice daily                      |
| Kremer 2012 [24]    | America and Europe          | NCT00413660      | 12 weeks  | 507            | 1, 3, 5, 10, 15 mg twice daily; 20 mg/day |
| Burmester 2013 [25] | America and Europe          | NCT00960440      | 12 weeks  | 399            | 5, 10 mg twice daily                      |
Table 1. Cont.

| Author (Year)  | Region          | Trial Identifier | Follow-Up | No. of Patients | Dose                        |
|----------------|-----------------|------------------|-----------|-----------------|-----------------------------|
| Kremer 2013 [26] | Worldwide       | NCT00856544      | 24 weeks  | 792             | 5, 10 mg twice daily        |
| Heijde 2013 [27] | Worldwide       | NCT00847613      | 24 weeks  | 797             | 5, 10 mg twice daily        |
| Boyle 2015 [28]  | Worldwide       | NCT00976599      | 4 weeks   | 29              | 10 mg twice daily           |
| Tanaka 2015 [29]  | Japan           | NCT00687193      | 12 weeks  | 317             | 1, 3, 5, 10, 15 mg twice daily, 20 mg/day |
| Kremer 2015 [30]  | Worldwide       | NCT01484561      | 6 weeks   | 148             | 10 mg twice daily           |

Baricitinib

| Author (Year)  | Region          | Trial Identifier | Follow-Up | No. of Patients | Dose                        |
|----------------|-----------------|------------------|-----------|-----------------|-----------------------------|
| Keystone 2015 [31] | Worldwide      | NCT01185353      | 12 weeks  | 301             | 1, 2, 4, 8 mg once daily    |
| Tanaka 2016 [32]  | Japan           | NCT01469013      | 12 weeks  | 145             | 1, 2, 4, 8 mg once daily    |
| Genovese 2016 [33] | Worldwide      | NCT01721044      | 24 weeks  | 527             | 2, 4 mg once daily          |
| Taylor 2017 [34]  | Worldwide       | NCT01710558      | 24 weeks  | 1307            | 4 mg once daily             |
| Dougados 2017 [35] | Worldwide      | NCT01721057      | 24 weeks  | 684             | 2, 4 mg once daily          |
| Li 2020 [36]     | China, Brazil, Argentina | NCT02265705 | 12 weeks  | 290             | 4 mg once daily             |

Upadacitinib

| Author (Year)  | Region          | Trial Identifier | Follow-Up | No. of Patients | Dose                        |
|----------------|-----------------|------------------|-----------|-----------------|-----------------------------|
| Kremer 2016 [37] | Worldwide       | NCT01960855      | 12 weeks  | 276             | 3, 6, 12, 18 mg twice daily |
| Genovese 2016 [38] | Worldwide      | NCT02066389      | 12 weeks  | 299             | 3, 6, 12, 18 mg twice daily, 24 mg once daily |
| Burmester 2018 [39] | Worldwide      | NCT02675426      | 12 weeks  | 661             | 15, 30 mg once daily        |
| Genovese 2018 [40] | Worldwide      | NCT02706847      | 24 weeks  | 499             | 15, 30 mg once daily        |
| Fleischmann 2019 [41] | Worldwide | NCT02629159      | 12 weeks  | 1304            | 15 mg once daily            |
| Kameda 2020 [42]  | Japan           | NCT02720523      | 12 weeks  | 148             | 15, 30 mg once daily        |

Decernotinib

| Author (Year)  | Region          | Trial Identifier | Follow-Up | No. of Patients | Dose                        |
|----------------|-----------------|------------------|-----------|-----------------|-----------------------------|
| Fleischmann 2015 [43] | Worldwide      | NCT01052194      | 12 weeks  | 204             | 25, 50, 100, 150 mg twice daily |
| Genovese 2016a [44] | Worldwide      | NCT01754935      | 12 weeks  | 43              | 100, 200, 300 mg once daily  |
| Genovese 2016b [45] | Worldwide      | NCT2011-004419-22 | 24 weeks  | 358             | 100, 150, 200 mg once daily, 100 mg twice daily |

Peficitinib

| Author (Year)  | Region          | Trial Identifier | Follow-Up | No. of Patients | Dose                        |
|----------------|-----------------|------------------|-----------|-----------------|-----------------------------|
| Takeuchi 2016 [46] | Japan          | NCT01649999      | 12 weeks  | 281             | 25, 50, 100, 150 mg once daily |
| Genovese 2017 [47] | Worldwide     | NCT01565655      | 12 weeks  | 289             | 25, 50, 100, 150 mg once daily |
| Kivitz 2017 [48]  | Worldwide       | NCT01554696      | 12 weeks  | 378             | 25, 50, 100, 150 mg once daily |
| Takeuchi 2019 [49] | Japan          | NCT02305849      | 12 weeks  | 519             | 100, 150 mg once daily      |
| Tanaka 2019 [50]   | Japan, Korea, Taiwan | NCT02308163 | 12 weeks  | 307             | 100, 150 mg once daily      |

Filgotinib

| Author (Year)  | Region          | Trial Identifier | Follow-Up | No. of Patients | Dose                        |
|----------------|-----------------|------------------|-----------|-----------------|-----------------------------|
| Kavanaugh 2017 [51] | Worldwide     | NCT01894516      | 24 weeks  | 283             | 50, 100, 200 mg once daily  |
| Westhovens 2017 [52] | Worldwide   | NCT01888874      | 24 weeks  | 594             | 50, 100, 200 mg once daily and twice daily |
| Vanhouotte 2017 1 [53] | Republic of Moldova | NCT01384422 | 4 weeks   | 36              | 100 mg twice daily or 200 once daily |
| Vanhouotte 2017 2 [53] | Worldwide   | NCT01668641      | 4 weeks   | 91              | 30, 75, 150, 300 mg once daily |
| Genovese 2019 [54]  | Worldwide      | NCT02873936      | 24 weeks  | 449             | 100, 200 mg once daily      |

Worldwide: more than three countries. Only data including placebo are selected; therefore, the selected study duration is different from the original research.
A total of 37 RCTs and 15,174 participants in total were enrolled in this systematic review and meta-analysis, including 12 tofacitinib, 6 baricitinib, 6 upadacitinib, 3 decernotinib, 5 peficitinib, and 5 filgotinib. The baseline patient characteristics of trials are shown in Table 1. Duration of treatment ranged from 4 to 24 weeks. The characteristics of the included trials are summarized in Table 1.

Key findings are summarized in Table 2.

Table 1. Characteristics of included trials. Only data including placebo and the doses of interest are selected; therefore, the selected study duration is different from the original research.

| Author (Year) | Region | Trial Identifier | Follow-Up | No. of Patients | Dose |
|---------------|---------|------------------|-----------|----------------|------|
| Kremer 2009 [19] | Worldwide | NCT00147498 | 6 weeks | 264 | 5, 15, 30 mg twice daily |
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| Fleischmann 2012a [22] | Worldwide | NCT00550446 | 24 weeks | 274 | 1, 3, 5, 10, 15 mg twice daily |
| Fleischmann 2012b [23] | Worldwide | NCT00814307 | 24 weeks | 611 | 5, 10 mg twice daily |

Table 2. Summary of results stratified by JAKinibs compared to placebo corresponding to respective outcomes.

| Outcomes | Studies (n) | RR | Lower 95% CI | Upper 95% CI | I² | Outcomes | Studies (n) | RR | Lower 95% CI | Upper 95% CI | I² |
|----------|-------------|----|--------------|--------------|----|----------|-------------|----|--------------|--------------|----|
| ACR-20 | All RCTs 36 | 2.03 | 1.85 | 2.23 | 65% | All RCTs 21 | 1.29 | 1.19 | 1.39 | 0% |
| Tofacitinib 11 | 2.21 | 1.86 | 2.63 | 52% | Tofacitinib 3 | 1.30 | 1.00 | 1.94 | 0% |
| Baricitinib 6 | 1.95 | 1.57 | 2.42 | 78% | Baricitinib 5 | 1.22 | 1.09 | 1.37 | 0% |
| Upadacitinib 6 | 1.99 | 1.68 | 2.36 | 64% | Upadacitinib 6 | 1.38 | 1.22 | 1.56 | 0% |
| Decernotinib 3 | 2.61 | 1.70 | 4.01 | 31% | Decernotinib 2 | 1.43 | 0.80 | 2.58 | 37% |
| Peficitinib 5 | 2.01 | 1.32 | 3.05 | 84% | Peficitinib 2 | 1.01 | 0.66 | 1.56 | 0% |
| Filgotinib 5 | 1.80 | 1.43 | 2.27 | 46% | Filgotinib 2 | 1.50 | 0.53 | 4.20 | 37% |
| ACR-50 | All RCTs 35 | 3.12 | 2.48 | 3.93 | 84% | All RCTs 33 | 3.87 | 3.02 | 4.97 | 56% |
| Tofacitinib 11 | 3.43 | 2.30 | 5.12 | 78% | Tofacitinib 11 | 4.15 | 2.21 | 7.80 | 74% |

Figure 1. Flow chart of study selection procedure.
Table 2. Cont.

| Outcomes (Studies (n)) | RR | Lower 95% CI | Upper 95% CI | f²  |
|------------------------|----|-------------|-------------|-----|
| Baricitinib            | 6  | 2.73        | 2.03        | 3.66 | 64% |
| Upadacitinib           | 6  | 2.25        | 1.12        | 4.52 | 96% |
| Decernotinib           | 3  | 4.72        | 2.48        | 8.96 | 0%  |
| Peficitinib            | 5  | 2.84        | 1.42        | 5.70 | 82% |
| Filgotinib             | 4  | 5.56        | 2.79        | 11.06| 11% |

| Outcomes (Studies (n)) | RR | Lower 95% CI | Upper 95% CI | f²  |
|------------------------|----|-------------|-------------|-----|
| Baricitinib            | 6  | 3.81        | 2.97        | 4.89 | 0%  |
| Upadacitinib           | 6  | 4.53        | 3.53        | 5.83 | 0%  |
| Decernotinib           | 3  | 4.06        | 1.50        | 10.98| 0%  |
| Peficitinib            | 5  | 3.64        | 1.32        | 10.05| 73% |
| Filgotinib             | 2  | 3.41        | 0.94        | 12.40| 45% |

**HAQ-DI Serious infections**

| Outcomes (Studies (n)) | RR | Lower 95% CI | Upper 95% CI | f²  |
|------------------------|----|-------------|-------------|-----|
| All RCTs               | 20 | −0.31       | −0.34       | −0.28| 0%  |
| Tofacitinib            | 7  | −0.34       | −0.39       | −0.28| 0%  |
| Baricitinib            | 2  | −0.24       | −0.33       | −0.15| 0%  |
| Upadacitinib           | 5  | −0.31       | −0.36       | −0.26| 0%  |
| Decernotinib           | 2  | −0.24       | −0.48       | −0.01| 72% |
| Peficitinib            | 1  | −0.22       | −0.42       | −0.02| 0%  |
| Filgotinib             | 3  | −0.33       | −0.44       | −0.22| 44% |

**Adverse events Herpes zoster**

| Outcomes (Studies (n)) | RR | Lower 95% CI | Upper 95% CI | f²  |
|------------------------|----|-------------|-------------|-----|
| All RCTs               | 34 | 1.10        | 1.05        | 1.14| 25% |
| Tofacitinib            | 11 | 1.06        | 0.98        | 1.15| 29% |
| Baricitinib            | 5  | 1.10        | 1.01        | 1.21| 48% |
| Upadacitinib           | 6  | 1.19        | 1.11        | 1.28| 7%  |
| Decernotinib           | 3  | 1.32        | 0.97        | 1.78| 40% |
| Peficitinib            | 5  | 1.04        | 0.94        | 1.16| 0%  |
| Filgotinib             | 5  | 0.96        | 0.84        | 1.10| 0%  |

**Serious adverse events Upper respiratory infection**

| Outcomes (Studies (n)) | RR | Lower 95% CI | Upper 95% CI | f²  |
|------------------------|----|-------------|-------------|-----|
| All RCTs               | 34 | 0.94        | 0.77        | 1.15| 0%  |
| Tofacitinib            | 11 | 0.74        | 0.47        | 1.18| 20% |
| Baricitinib            | 5  | 0.92        | 0.65        | 1.31| 0%  |
| Upadacitinib           | 6  | 1.72        | 0.92        | 3.25| 18% |
| Decernotinib           | 3  | 1.47        | 0.58        | 3.71| 0%  |
| Peficitinib            | 5  | 0.95        | 0.46        | 1.96| 0%  |
| Filgotinib             | 3  | 0.70        | 0.24        | 2.07| 46% |

**Thromboembolic events MACE**

| Outcomes (Studies (n)) | RR | Lower 95% CI | Upper 95% CI | f²  |
|------------------------|----|-------------|-------------|-----|
| All RCTs               | 13 | 1.04        | 0.38        | 2.84| 0%  |
| Tofacitinib            | 2  | 0.19        | 0.01        | 2.91| 35% |
| Baricitinib            | 2  | 2.38        | 0.27        | 20.84| 0% |
| Upadacitinib           | 5  | 1.65        | 0.33        | 8.35| 0%  |
| Decernotinib           | 1  | 0.77        | 0.03        | 18.52| -  |
| Peficitinib *          | 2  | -           | -           | -   | -   |
| Filgotinib             | 1  | 1.49        | 0.06        | 36.24| -  |

**Neoplasms**

| Outcomes (Studies (n)) | RR | Lower 95% CI | Upper 95% CI | f²  |
|------------------------|----|-------------|-------------|-----|
| All RCTs               | 19 | 1.70        | 0.74        | 3.89| 0%  |
| Tofacitinib            | 1  | 9.50        | 0.56        | 162.20| -  |
| Baricitinib            | 5  | 1.03        | 0.26        | 4.10| 0%  |
| Upadacitinib           | 6  | 1.50        | 0.40        | 5.54| 0%  |
| Decernotinib           | 5  | 2.92        | 0.35        | 24.20| 0%  |
| Peficitinib            | -  | -           | -           | -   | -   |
| Filgotinib *           | 2  | -           | -           | -   | -   |

* No events in placebo or JAKinib group. RR: risk ratio; CI: confidence intervals; RCT: randomized controlled trials; ACR-20: American College of Rheumatology 20%; ACR-50: American College of Rheumatology 50%; ACR-70: American College of Rheumatology 70%; HAQ-DI: Health Assessment Questionnaire—Disability Index; MACE: major adverse cardiovascular events.
3.2. Risk of Bias Assessment

All the studies included in the meta-analysis were deemed to be a low risk of bias (Figure 2A). Most studies used random sequence generation and allocation concealment. Blinding of study subjects and investigators was universally maintained by the use of placebo. All trials reported the outcome data; baselines of the subjects involved in the studies were similar. No evidence for publication bias was detected using the funnel plot (Figure 2B).

Figure 2. The risk of bias assessment and publication bias. (A) Risk of bias summary of included trials; (B) funnel plot of the included trials evaluating the effect of JAKinibs on adverse events. RR = relative risks.
3.3. Efficacy

3.3.1. ACR20, ACR50, and ACR70

All the studies reported the data of ACR20 except one [30]. The pooled effect of JAKinibs on ACR20 was significant (RR = 2.03, 95% CI: 1.85 to 2.23, \( p < 0.001 \), NNT = 4), with moderate heterogeneity (\( I^2 = 65\% \), \( p < 0.001 \)) (Figure S1). Figure S1 shows that ACR20 response was higher for decernotinib than other JAKinibs (RR = 2.61, 95% CI: 1.70 to 4.01, \( p < 0.001 \)), with minimal heterogeneity (\( I^2 = 31\% \)), but the results should be interpreted with caution due to the small number of studies involved. Filgotinib seemed to be the least effective drug in terms of ACR20 (RR = 1.80, 95% CI: 1.43 to 2.27, \( p < 0.001 \)). Certainty in the evidence was judged to be moderate, mainly because of the possibility of publication bias (Table 3). Figures S2 and S3 showed that JAKinibs were more effective than placebo on ACR50 (RR = 3.12, 95% CI: 2.48 to 3.83, \( p < 0.001 \), NNT = 5) and ACR 70 (RR = 3.87, 95% CI: 3.02 to 4.97, \( p < 0.001 \), NNT = 7), with significant heterogeneity (\( I^2 = 84\% \) and \( I^2 = 56\% \), respectively). Sensitivity analysis indicated that varied subjects among studies may contribute to the heterogeneity of ACR20 and ACR50 (Table S1).

Table 3. Summary of findings, including GRADE quality assessment of evidence from trials.

| Variables            | No. of Studies | No. of Patients | Effect                          | Quality of the Evidence (GRADE) | Quality Domains and Assessments | Importance |
|----------------------|----------------|-----------------|---------------------------------|---------------------------------|---------------------------------|------------|
|                      | JAKinibs Group | Placebo Group   | Relative Absolute (95% CI)      | NNT/NNH                         |                                 |            |
| ACR20                | 36             | 6191/10,361 (59.8%) | 1251/4255 (29.4%) | RR 2.03 (1.85 to 2.23) | 303 more per 1000 (from 250 more to 362 more) | 4          | MODERATE | Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Other: publication bias strongly suspected a Critical |
|                      |                |                 |                                 |                                 |                                 |            |
| ACR50                | 35             | 3800/10,061 (37.8%) | 551/4107 (13.4%)  | RR 3.10 (2.63 to 3.66) | 282 more per 1000 (from 219 more to 357 more) | 5          | MODERATE | Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Other: publication bias strongly suspected a Important |
| ACR70                | 33             | 1946/9963 (19.5%) | 212/4078 (5.2%)   | RR 3.87 (3.02 to 4.97) | 149 more per 1000 (from 105 more to 206 more) | 7          | MODERATE | Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Other: publication bias strongly suspected a Important |
| Adverse events       | 34             | 5735/10,181 (56.3%) | 2162/4079 (53.0%) | RR 1.10 (1.05 to 1.14) | 53 more per 1000 (from 27 more to 74 more) | 30         | HIGH      | Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Other: publication bias strongly suspected a Important |
| Serious adverse events | 34             | 322/9898 (3.2%)  | 136/4181 (3.3%)  | RR 0.94 (0.77 to 1.15) | 2 fewer per 1000 (from 7 fewer to 5 more) | 1000       | MODERATE | Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Other: publication bias strongly suspected a Important |
| Infection            | 21             | 1696/6292 (27.0%) | 695/2948 (23.6%) | RR 1.29 (1.19 to 1.39) | 68 more per 1000 (from 45 more to 92 more) | 30         | HIGH      | Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Other: none Important |
| Serious infection    | 29             | 155/9043 (1.7%)  | 37/3879 (1.0%)  | RR 1.30 (0.92 to 1.86) | 3 more per 1000 (from 1 fewer to 8 more) | 143        | HIGH      | Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Other: none Important |
| Herpes zoster        | 25             | 160/7700 (2.1%)  | 28/3533 (0.8%)  | RR 1.59 (1.09 to 2.32) | 5 more per 1000 (from 1 more to 10 more) | 77         | HIGH      | Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Other: none Important |
### Table 3. Cont.

| Variables                     | No. of Studies | JAKinibs Group | Placebo Group | Effect | Absolute (95% CI) | NNT/NNH | Quality of the Evidence (GRADE) | Quality Domains and Assessments | Importance |
|-------------------------------|----------------|----------------|---------------|--------|-------------------|--------|---------------------------------|----------------------------------|------------|
| Upper respiratory infection   | 15             | 315/5491 (5.7%)| 74/1733 (4.3%)| RR 1.26 (0.97 to 1.63) | 11 more per 1000 (from 1 more to 27 more) | 72     | ⧫⧫⧫MODERATE                     | Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Imprecision: not serious Other: publication bias strongly suspected * | Not important |
|                              |                |                |               |        |                   |        |                                 |                                   |            |
| Thromboembolic events        | 13             | 12/4455 (0.3%) | 3/2241 (0.1%) | RR 1.04 (0.38 to 2.84) | 0 fewer per 1000 (from 1 fewer to 2 more) | 500    | ⧫⧫LOW                          | Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Imprecision: serious b; Other: publication bias strongly suspected * | Important   |
|                              |                |                |               |        |                   |        |                                 |                                   |            |
| MACE                          | 16             | 20/5704 (0.4%) | 5/2735 (0.2%) | RR 1.02 (0.45 to 2.34) | 0 fewer per 1000 (from 1 fewer to 2 more) | 500    | ⧫⧫LOW                          | Risk of bias: serious Inconsistency: not serious Indirectness: not serious Imprecision: serious b; Other: publication bias strongly suspected * | Not IMPORTANT|
|                              |                |                |               |        |                   |        |                                 |                                   |            |
| Neoplasms                     | 19             | 27/5885 (0.5%) | 4/3051 (0.1%) | RR 1.70 (0.74 to 3.89) | 1 fewer per 1000 (from 0 fewer to 4 more) | 250    | ⧫⧫LOW                          | Risk of bias: serious Inconsistency: not serious Indirectness: not serious Imprecision: serious b; Other: publication bias strongly suspected * | Not IMPORTANT|

CI: confidence interval; RR: risk ratio; a publication bias, Egger’s p = 0.00; b wide confidence interval. NNT: number needed to treat; NNH: number needed to harm. MACE: major adverse cardiovascular events; ⧫: the certainty of evidence is high; ⧫⧫: the certainty of evidence is low

3.3.2. HAQ-ID

Nineteen trials totaling 8703 subjects were included. Peficitinib was evaluated in only one study. Overall, JAKinib administration produced a significant decrease in HAQ-ID (MD = −0.31, 95% CI: −0.34 to −0.28, p < 0.001) compared to placebo (Figure S4). There was no significant heterogeneity among the included studies (I² = 0%, p = 0.69). Among the subgroups, tofacitinib seemed to show the most beneficial effect on HAQ-ID (MD = −0.34, 95% CI: −0.39 to −0.28, p < 0.001), without significant heterogeneity (I² = 0%, p = 0.94).

3.4. Safety

3.4.1. AEs and SAEs

Across all studies, 7897 of 14,260 randomized patients experienced one or more AEs. The pooled RR was 1.10 (95% CI: 1.05–1.14, NNT = 30), which shows that the highest AE incidence was slightly in the JAKinib group (p < 0.001), with mild heterogeneity (I² = 25%, p = 0.09) (Figure S5). Upadacitinib seemed to show the highest trend towards increasing in any adverse events (RR = 1.19, 95% CI, 1.11–1.28, p < 0.001, I² = 7%) compared to placebo. On subgroup analysis, tofacitinib, decernotinib, peficitinib, and filgotinib seemed to show similar AEs to the placebo group (RR = 1.06, 1.32, 1.04, 0.96 p = 0.16, 0.07, 0.41, and 0.57 respectively). The GRADE quality of adverse events was judged to be high (Table 3), and the absolute effect was 53 fewer per 1000 (from 27 fewer to 74 more). A total of 34 studies evaluated SAEs, with a pooled RR of 0.94 (95% CI, 0.77–1.15, I² = 0%, NNT = 1000) (Figure S6), and subgroup analysis showed that none of the JAKinibs were associated with a trend of high SAE. Certainty in the evidence about the risks of serious adverse events was judged as moderate (Table 3).

3.4.2. Infections and Serious Infections

There were 21 studies that evaluated infections, and treatment with JAKinibs was associated with a significantly increased risk of infections (RR = 1.29, 95% CI, 1.19–1.39, p < 0.001, I² = 0%, NNT = 30) (Figure S7). Tofacitinib, decernotinib, peficitinib, and filgotinib were not associated with high incidence of infections (RR = 1.39, 1.43, 1.01, 1.50, p = 0.05,
0.23, 0.96, and 0.44, respectively), but only a small number of trials were analyzed for each. Certainty in the evidence about the risk of infections was high. Serious infections occurred in a similar proportion of patients in the placebo and JAKinib groups without heterogeneity (RR = 1.30, 95% CI, 0.92–1.86, \( p = 0.14, I^2 = 0\%\), NNT = 143) (Figure S8). Proportions of patients with serious infections were similar across all subgroups. Certainty in the evidence about the risk of serious infections was high (Table 3).

3.4.3. HZ

A total of 25 studies reported HZ. Prominent risk of HZ was observed in the JAKinib group compared to placebo (RR = 1.59, 95% CI, 1.09–2.32, \( p = 0.02, \text{NNT} = 77\)). Heterogeneity was not statistically significant (\( I^2 = 0\%\), \( p = 0.79\)) (Figure S9). However, HZ risk was higher only for baricitinib and not other JAKinibs (RR = 3.15, 95% CI, 1.19–8.33, \( p = 0.02, I^2 = 0\%\)). However, the pooled effect of JAKinibs on HZ was not significant, and baricitinib groups were excluded (RR = 1.41, 95% CI: 0.94–2.11, \( p = 0.10\)), which indicates that the baricitinib groups significantly affected the pooled results. Certainty in the evidence about the risk of herpes zoster was high (Table 3).

3.4.4. Upper Respiratory Tract Infections

Fifteen trials were included in the analysis. Overall, JAKinibs showed no significant increase in risk of upper respiratory tract infections compared with placebo (RR = 1.26, 95% CI, 0.97–1.63, \( p = 0.08, I^2 = 0\%\), \( \text{NNT} = 72\)) (Figure S10). In addition, all of these drugs resulted in a numerically but not statistically increased risk of upper respiratory tract infections (RR = 1.20, 1.22, 1.34, 1.24, 1.60, 0.89, \( p = 0.52, 0.38, 0.44, 0.78, 0.27, \) and 0.22, respectively). The certainty in the evidence was moderate (Table 3).

3.4.5. Thromboembolic Events

Only 13 trials reported thromboembolic events, and the pooled results of JAKinibs revealed no significant increased risk compared to placebo (RR = 1.04, 95% CI, 0.38–2.84, \( p = 0.94, I^2 = 0\%\), \( \text{NNT} = 500\)) (Figure S11). Unfortunately, only a few trials reported the data of this outcome, and certainty in the evidence was very low due to the wide confidence intervals and suspected publication bias (Table 3).

3.4.6. MACE

Sixteen trials reported the MACE, and the pooled results of JAKinibs revealed no significant increased risk compared to placebo (RR = 1.02, 95% CI, 0.45–2.34, \( p = 0.96, I^2 = 0\%\), \( \text{NNT} = 500\)) (Figure S12). Less than half of the trials reported the data of this outcome, and certainty in the evidence was very low due to the wide confidence intervals and suspected publication bias (Table 3).

3.4.7. Neoplasm

Nineteen trials were included in the analysis, and the pooled results of JAKinibs revealed no significant increased risk compared to placebo (RR = 1.70, 95% CI, 0.74–3.89, \( p = 0.96, I^2 = 0\%\), \( \text{NNT} = 250\)) (Figure S13). Some trials did not provide the data of this outcome, and certainty in the evidence was very low due to the wide confidence intervals and suspected publication bias (Table 3).

4. Discussion

This meta-analysis investigated the efficacy and safety of six different oral JAKinibs in the treatment of patients with RA. All JAKinibs were found to be consistently more effective than placebo. However, the safety issues should be considered with caution. Overall, JAKinibs increased the adverse events, risk of infection, and herpes zoster compared to placebo. Subgroup analysis revealed that baricitinib was the only JAKinib to show significantly higher risk of herpes zoster. Additionally, baricitinib and upadacitinib significantly increased the adverse events and infections compared to placebo.
RA is a chronic autoimmune disease characterized by systemic, destructive, and progressive inflammatory polyarthritis, driven by immune system dysregulation [14]. JAK/STAT signaling pathway is involved in the pathogenesis of inflammatory and autoimmune diseases such as RA, psoriasis, and inflammatory bowel disease [7]. Given the major role played by JAKs and STATs in the pathogenesis of autoimmunity [55,56], small molecules targeted against JAKs or JAKinibs are developed. However, only 5 mg tofacitinib taken twice daily, 2 mg baricitinib taken daily, and 15 mg upadacitinib taken daily are FDA-approved doses for the treatment of adult patients with moderately to severely active RA with a prior inadequate response or intolerance to methotrexate [57–59]. Since there were no head-to-head randomized trials to compare different JAKinibs, the evidence is inadequate for drawing robust conclusions of the benefit–risk for each JAKinib.

Previous meta-analysis [60] and network meta-analysis [61] also evaluated JAKinibs, but they only included tofacitinib, baricitinib, and upadacitinib. Consistent with the previous meta-analysis [60], a statistically significant increased risk of HZ was apparent with baricitinib. Furthermore, this study also demonstrated a notable increased risk of infections with baricitinib and upadacitinib, which was not observed in the previous meta-analysis. This is attributed to more trials of upadacitinib, which were included in this study. Consistent with the previous network meta-analysis, a notable increased risk of SAE with JAKinibs was not observed; however, that network analysis did not include AE analysis in the report and included fewer patients compared to the current study, whereas a significant increased risk of AE was observed in our study.

Based on the pooled analyses, JAKinibs could show a significant benefit in achieving ACR20 responses compared to placebo. Although decemotinib seemed to be the most effective drug followed by tofacitinib among all the JAKinibs according to the results, we had no confidence in this due to the small number of trials and patients (only three trials and 316 patients involved), as well as the relatively short duration of the trials (the longest follow-up time was 24 weeks). Anyway, these six JAKinibs showed no huge efficacy differences in terms of ACR20. With regards to HAQ-ID, the results showed that treatment with JAKinibs led to a statistically significant improvement from baseline compared to placebo. The minimal clinically important difference in HAQ-DI was defined as 0.22 or more [62,63]. Importantly, all the improvements caused by JAKinibs were higher than 0.22. Tofacitinib demonstrated the most effective benefit in HAQ-DI, followed by filgotinib, but the results of filgotinib need to be interpreted with caution, as only three trials were included.

For safety, baricitinib and upadacitinib seemed to be only two JAKinibs that could increase the risk of AEs, infections, and HZ compared to placebo. However, the results of decemotinib, peficitinib, and filgotinib are limited (less than five trials included for each); we are not confident about the results. Additionally, the short duration of the trials related to these three JAKinibs limits any conclusions that can be made on the safety of long-term use. Therefore, more data are needed to support the safety profile of decemotinib, peficitinib, and filgotinib. Considering that large phase 3 trials of filgotinib, decemotinib, and peficitinib are still ongoing, we recognize that the small number of patients treated for a short period of time was insufficient to reach maximal efficacy levels or to obtain a full safety picture of them. Therefore, the results related to these three JAKinibs should be interpreted with caution. Of note, consistent with previous meta-analysis [64,65], baricitinib was found to increase the risk of HZ. However, the pathogenesis underlying the risk of HZ is poorly understood. The potential mechanisms explaining this association may have to do with the role of JAK2, because baricitinib is a more highly selective inhibitor of JAK2 than other JAKinibs. Besides, Japanese and Korean populations appeared to be more likely to suffer from HZ infections [1]. HZ may be significantly influenced by ethnicity and geographical differences, according to different studies.

Overall, tofacitinib, decemotinib, peficitinib, and filgotinib are superior to baricitinib and upadacitinib regarding the safety profile. Considering the low confidence for results of decemotinib, peficitinib, and filgotinib, tofacitinib seemed to the most beneficial and
safe JAKinib comparing to baricitinib and upadacitinib (more AE, infections, and HZ occur). However, the FDA and post-marketing safety surveillance have identified a higher risk of pulmonary embolism and death with the 10 mg twice daily dose of tofacitinib in RA patients [66]. Although this meta-analysis provided no support of thromboembolic events warning across all the JAKinibs, this analysis could not be extended to the real world due to lack of data. On the contrary, a real-world data analysis revealed similar incidence rates of thromboembolic events across tofacitinib doses [67]. Venous thromboembolic events, including pulmonary embolism, have also emerged for both baricitinib and upadacitinib [68]. A recent meta-analysis evaluated the venous thromboembolism risk of JAKinibs in immune-mediated inflammatory diseases; however, their results did not provide evidence of an increased risk for JAKinibs [69]. In addition, whether the increased thromboembolic risk is related to RA disease activity and drug safety is uncertain. Thus, current information regarding this risk is not confirmed yet and further accruing, full details of thromboembolic events in trials of JAKinibs need to be published.

Several limitations deserve consideration. First, the varied severity and baseline therapy of RA among studies limited generalizability to individual patients. Second, there were limited trials for the effect of decenrotinib, peficitinib, and fligotinib. Third, a significant heterogeneity was noted among trials evaluating ACR 20, ACR50, and ACR70. Although a random-effects model was used, the correction is only partial, and possible sources of heterogeneity might include ethnicity and geographic factors, different enrollment criteria of participants, and definable differences in study populations included. Fourth, in some trials, a subgroup or all the placebo patients switched to treatment groups to address ethical concerns about continuing placebo in patients with active disease; therefore, only short-term data for comparing treatment with placebo were included, which prevented us from analyzing the long-term adverse effects of JAKinibs.

5. Conclusions

In conclusion, in this systematic review and meta-analysis, we demonstrate that JAKinibs are effective at reducing RA signs and symptoms of RA, and improve health-related quality of life, but the safety concerns should be paid attention. Increased risk of infections and AE were observed in baricitinib and upadacitinib, whereas only baricitinib statistically increased the risk of HZ. However, this study was limited by its short duration (less than 24 weeks). Further trials are necessary to assess long-term safety, especially for decenrotinib, peficitinib, and fligotinib.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11154459/s1. Figure S1: Forest plot of the effect of JAKinibs on ACR20 (American College of Rheumatology 20 response rates) verse placebo. Figure S2: Forest plot of the effect of JAKinibs on ACR50 (American College of Rheumatology 50 response rates) verse placebo. Figure S3: Forest plot of the effect of JAKinibs on ACR70 (American College of Rheumatology 70 response rates) verse placebo. Figure S4: Forest plot of the effect of JAKinibs on HAQ-ID (Health Assessment Questionnaire–Disability Index) verse placebo. Figure S5: Forest plot of the effect of JAKinibs on AEs. Figure S6: Forest plot of the effect of JAKinibs on SAEs. Figure S7: Forest plot of the effect of JAKinibs on infections. Figure S8: Forest plot of the effect of JAKinibs on serious infections. Figure S9: Forest plot of the effect of JAKinibs on HZ. Figure S10: Forest plot of the effect of JAKinibs on upper respiratory infection. Figure S11: Forest plot of the effect of JAKinibs on thromboembolic events. Figure S12: Forest plot of the effect of JAKinibs on MACE (major adverse cardiovascular events). Figure S13: Forest plot of the effect of JAKinibs on neoplasms. Table S1: Sensitivity analyses of ACR20 and ACR50 in RCTs Stratification. Table S2: Search strategies. PRISMA 2009 Checklist [70].

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Abbreviations

RA | Rheumatoid arthritis
csDMARDs | Conventional disease-modifying-drugs
MTX | Methotrexate
DAS28-4[ESR] | 28-joint disease activity score using erythrocyte sedimentation rate
JAK | Janus kinases
STAT | Signal transduction and activator of transcription
JAKinibs | JAK inhibitors
ACR 20 | American College of Rheumatology 20%
HAQ-DI | Health Assessment Questionnaire—Disability Index
AE | Adverse events
SAE | Serious adverse events
HZ | Herpes zoster
MD | Mean differences
RR | Risk ratio
CI | Confidence intervals

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