**Title:** Comparative efficacy and safety of JAK inhibitors as monotherapy and in combination with methotrexate in patients with active rheumatoid arthritis: A meta-analysis of randomized controlled trials

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**Supplementary Tables**

**Table S1 Search strategy used in May 17, 2022**

|  |  |  |
| --- | --- | --- |
| **Literature databases** | **Search items** | **Items found** |
| Medline | (((rheumatoid arthritis[Title/Abstract]) OR (RA[Title/Abstract])) AND ((((((((((((((((((((JAKi[Title/Abstract]) OR (Janus kinase inhibitor[Title/Abstract])) OR (tofacitinib[Title/Abstract])) OR (Xeljanz[Title/Abstract])) OR (XELJANZ XR[Title/Abstract])) OR (CP-690550[Title/Abstract])) OR (LY3009104[Title/Abstract])) OR (tasocitinib[Title/Abstract])) OR (baricitinib[Title/Abstract])) OR (Olumiant[Title/Abstract])) OR (LY-3009104[Title/Abstract])) OR (INCB-028050[Title/Abstract])) OR (upadacitinib[Title/Abstract])) OR (Rinvoq[Title/Abstract])) OR (ABT-494[Title/Abstract])) OR (filgotinib[Title/Abstract])) OR (GLPG0634[Title/Abstract])) OR (GS-6034[Title/Abstract])) OR (peficitinib[Title/Abstract])) OR (ASP015K[Title/Abstract]))) AND (((randomized controlled trial) OR (controlled clinical trial)) OR (clinical trial)) | 298 |
| Embase | ('rheumatoid arthritis':ti,ab,kw OR ra:ti,ab,kw) AND (jaki:ti,ab,kw OR 'janus kinase inhibitor':ti,ab,kw OR tofacitinib:ti,ab,kw OR xeljanz:ti,ab,kw OR 'xeljanz xr':ti,ab,kw OR 'cp 690550':ti,ab,kw OR ly3009104:ti,ab,kw OR tasocitinib:ti,ab,kw OR baricitinib:ti,ab,kw OR olumiant:ti,ab,kw OR 'ly 3009104':ti,ab,kw OR 'incb 028050':ti,ab,kw OR upadacitinib:ti,ab,kw OR rinvoq:ti,ab,kw OR 'abt 494':ti,ab,kw OR filgotinib:ti,ab,kw OR glpg0634:ti,ab,kw OR 'gs 6034':ti,ab,kw OR peficitinib:ti,ab,kw OR asp015k:ti,ab,kw) AND (randomized AND controlled AND trial OR (controlled AND clinical AND trial) OR (clinical AND trial)) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) | 1,130 |
| Cochrane | ((rheumatoid arthritis):ti,ab,kw OR (RA):ti,ab,kw) AND (JAKi):ti,ab,kw OR(janus kinase inhibitor):ti,ab,kw OR (tofacitinib):ti,ab,kw OR (xeljanz):ti,ab,kw OR (xeljanz xr):ti,ab,kw OR (cp 690550):ti,ab,kw OR (ly3009104):ti,ab,kw OR (tasocitinib):ti,ab,kw OR (baricitinib):ti,ab,kw OR (Olumiant):ti,ab,kw OR (ly 3009104):ti,ab,kw OR (incb 028050):ti,ab,kw OR (upadacitinib):ti,ab,kw OR (rinvoq):ti,ab,kw OR (abt 494):ti,ab,kw OR (filgotinib):ti,ab,kw OR (glpg0634):ti,ab,kw OR (gs 6034):ti,ab,kw OR (peficitinib):ti,ab,kw OR (asp015k):ti,ab,kw) AND (randomized controlled trial OR (controlled clinical trial) OR (clinical trial)) | 912 |
| Overall |  | 2,340 |
| Duplicates |  | 793 |

**Table S2 Excluded studies with reasons**

|  |  |  |  |
| --- | --- | --- | --- |
| **Number** | **Drugs** | **Study** | **Reason for exclusion** |
| 1 | Tofacitinib | Burmester 2013 [1] | Not report JAKi monotherapy |
| 2 | Tofacitinib | Cohen 2019 [2] | Open-label study |
| 3 | Tofacitinib | Fleischmann 2012 [3] | Not report JAKi plus MTX |
| 4 | Tofacitinib | Fleischmann 2012 [4] | Not report JAKi plus MTX |
| 5 | Tofacitinib | Kremer 2012 [5] | Not report JAKi monotherapy |
| 6 | Tofacitinib | Kremer 2013 [6] | Not report JAKi monotherapy |
| 7 | Tofacitinib | Kremer 2015 [7] | Phase 1 study |
| 8 | Tofacitinib | Mcinnes 2014 [8] | Not report JAKi plus MTX |
| 9 | Tofacitinib | Nakamura 2018 [9] | Open-label study |
| 10 | Tofacitinib | Tanaka 2011 [10] | Not report JAKi monotherapy |
| 11 | Tofacitinib | Tanaka 2015 [11] | Not report JAKi plus MTX |
| 12 | Tofacitinib | Van der Heijde 2019 [12] | Not report JAKi monotherapy |
| 13 | Tofacitinib | Vollenhoven 2012 [13] | Not report JAKi monotherapy |
| 14 | Tofacitinib | Winthrop 2017 [14] | Not report JAKi monotherapy |
| 15 | Tofacitinib | Wollenhaupt 2019 [15] | Long-term extension study |
| 16 | Tofacitinib | Yamanaka 2016 [16] | Long-term extension study |
| 17 | Baricitinib | Dougados 2017 [17] | Not report JAKi monotherapy |
| 18 | Baricitinib | Genovese 2016 [18] | Not report JAKi plus MTX |
| 19 | Baricitinib | Keystone 2015 [19] | Not report JAKi monotherapy |
| 20 | Baricitinib | Keystone 2018 [20] | Long-term extension study |
| 21 | Baricitinib | Takeuchi 2019 [21] | Long-term extension study |
| 22 | Baricitinib | Tanaka 2016 [22] | Not report JAKi monotherapy |
| 23 | Baricitinib | Tanaka 2018 [23] | Long-term extension study |
| 24 | Baricitinib | Taylor 2017 [24] | Not report JAKi monotherapy |
| 25 | Filgotinib | Combe 2021 [25] | Not report JAKi monotherapy |
| 26 | Filgotinib | Genovese 2019 [26] | Not report JAKi monotherapy |
| 27 | Filgotinib | Kavanaugh 2017 [27] | Not report JAKi plus MTX |
| 28 | Filgotinib | Westhovens 2017 [28] | Not report JAKi monotherapy |
| 29 | Peficitinib | Genovese 2017 [29] | Not report JAKi plus MTX |
| 30 | Peficitinib | Genovese 2019 [30] | Long-term extension study |
| 31 | Peficitinib | Kivitz 2017 [31] | Not report JAKi monotherapy |
| 32 | Peficitinib | Takeuchi 2016 [32] | Not report JAKi plus MTX |
| 33 | Peficitinib | Takeuchi 2019 [33] | Not report JAKi monotherapy |
| 34 | Peficitinib | Takeuchi 2020 [34] | Long-term extension study |
| 35 | Peficitinib | Takeuchi 2021 [35] | Long-term extension study |
| 36 | Peficitinib | Tanaka 2019 [36] | Not report JAKi plus MTX |
| 37 | Upadacitinib | Burmester 2018 [37] | Not report JAKi monotherapy |
| 38 | Upadacitinib | Fleischmann 2019 [38] | Not report JAKi monotherapy |
| 39 | Upadacitinib | Fleischmann 2019 [39] | Not report JAKi monotherapy |
| 40 | Upadacitinib | Genovese 2016 [40] | Not report JAKi monotherapy |
| 41 | Upadacitinib | Genovese 2018 [41] | Not report JAKi monotherapy |
| 42 | Upadacitinib | Kameda 2020 [42] | Not report JAKi monotherapy |
| 43 | Upadacitinib | Kameda 2021 [43] | Not report JAKi plus MTX |
| 44 | Upadacitinib | Kremer 2016 [44] | Not report JAKi monotherapy |
| 45 | Upadacitinib | Rubbert-Roth 2020 [45] | Not report JAKi plus MTX |
| 46 | Upadacitinib | Smolen 2019 [46] | Not report JAKi plus MTX |
| 47 | Upadacitinib | Vollenhoven 2020 [47] | Not report JAKi plus MTX |

JAKi, Janus kinase inhibitors; MTX, methotrexate.

**Table S3 Summarized efficacy outcomes in the included studies**

|  |  |  |
| --- | --- | --- |
| **Efficacy outcomes** | **JAKi + MTX (n=1,007)** | **JAKi (n=753)** |
| ACR20 | 732 (72.69%) | 510 (67.74%) |
| ACR50 | 571 (56.72%) | 371 (49.26%) |
| ACR70 | 407 (40.40%) | 243 (32.26%) |
| SDAI ≤ 11\* | 320 (54.15%) | 265 (48.80%) |
| CDAI ≤ 10\* | 321 (54.31%) | 267 (49.17%) |
| DAS28-4 (ESR) ≤ 3.2\* | 198 (33.50%) | 145 (26.70%) |
| DAS28-4 (CRP) ≤ 3.2 | 598 (59.39%) | 386 (51.26%) |
| SDAI ≤ 3.3 | 272 (27.01%) | 146 (19.39%) |
| CDAI ≤ 2.8 | 276 (27.43%) | 149 (19.79%) |
| DAS28-4 (ESR) < 2.6\* | 118 (19.97%) | 78 (14.36%) |
| DAS28-4 (CRP) < 2.6 | 441 (43.81%) | 259 (34.40%) |
| HAQ-DI improvement ≥ 0.22 | 798 (79.25%) | 553 (73.44%) |

Data are *n* (%), with *n* presented the number of patients in that group. \* FINCH 3 did not report the related outcomes, so the total number of patients in the remaining trials was 591 in JAKi + MTX group and 543 in JAKi group, respectively.

**Table S4 Summarized adverse events in the included studies**

|  |  |  |
| --- | --- | --- |
| **Adverse events** | **JAKi + MTX (n=1,007)** | **JAKi (n=753)** |
| TEAEs | 596 (59.19%) | 357 (47.41%) |
| SAEs | 70 (6.95%) | 64 (8.50%) |
| AEs leading to study discontinuation | 77 (7.65%) | 37 (4.91%) |
| Deaths | 3 (0.30%) | 2 (0.27%) |
| Serious infections\* | 15 (1.89%) | 11 (1.85%) |
| Herpes zoster | 19 (1.89%) | 12 (1.59%) |
| Opportunistic infections\* | 2 (0.25%) | 2 (0.34%) |
| Malignancy | 7 (0.70%) | 4 (0.53%) |
| VTE | 1 (0.10%) | 1 (0.13%) |
| MACE | 4 (0.40%) | 3 (0.40%) |

Data are *n* (%), with *n* presented the number of patients occurred the adverse events in that group.

TEAEs, treatment-emergent adverse events; SAEs, serious adverse events; AEs, adverse events; VTE, venous thromboembolism; MACE, major adverse cardiovascular events.

\* RA-BEGIN did not report the related adverse events, so the total number of patients in the remaining trials was 792 in JAKi + MTX group and 594 in JAKi group, respectively.

**Table S5 PRISMA checklists**

| **Section and Topic** | **Item #** | **Checklist item** | **Location where item is reported** |
| --- | --- | --- | --- |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review. | P1 |
| **ABSTRACT** | | |  |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | P2 |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | P3 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | P3-4 |
| **METHODS** | | |  |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | P5 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | P5 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | P5 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | P5 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | P5-6 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | P5-6 |
| 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | P5-6 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | P5-6 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | P5-6 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | P6 |
| 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | P6 |
| 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | P6 |
| 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | P6 |
| 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). |  |
| 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | P6 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | P6 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | P5-6 |
| **RESULTS** | | |  |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | P6 |
| 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | P6 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | P6-7 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | P7 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | P7-9 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | P7-9 |
| 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | P7-9 |
| 20c | Present results of all investigations of possible causes of heterogeneity among study results. | P7-9 |
| 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | P7-9 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | P7-9 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | P7-9 |
| **DISCUSSION** | | |  |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | P9 |
| 23b | Discuss any limitations of the evidence included in the review. | P9-12 |
| 23c | Discuss any limitations of the review processes used. | P9-12 |
| 23d | Discuss implications of the results for practice, policy, and future research. | P9-12 |
| **OTHER INFORMATION** | | |  |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | P4 |
| 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. |  |
| 24c | Describe and explain any amendments to information provided at registration or in the protocol. |  |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | P13 |
| Competing interests | 26 | Declare any competing interests of review authors. | P13 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | P13 |

*From:*  Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>

**Supplementary Figures**

**Figure S1 Forest plots of primary efficacy outcomes (week 52) for JAKi combination therapy versus JAKi monotherapy**



**Figure S2 Forest plots of secondary efficacy outcomes (week 24) for JAKi combination therapy versus JAKi monotherapy**



**Figure S3 Forest plots of safety outcomes for JAKi combination therapy versus JAKi monotherapy**



**References of excluded studies**

1. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, Gruben D, Wallenstein G, Krishnaswami S, Zwillich SH 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 (London, England) 2013, 381(9865):451‐460.

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3. Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S, Connell CA, Gruben D, Krishnaswami S, Wallenstein G 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 and rheumatism 2012, 64(3):617‐629.

4. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, Gruben D, Wallenstein GV, Zwillich SH, Kanik KS: Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. New England journal of medicine 2012, 367(6):495‐507.

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9. Nakamura Y, Suzuki T, Yamazaki H, Kato H: Tofacitinib versus non-tumor necrosis factor biologics for patients with active rheumatoid arthritis. Archives of rheumatology 2018, 33(2):154‐159.

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12. van der Heijde D, Strand V, Tanaka Y, Keystone E, Kremer J, Zerbini CAF, Cardiel MH, Cohen S, Nash P, Song YW 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 & rheumatology (Hoboken, NJ) 2019, 71(6):878-891.

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