Impact of upadacitinib on the risk of digestive events in patients with rheumatoid arthritis: A systematic review and meta-analysis of randomized controlled trials

Nie Liu-yan [a,1], Zhao Kun [b,1], Xu Cheng [a], Liu Ming-hao [a], Jin Xue-xiao [a,c,*], Han Yong-mei [a,**]

[a] Department of Rheumatology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China
[b] Center for Rehabilitation Medicine, Rehabilitation & Sports Medicine Research Institute of Zhejiang Province, Department of Rehabilitation Medicine, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, Zhejiang, China
[c] Institute of Immunology, Zhejiang University School of Medicine, Hangzhou, China

A B S T R A C T

Background: Upadacitinib (UPA), an oral Janus kinase (JAK) inhibitor, is an effective treatment option for rheumatoid arthritis (RA), but its use has been associated with an increased risk of digestive events. This systematic review aimed to investigate the risk of digestive events in RA patients treated with UPA.
Methods: Systematic searches of electronic databases (PubMed, Cochrane Library, and EMBASE) from inception to September 2022 were conducted to locate randomized controlled trials (RCTs) that compared UPA with control treatment and reported digestive events in RA patients. We pooled data using the random-effects model and meta-analysis was conducted by Stata software.
Results: Ten RCTs met the inclusion criteria and were analyzed, with a total of 6103 patients. Compared with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), pooled analysis of 8 trials revealed no statistical difference in hepatic disorder (HD) risk and gastrointestinal (GI) perforation (GIP) risk ((OR = 1.16, 95% CI 0.86 to 1.56, I^2 = 0.00%); OR = 4.49, 95% CI 0.56 to 35.93, I^2 = 0.00%)). When we considered the influence of UPA on the grade of liver enzymes, the data indicated that grade 3 and 4 elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were infrequent. Additionally, a dose-dependent impact of UPA on the risks of HD was not observed. The results suggested no interaction by dose of drug, or indication for treatment of GIP risk.

Conclusion: Our results showed that RA patients receiving UPA compared with csDMARDs had no significant increased risk associated with digestive events. Further long-term research of emerging data is urgently needed to gain a better understanding of the association between UPA and digestive events in the RA population.

1. Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory and autoimmune disease characterized by chronic joint inflammation [1]. The pathological changes seen in RA joints include persistent joint synovial inflammation, progressive articular cartilage, and bone destruction, resulting in joint deformity [2,3]. The 3-year disability rate of RA patients without formal treatment is as high as 75% [4]. Just as importantly, extra-articular organ involvement in RA can have various manifestations, and they have profound effects that tend to be borne by families, friends, and society at large [5].

Upadacitinib (UPA), an oral JAK inhibitor, received FDA approval in 2019 for the second-line treatment of moderately to severely active RA [6]. The efficacy and safety of upadacitinib 15 mg per day for RA, administered as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) treatment for moderately to severely active RA patients, have been demonstrated in a global meta-analysis of up to 12- or 48-weeks' duration [7,8]. Although UPA was established to be a selective JAK1 inhibitor, compared with tofacitinib and baricitinib, it was the most potent and equivalent inhibitor of the interleukin (IL)-2/3/15/21 JAK1/3-dependent cytokine in monocytes as well as JAK2-dependent IL-3 and granulocyte/macrophage colony-stimulating factor signaling [9].

UPA has been associated with potential adverse events (AEs), including major adverse cardiovascular events, infections, herpes zoster, thromboembolic events, and gastrointestinal (GI) perforation (GIP). Currently, a published meta-analysis about AEs in UPA with RA reported the incidence of herpes zoster, tumors, cardiovascular events, and other AEs [10–12]. However, no meta-analysis has explored the risk of AEs of UPA in the digestive system, especially GIP and hepatic disorder (HD). GIP is a rare but severe complication that occasionally occurs in RA, with an incidence of GIP (0.2–1.2/1000 person-years (PY)) [13]. Multiple studies have concordantly identified that GIP is related to drug treatments (i.e., Nonsteroidal anti-inflammatory drugs (NSAIDs), csDMARDs, and glucocorticoids (Gc)) [14,15]. With the use of biological agents in recent years, various studies in RA revealed the risk of GIP in patients receiving UPA [16–25]. HD comprised mostly elevated levels on liver function tests, including grade 1–4 aspartate aminotransferase (AST) and alanine aminotransferase (ALT) abnormalities. Additionally, Trueman et al. found that mild and moderate hepatic insufficiency have no clinically relevant influence on the pharmacokinetics of UPA exposure [26]. However, to our knowledge, the risk of different levels of HD in RA patients receiving UPA has never been explored. With increasing therapeutic drugs, treatment in RA will become more complex, making it difficult to determine an adequate drug.

Therefore, in this meta-analysis, we identified all UPA clinical trials published to date and analyzed all that fulfilled the required inclusion criteria to provide statistical support for the risk of digestive events, and to identify potential risk factors for the development of digestive events in UPA-treated RA patients for a better treatment option.

2. Method

This systematic review was conducted based on the Cochrane Handbook for Systematic Reviews and presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27,28].

2.1. Data sources and search strategy

PubMed, the Cochrane Library database, and EMBASE were conducted a literature searched for studies published up to September 2022, with no specified start date. Appendix Table A1 shows the detailed search strategies for each electronic database. Additionally, we manually extracted other primary studies by checking the reference lists of the included studies or published meta-analyses.

2.2. Eligibility criteria

The trials met the following 3 criteria were included: (1) patients above 18 years old who fulfilled the 1987 American College of Rheumatology (ACR) or 2010 ACR/The European Alliance of Associations for Rheumatology (EULAR) classification criteria for RA; (2) original clinical studies of phase II or phase III randomized controlled trials of UPA, with comparator arm, that reported AEs in treatment and control groups (AEs included all digestive events (GIP and HD)); (3) published in English. Studies if containing duplicate data or missing information were excluded.

2.3. Data extraction

Two authors (NLY and ZK) independently screened titles and abstracts retrieved by this literature search and selected eligible studies. Data were extracted, and discrepancies between authors were resolved by discussion before the analysis. Studies that were found to be eligible after a full transcript review were included. Extracted data included characteristics of the study design for the risk

of bias assessment, baseline demographic characteristics (citation details, published year, author list, study design, study location, patient number, mean age of patients, sex ratio, inclusion criteria), control group intervention (methotrexate (MTX) or other csDMARDs), study duration, drug doses, and AEs. HD and GIP were considered digestive events. We extracted details about AEs from full-text articles, supplemental materials, and appendices.

2.4. Quality and risk-of-bias assessments

Two reviewers (NLY and ZK) independently assessed the quality and risk of bias of the included studies. The risk of bias was evaluated in accordance with the Cochrane Collaboration tool (27). The included studies were graded as low, high, or moderate quality based on the criteria. Disagreements were discussed and resolved by consensus.

2.5. Statistical analysis

Extracted data were combined using Stata 17 software. The risk of GIP and HD in patients receiving UPA compared with placebo (PBO), adalimumab (ADA), abatacept (ABA), MTX, and other csDMARDs, and the same UPA with different dosages were calculated by the DerSimonian and Laird random effects model to estimate odds ratios (ORs) and 95% confidence intervals (CIs). If a study included multiple control arms (e.g., UPA control with PBO, and ADA) [20], we separately compared the treatment arm with each control. Because all PBO-controlled trials have background MTX or other csDMARDs, which makes them comparable to MTX-controlled trials, so PBO- and MTX-controlled trials were analyzed together and regarded as the DMARDs group. For binary studies with rare events, the Peto odds ratio (POR) method was used as the relative effect estimator. We performed subgroup analysis to examine the risk of digestive events by using different dosages for UPA when possible. Similarly, we further explored the connection of different control groups and liver enzymes with HD. Statistical heterogeneity across studies was evaluated with Higgins (I^2) (I^2, considerable heterogeneity, $100\% > I^2 > 75\%$; substantial heterogeneity, $90\% > I^2 > 50\%$; moderate heterogeneity, $30\% > I^2 > 60\%$; insignificant heterogeneity, $I^2 < 40\%$) [29], Breslow (τ^2), and Birge's ratio (H^2) indices. $P < 0.05$ was regarded as statistically significant. Forest plots were constructed to summarize the OR and POR estimates and their 95% CIs. Sensitivity analyses were constructed with a leave-one-out approach by removing one study each time and repeating the step to estimate the effect of each study on the overall effect size [29]. The potential publication bias was evaluated by Egger's test in this systemic review [30].

3. Results

3.1. Literature search results

From the electronic database search, we retrieved 1219 potentially eligible records, of which 464 duplicate articles were removed. Following title, abstract and full-text review, 701 articles were excluded for not meeting our inclusion criteria. Ultimately, this led to 10 [16–25] articles being included, leaving an additional 44 articles excluded for not meeting eligibility criteria (i.e., the same data, no available data, missed information, or lack of RCT) (Fig. 1).

3.2. Characteristics of the included studies

Table 1 shows the characteristics of the included clinical trials. All studies were randomized and double-blinded, of which 7 [18–21, 23–25] were phase III and 2 [16,17] were phase II RCTs. One study [22] was described as phase IIb/III. The risk of bias in included trials is shown in Appendix Table A2. Even though all articles had industry funding, we believed that they should be regarded as high-quality research. Overall, the quality of the reported trials was acceptable, with 10 high-quality RCTs.

Articles were published between 2016 and 2021, with follow-up times for UPA compared with placebo, MTX, other drugs and different-dose comparisons ranging from 12 to 26 weeks. ADA as a control drug was investigated in 1 trial [20], ABA in 1 trial [23], MTX in 2 trials [21,24], and PBO in 6 trials [16–19,22,25]. The sample sizes of the 10 studies ranged from 197 to 1629 patients, and a total of 6103 patients, of whom 3890 patients were exposed to UPA.

4. Meta-analysis

4.1. Overview of digestive events in patients receiving UPA

A total of 196 digestive events (190 HD, 6 GIP) were reported in patients receiving UPA therapy over 6103 patients. Concerning the included trials that had different control drugs, we performed a subgroup analysis of 10 trials in HD events (Fig. 2). Due to the MTX or other csDMARDs background of all PBO-controlled trials, we analyzed PBO- and MTX-controlled trials together. Statistical differences of 8 trials of UPA vs. DMARDs remained undetectable in HD events (OR = 1.16, 95% CI 0.86 to 1.56, $I^2 = 0.00\%$). 1 trial of UPA vs ADA reported a significant difference in HD events (OR = 1.86, 95% CI 0.97 to 3.58, $I^2 = 0.00\%$). There was a statistically significant difference between UPA and ABA in HD risk (OR = 4.99, 95% CI 1.87 to 13.32), however, only 1 study was included (Fig. 2A).

For comparison of UPA against other drugs, subgroup analysis of 8 trials about UPA vs. DMARDs did not increase statistically significant risk in GIP (POR = 4.49, 95% CI 0.56 to 35.93, $I^2 = 0.00\%$) (Fig. 2B). Moreover, 1 trial showed no statistically significant risk between UPA and ADA (POR = 7.42, 95% CI 0.46 to 118.81, $I^2 = 0.00\%$) (Fig. 2B). Because of the small number of GIP events and a
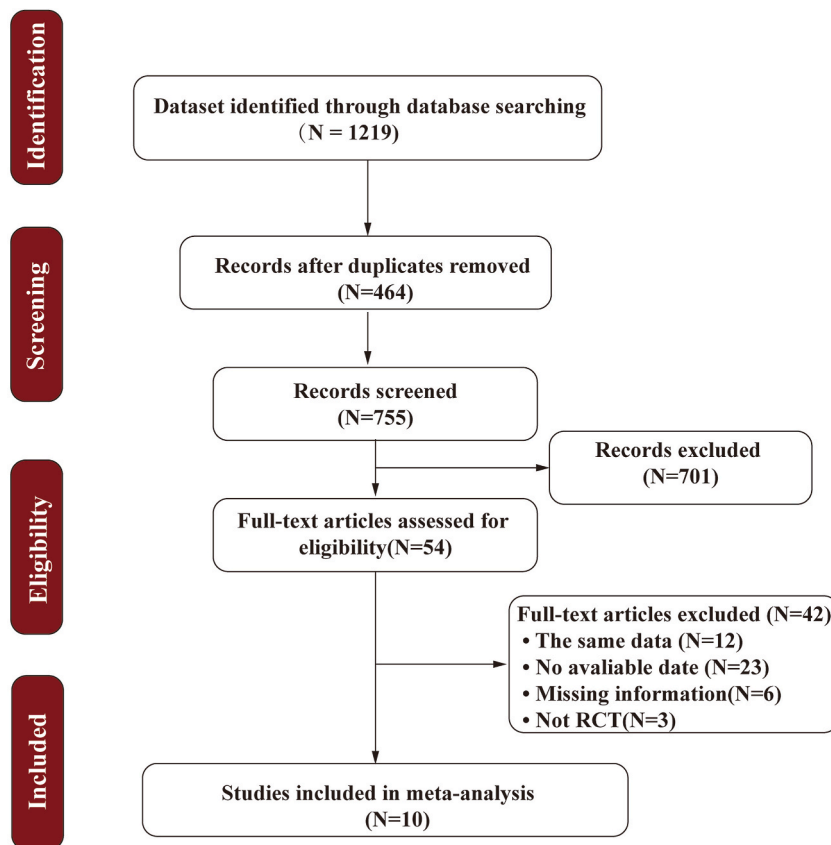
Fig. 1. Flowchart of the study-selection process.

wide confidence interval, the risk of GIP was not different between UPA and other drugs.

We classified HD and GIP as digestive events, and performed a pooled analysis of 10 trials in digestive events. Compared with DMARDs, no significant risk was shown (OR = 1.20, 95% CI 0.90 to 1.61, I^2 = 0.00%) (Appendix Figure A1).

4.2. Subgroup meta-analysis of liver enzymes

7 trials [16,17,19–21,24,25] reported grade 3 or grade 4 AST or ALT abnormalities during the studies. A total of 24 AST abnormalities and 36 ALT abnormalities were reported in 4598 patients receiving UPA therapy. Pooling showed that grade 3 or 4 AST had no statistical significance between UPA and DMARDs (Grade 3 AST: POR = 1.01, 95% CI 0.29 to 3.56, I^2 = 61.39%), (Grade 4 AST: POR = 2.78, 95% CI 0.40 to 19.37, I^2 = 9.50%). Similarly, analysis between UPA and DMARDs in ALT abnormalities showed no significant difference (Grade 3 ALT: POR = 0.61, 95% CI 0.21 to 1.76, I^2 = 70.95%), (Grade 4 ALT: POR = 0.47, 95% CI 0.13 to 1.79, I^2 = 0.00%). More details about each study were shown in Appendix Figure A2, 3.

4.3. Subgroup meta-analysis of the two dosages of UPA

Considering the potential increased risk of digestive events in higher doses of UPA, we conducted dose comparisons in 6 trials [17–19,21,22,24]. 31 out of 1073 patients in the UPA 15 mg dosage group presented with digestive events. Meanwhile, A total of 33/1173 patients in the 30 mg group presented digestive events. In comparison with 30 mg UPA, the ORs (95% CI) of all digestive events for the 15 mg dosage was 0.98 (0.59–1.62), and no significant results were identified (Appendix Figure A4).

4.4. Sensitivity analysis and publication bias

Sensitivity analysis of the included trials indicated that the risk of digestive events observed after treatment with UPA was robust (Appendix Figure A5). Egger's linear regression test was used to analyze publication bias [30]. The *P*-value of the Egger test was 0.4559, which indicated that publication bias was not observed.

Table 1
Characteristic of included studies.

	Study design	No. of patients	Mean age(y)	Female, n (%)	Race, n (%)	Study duration	RF+ and/or anti-CCP+, n (%)	Treatments at baseline, n (%)	Prior biologic use,n (%)	No. of subjects receiving UPA	Exposure
Genovese MC, 2016	BALANCE II, Phase IIb,double-blind, parallel-group, placebo-controlled, Randomized controlled trial	299	UPA3mg: 55 ± 12 UPA6 mg: 53 ± 12 UPA12 mg: 55 ± 12 UPA18 mg: 56 ± 12 UPA24 mg: 55 ± 14 PBO: 56 ± 12	237 (79.3)	Europe 179 (59.9) America120 (40.1)	12w	262 (87.6)	Gc 61 (20.4) Other DMARDs[a] 53 (17.7)	0	249	UPA 3 mg BID; UPA 6 mg BID; UPA 12 mg BID; UPA 18 mg BID; UPA 24 mg BID; PBO
Kremer JM, 2016	BALANCE I, phase IIb, double-blind, parallel-group, placebo-controlled, Randomized controlled trial	276	UPA 3 mg: 58 ± 12 UPA 6 mg:57 ± 13 UPA 12 mg: 56 ± 12 UPA 18 mg:59 ± 11 PBO: 57 ± 12	221 (80.1)	America 187 (68), Australia and New Zealand 6 (2) Europe 83 (30)	12w	232 (84.1)	MTX	254 (92)	220	UPA 3 mg BID; UPA 6 mg BID; UPA 12 mg BID; UPA 18 mg BID; PBO
Burmester GR, 2018	SELECT-BEYOND, Phase III, placebo-controlled, double-blind period study	661	UPA15 mg: 56.0 (12.2) UPA30 mg:55.3 (11.5) PBO:55.8 (11.3)	520 (78.7)	America 296 (44.8) Europe 292 (44.2) Asia 48 (7.2) Other 25 (3.8)	12w	529 (80.0)	Gc 305 (46.1) csDMARDs	84 (12.7)	440	UPA 15 mg QD; UPA 30 mg QD; PBO
Genovese MC, 2018	SELECT-BEYOND, Phase III, double-blind, parallel-group, placebo-controlled, Randomized controlled trial	498	UPA15 mg:57.6 (11.4) UPA30 mg:56.3 (11.3) PBO: 57.3 (11.6)	418 (83.9)	America 328 (65.9) Europe 164 (32.9) Asia 1 (0.2) Other 5 (1)	12w	391 (78.5)	Gc 244 (49.0) MTX 364 (73.1) MTX + other csDMARDs 47 (9.4) Other csDMARDs 82 (16.5)	497 (99.8)	329	UPA 15 mg QD; UPA 30 mg QD; PBO
Fleischmann R, 2019	SELECT- COMPARE, Phase III, double-blinded, Randomized controlled trial	1629	UPA15 mg: 54 ± 12 ADA40 mg: 54 ± 12 PBO: 54 ± 12	1301 (79.8)	Not report	26w	1425 (87.5)	Gc 982 (60.3) MTX	151 (9.3)	978	UPA 15 mg QD; ADA 40 mg EOW; PBO
Smolen JS, 2019	SELECT-MONOTHERAPY, Phase III, double-blind, double-dummy study	648	UPA15 mg:55.3 (11.1) UPA30 mg:54.5 (12.2) MTX:53.1 (12.7)	523 (80.7)	America 283 (43.7) Europe 263 (40.6) Asia 65 (10.0) Other 37 (5.7)	14w	512 (79.0)	Gc 327 (50.5)	0	423	UPA 15 mg QD; UPA 30 mg QD; MTX

Table 1 (*continued*)

	Study design	No. of patients	Mean age(y)	Female, n (%)	Race, n (%)	Study duration	RF+ and/ or *anti-*CCP+, n (%)	Treatments at baseline, n (%)	Prior biologic use,n (%)	No. of subjects receiving UPA	Exposure
Kameda H, 2020	SELECT-SUNRISE, Phase IIb/III, double-blind, double-blind study	197	UPA7.5 mg: 55.8 (11) UPA15mg:56 (12.5) UPA30mg:54.7 (12.2) PBO: 54.3 (13)	155 (78.7)	Japan (100)	12w	136 (69.0)	MTX 119 (60.4) MTX + other csDMARDs 33 (16.7) Other csDMARDs 32 (16.2) GC 102 (51.8)	17 (8.6)	148	UPA 7.5 mg QD; UPA 15 mg QD; UPA 30 mg QD; PBO
Rubbert RA, 2020	SELECT-CHOICE, Phase III, double-blinded, Randomized controlled trial	612	UPA:55.3 ± 11.4 Abatacept:55.8 ± 11.9	502 (82.0)	America 342 (55.9) Europe 242 (39.5) Asia 8 (1.3) Other 20 (3.3)	24 W	462 (75.5)	Gc 327 (53.4)	606 (99.0)	303	UPA 15 mg QD; Abatacept[b]
vanVollenhoven R, 2020	SELECT-EARLY, Phase III, double-blinded, Randomized controlled trial	945	UPA15mg:51.9 ± 12.6 UPA30mg:54.9 ± 12.6 MTX: 53.3 ± 12.9	721 (76.3)	America 416 (44.0) Europe 368 (39) Asia 95 (10) Other 66 (7)	24w	786 (83.2)	Gc 447 (47.3) Other csDMARDs 239 (25.3)	0	631	UPA 15 mg QD; UPA 30 mg QD; MTX
Zeng XF, 2021	Phase III, double-blind, placebo controlled, Randomized controlled trial	338	UPA15mg:51.7 (10.6) PBO:51.7 (11.4)	274 (80.1)	China 228 (67.5) Brazil 52 (15.4) South Korea 58 (17.1)	12w	311 (92.0)	Gc 220 (65.1) csDMARDs	8 (2.4)	169	UPA 15 mg QD; PBO

Other csDMARDs Not MTX; b ﹒ intravenous abatacept (at day 1 and weeks 2, 4, 8, 12, 16, and 20 [500 mg in patients with a body weight of <60 kg, 750 mg in those with a weight of 60–100 kg, and 1000 mg in those with a weight of >100 kg]); UPA: Upadacitinib; Gc: Glucocorticoids; DMARDs: Disease-modifying antirheumatic drugs; MTX: Methotrexate; QD: quaque die; BID: bis in die; PBO:Placebo; ADA: Adalimumab; EOW: every other week; csDMARDs: Conventional synthetic DMARDs.
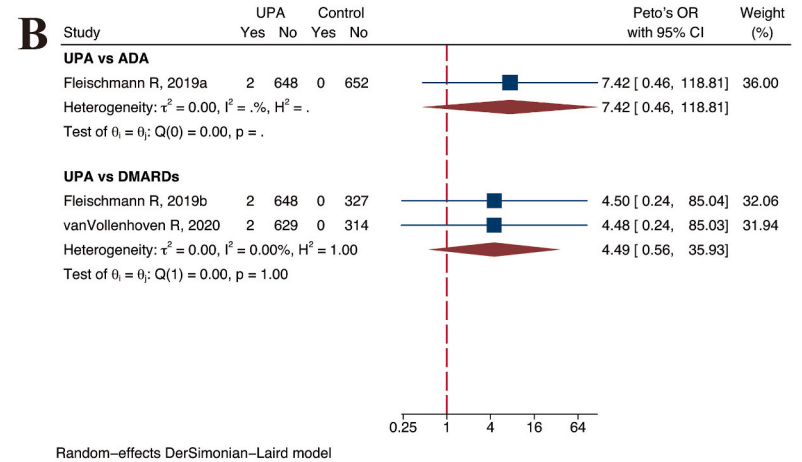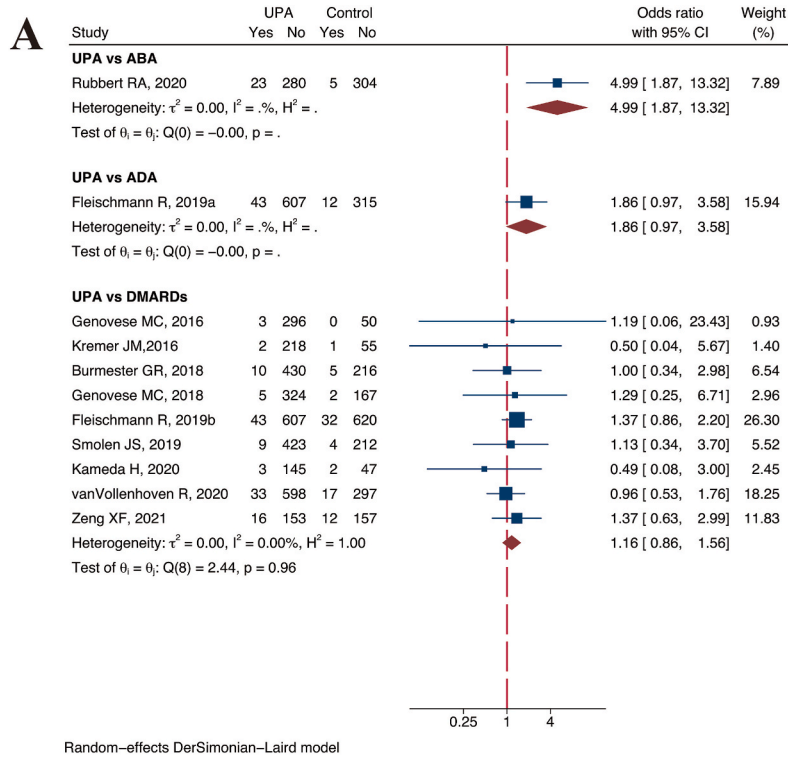
Fig. 2. Forest plot for risk of overall digestive events in UPA. A: Risk of overall GIP; B: Risk of HD.

5. Discussion

The primary finding of this meta-analysis is the risk of digestive events with UPA in RA patients across RCTs. Due to different controls, we did not pool analysis of all the included studies together. Compared with DMARDs, our study including 8 RCTs totaling 5214 patients found that there was no statistical significance of HD risk with the use of UPA in RA (OR = 1.16, 95% CI 0.86 to 1.56, I^2 = 0.00%). Sub-analysis revealed that compared with ADA and ABA, UPA had a significant difference in HD events. However, there was only one trial of UPA vs. ADA and one trial of UPA vs. ABA. A product warning is in place for UPA on the risk of HD, but when we discussed the grades of elevated liver enzymes further, the outcomes indicated that grade 3 and 4 elevations in AST and ALT were infrequent, with insignificant differences between UPA and the control. Based on our results, it appears speculative that hepatotoxicity in UPA always manifests as transient increases in AST and ALT levels, mostly in grade 1 and 2. These results are consistent with those of prior studies with smaller patient samples and fewer disease conditions [31,32]. Similarly, we did not find an increasing risk of GIP in UPA stacked against the control group. However, given the low incidence of events, and thus less imprecise data, a true influence involving a small increase in risk cannot be excluded, nor can small-to-large protective effects.

A degree of dose dependency wasn't observed for digestive events in the UPA group, while the increasing risk was similar in the UPA 15 and 30 mg UPA groups. 5 included trials [18–20,22,24] continuously reported the long-term follow-up studies ranging from 24 to 156 weeks [33–37]. We intentionally excluded these studies, because they are open-label trials with alternate therapy switched in patients with insufficient responses. Therefore, although we found an increased risk of digestive events between UPA and other drugs, no statistical analysis was performed.

Currently, a product warning is in place for UPA on the risk of digestive events [6]. Studies have indicated that the risk of lower intestinal perforations in patients treated with tocilizumab (TCZ), an IL-6 receptor inhibitor, is higher than in other DMARDs [38]. It is hypothesized that the IL-6 receptor has a significant function in the intestinal barrier. Research suggests that even though JAKis also inhibits IL-6 signaling, a similar incidence of GIP with UPA was observed with tumor necrosis factor inhibitors and other JAKis [38,39]. Similarly, our outcome confirmed this conclusion. Trueman et al. explored the effect of hepatic impairment on UPA pharmacokinetics, and found that compared with healthy subjects, a clinically meaningful impact of mild and moderate hepatic impairment on UPA exposure was not observed [26]. Given that UPA is not extensively bound to plasma proteins, they believed that changes in the free fraction associated with decreased protein binding in liver injury were not expected to have a relevant effect on UPA clearance or total exposure. Our study also found that compared with other drugs, UPA had no statistical difference in the severe HD risk. Therefore, when met mild and moderate hepatic disorders occurred during UPA treatment in RA, no dose adjustment was required. Similarly, when considering the risk of hepatic impairment in choosing treatment options, UPA has an equal right to be selected.

Our study has important implications for clinical practice, providing the most extensive meta-analysis evidence on the risk of digestive events in RA patients using UPA. By systematically and quantitatively evaluating the data from high-quality RCTs, we performed various subgroup analyses to provide another perspective on the treatment effect of UPA in RA patients.

There are several noteworthy limitations in our study, as well. Firstly, the reason why we classified HD and GIP as digestive events, was because all trials only reported the two events in the digestive system. Therefore, the impact of UPA on the risk of digestive events may be influenced by data limitations. Secondly, the outcome of interest (risk of digestive events) was rare events, which may be affected by small changes in event distribution. Thirdly, even though we discussed the influence of doses on the impact of digestive events. However, our study used aggregate data, instead of a full survival model approach employing individual patient-level data and time-to-event analyses, which may help us to sub-analyze more influential factors between UPA and digestive events in RA; At the same time, concomitant medications cannot be considered in the meta-analysis, e.g., GCs and csDMARDs. Even though Researchers have found an established risk between GCs or csDMARDs and digestive events [40,41]. Lastly, the follow-up periods of the included trials were limited. Although some studies [33–37] had further reported long follow-up periods, however, they had drugs withdrawn or switched for rescue or AEs. Urgent analysis only includes data from the short-term controlled periods of the trials. Therefore, a long-term safety profile of UPA cannot be extrapolated.

6. Conclusion

In conclusion, based on the best available evidence from RCTs, our results showed that RA patients receiving UPA compared with csDMARDs had no significant increased risk associated with digestive events. Further long-term research of emerging data is urgently needed to gain a better understanding of the association between UPA and digestive events in the RA population.

Author contribution statement

Nie Liu-yan, Zhao Kun: Conceived and designed the experiments; Performed the experiments; Wrote the paper.

Xu Cheng, Liu Ming-hao: Analyzed and interpreted the data; Wrote the paper.

Jin Xue-xiao, Han Yong-mei: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data included in article/supp. material/referenced in article.

Additional information

Supplementary content related to this article has been publish online at [URL].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e17002.

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