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An updated systematic review and meta-analysis of randomised controlled trials on the effects of urate-lowering therapy initiation during a gout flare

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ABSTRACT

Background: There is uncertainty about the optimal time to start urate-lowering therapy (ULT) in the setting of a gout flare. The aim was to perform a systematic review and meta-analysis of randomised controlled trials (RCTs) assessing the effects of ULT initiation during a gout flare.
Methods: This systematic review was conducted in accordance with PRISMA methodology. MEDLINE, EMBASE and The Cochrane Library were searched for studies published between database inception to 1 March 2023. RCTs published in English that examined ULT initiation during a gout flare in adults ≥18 years were included. The quality of included studies was assessed using the revised Cochrane Risk of Bias tool 2.0. Data were extracted for the following outcomes: patient-rated pain score, duration of gout flare, recurrent gout flares, time to achieve target serum urate, adherence to ULT, patient satisfaction with treatment and adverse events. Meta-analyses were performed using Review Manager v5.4. This study is registered on PROSPERO, number CRD42023404680.
Results: A total of 972 studies were identified and of these, six RCTs met the criteria for inclusion in the analysis. Three studies were assessed as having high risk of bias, one study as having some concerns, and two studies as having low risk of bias. In total, there were 445 pooled participants; 226 participants randomised to early initiation of ULT and 219 to placebo or delayed initiation of ULT. Allopurinol was used in three studies, febuxostat in two studies and probenecid in one study. Few participants ($n = 62$, 13.9 %) had tophaceous gout. Participants with renal impairment were excluded from most studies. There were no differences in patient-rated pain scores at baseline, days 3–4, days 7–8, day 10 or days 14–15 ($p \geq 0.42$). Additionally, there was no significant difference in time to resolution of gout flare (standardised mean difference 0.77 days; 95 % CI -0.26 to 1.79; $p = 0.14$) or the risk of recurrent gout flare in the subsequent 28 to 30 days (RR 1.06; 95 % CI 0.59 to 1.92; $p = 0.84$). Adverse events were similar between groups. The included studies did not report time to achieve target serum urate, long-term adherence to ULT, or patient satisfaction with treatment.
Conclusion: There appears to be no evidence for harm or for benefit to initiating ULT during a gout flare. These findings have limited applicability to patients with tophaceous gout, or those with renal impairment.

Introduction

Gout is a common inflammatory condition caused by the deposition of monosodium urate (MSU) crystals in articular and non-articular structures [1]. It affects up to 6.8 % of the population in certain geographical locations, and with rising global incidence and prevalence [2]. Effective long-term treatment of gout requires urate-lowering therapy (ULT) to reduce the serum urate level to <6.0 mg/dl (0.36 mmol/L) to allow for dissolution of MSU crystals, and ultimately prevent further gout flares [3,4]. Indications for initiating ULT include frequent

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gout flares (≥2/year), evidence of radiographic damage attributable to gout, the presence of tophi and nephrolithiasis [3–5].

Despite being a well-established therapy for gout, the timing of ULT initiation in relation to a gout flare remains debated. Traditionally, for people with indications for ULT, ULT initiation has been delayed for 1–2 weeks after resolution of a gout flare due to concerns that sudden changes in serum urate levels will result in remodelling of microscopic tophi leading to exacerbation or prolongation of the flare [6]. International guidelines on gout management have provided conflicting recommendations on this issue. The 2016 updated EULAR guidelines did not provide specific guidance on timing of ULT in relation to a gout flare [3], while the British Society of Rheumatology 2017 guidelines recommended that ULT is best delayed until the gout flare has resolved [5]. In contrast, the American College of Rheumatology 2020 guidelines conditionally recommended ULT initiation during a flare for patients with indications for ULT, citing conceptual benefits including the time efficiency of initiating ULT during the visit rather than risk of the patient not returning for ULT initiation, and higher motivation levels to initiate ULT and persist with therapy when experiencing symptoms relating to a flare [4].

Over the past decade, randomised controlled trials (RCTs) have reported the effects of ULT initiation during a gout flare compared with no ULT initiation or delayed ULT initiation. Systematic reviews and meta-analyses of these RCTs have been published by various groups to assess the effect of ULT initiation during a gout flare on the duration and severity of the flare, recurrent gout flares, persistence on ULT and adverse events [7–9]. Our aim was to conduct an updated systematic review and meta-analysis of RCTs on this topic, including newly published RCTs and examining additional endpoints including long-term adherence to ULT, time to achieve target serum urate and patient satisfaction with treatment.

Methods

This systematic review and meta-analysis was conducted according to a pre-defined protocol using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [10]. The study protocol has been registered in the PROSPERO international prospective register of systematic reviews (CRD42023404680).

Search strategy

Electronic databases (MEDLINE, EMBASE and the Cochrane Library) were searched from inception to 1 March 2023 using the following keywords in the search term: gout AND (‘uric acid lowering’ OR ‘urate-lowering’ OR ‘lowering serum urate’). Due to the large number of publications retrieved, filters were applied in MEDLINE and EMBASE to restrict the search to studies published in English and those reporting on clinical trials, RCTs, and controlled clinical trials. Filters were not applied in the Cochrane Library. Bibliographical references from individual included studies and review articles were also hand-searched to identify additional relevant studies.

Study selection

All studies generated from the search were exported to RefWorks and screened to remove duplicates. Title and abstract screening, followed by full-text screening was undertaken by VT. The titles and abstracts screened by VT were also cross-checked by a second reviewer (ND, the senior author). Studies were included if they were a RCT examining the initiation of ULT during a gout flare compared to no ULT or delayed initiation of ULT in adults ≥18 years and published in English. The following exclusion criteria were applied: (1) trials of ULT initiation during the inter-critical period; (2) trials comparing different doses of the same medication; (3) animal studies; (4) conference abstracts.

Quality assessment

The quality of all included studies was assessed independently by two reviewers (VT, ND) using the revised Cochrane ‘Risk of Bias’ tool for randomised trials (RoB 2.0) [11]. RoB 2.0 addresses five specific domains: (1) bias arising from the randomisation process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcomes; and (5) bias in selection of the reported result. Any disagreements were resolved by discussion between the two reviewers. Following guidance given for RoB 2.0, we derived an overall summary ‘Risk of Bias’ judgement (low; some concerns; high) for each specific outcome, whereby the overall RoB for each study was determined by the highest RoB level in any of the domains assessed.

Data extraction

Data extraction was performed by VT using a standardised form in Microsoft Excel. Data extraction included publication details (author, year of publication, country), participant characteristics (gender, mean age, mean baseline serum urate level, mean gout disease duration, number of previous gout flares, n (%) with tophi), and study characteristics (trial design, sample size, duration of follow-up, intervention and control groups, background therapy). Data were also extracted for the following outcomes: severity of gout flare, duration of gout flare, recurrent gout flares during the study period, time to achieve target serum urate, adherence to ULT, patient satisfaction with treatment and adverse events. Means and standard deviations (SDs) were extracted for continuous outcomes and n for dichotomous outcomes.

Severity of gout flare was assessed by patient rated-pain score, either using a 10-cm visual analogue scale (VAS) [12–15], 10-point numerical rating scale [16], or 5-point Likert scale [17]. In the study where a 5-point Likert scale was used, mean and SD values were converted to a standardised 10-point pain score by doubling the reported values. In studies where raw data was not available for pain scores but presented graphically in a figure, values were derived from standardised calliper measurements. Where 95 % confidence intervals were presented, these were converted to standard deviations. Attempts were also made to contact study authors for missing data.

Data analyses

Meta-analyses were performed using Review Manager version 5.4. For individual studies, we imputed the total number of participants who completed the study protocol and were analysed in each arm, rather than the total number of participants randomised, as the included studies presented either their per-protocol or modified intention-to-treat (ITT) analyses in the main text of the paper. For continuous outcomes, data were pooled with the standardised mean difference (SMD) and 95 % confidence interval (CI) of the final value across groups. For dichotomous data, the relative risk (RR) and 95 % CI were calculated. Heterogeneity was quantified using the I^2 statistic. Random effects models were used for all I^2 values greater than 0 %, otherwise, fixed-effects models were used. Subgroup analyses were undertaken, where possible, to determine differences in key outcomes by gout disease severity (tophaceous gout vs. not tophaceous gout), ULT starting dose (low vs. high), ULT agent, and healthcare setting (inpatient vs. outpatient).

Results

Study characteristics

A total of 632 studies were identified through the search following the deletion of duplications (Fig. 1). After title and abstract screening, 13 full-text articles were assessed for eligibility. After the exclusion of seven

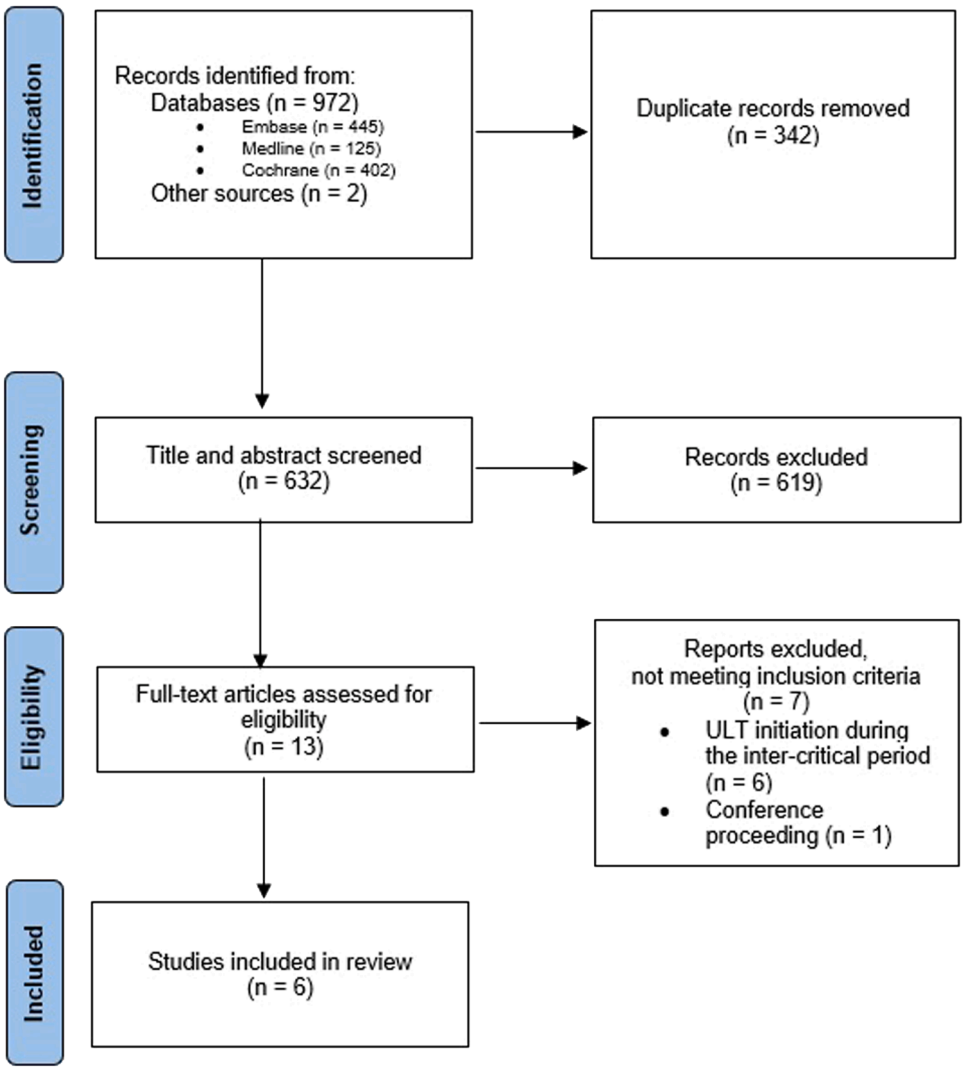

Fig. 1. Flow diagram of study selection.

studies (reasons for exclusion are presented in Fig. 1), six RCTs were included in this review [12–17]. The full characteristics of included studies are presented in Table 1. There was a total of 445 pooled participants, with 226 participants randomised to early initiation of ULT (experimental group) and 219 to placebo or delayed initiation of ULT (control group). In total, there were 405 participants who completed the full trial protocol and were analysed in their respective studies (204 in the experimental group, 201 in the control group). Three studies used allopurinol [12,14,16], two studies used febuxostat [13,17], and one study used probenecid [15]. Four studies compared early initiation of ULT to delayed initiation of ULT [12–14,17], whilst two studies compared early initiation of ULT to placebo [15,16]. Background anti-inflammatory prophylaxis was used in all studies and this included non-steroidal anti-inflammatories and colchicine. Of the six studies, five excluded participants with renal impairment – two studies excluded participants with eGFR <50 ml/min/1.73m^2 [16,17], one study excluded participants with eGFR <30 ml/min/1.73m^2 [15], one study excluded participants with eGFR <15 ml/min/1.73m^2 [14], and one study excluded participants with a serum creatinine >1.3 mg/dl [12]. Study follow-up ranged from 15 days to 12 weeks (median 28 days).

Quality assessment

The results from the quality assessment are presented in Fig. 2. Three studies were assessed as high risk of bias [13,14,16], one study as having some concerns [17], and two as low risk of bias [12,15]. The three studies with high risk of bias were either non-blinded studies or experienced loss of blinding during the follow-up period.

Participant characteristics

Characteristics of participants in the included studies are shown in Table 2. Most participants were outpatients and were middle-aged men with a mean serum urate level >7.0 mg/dL. Participants had a mean of 3 to 4 previous gout flares and a mean disease duration of 3 to 5 years. Few participants (n = 62, 13.9 %) had tophaceous gout.

Severity of gout flare

Patient-rated pain scores were available for all studies (n = 424) at baseline and on days 3–4 [12–17], for five studies (n = 393) on days 7–8 [12–15,17], for two studies (n = 103) on day 10 [12,13], and for three studies (n = 202) on days 14–15 [13–15]. Meta-analysis revealed no differences in patient-rated pain scores at baseline (SMD 0.08; 95 % CI −0.11 to 0.27; I^2=0 %; p = 0.42), days 3–4 (SMD −0.01; 95 % CI −0.21 to 0.18; I^2=0 %; p = 0.88), days 7–8 (SMD 0.07; 95 % CI −0.13 to 0.27; I^2=0 %; p = 0.50), day 10 (SMD −0.11; 95 % CI −0.49 to 0.28; I^2=0 %; p = 0.59) or days 14–15 (SMD −0.08; 95 % CI −0.36 to 0.20; I^2=0 %; p =

Table 1
Characteristics of included studies.

Study	Blinding	Number of participants randomised	Number of participants analysed	Follow-up time	Background therapy	Exposure Group	Comparison Group	Primary Outcomes	Secondary Outcomes
Taylor 2012 [12]	Double-blind	57	51	30 days	Indomethacin 50 mg TDS for 10 days and colchicine 0.6 mg BD for 90 days	Allopurinol 300 mg daily from day 1 to 30	Placebo from day 1 to 10, then allopurinol 300 mg daily from day 11 to 30	VAS for pain Recurrent gout flare	Serum urate level CRP/ESR Complete blood count Creatinine Liver function Adverse events
Hill 2015 [16]	Double-blind	35	31	28 days	Colchicine 0.6 mg daily on day 1 and 2, then 0.6 mg BD from day 3 to 28	Allopurinol 100 mg daily from day 1 to 14, then 200 mg daily from day 15 to 28	Placebo	Time to resolution	Recurrent gout flare Patient-rated pain Physician global assessment Serum urate level Adverse events
Sun 2020 [13]	Not reported	56	52	12 weeks	Etoricoxib for 1 week, colchicine 0.5 mg BD and sodium bicarbonate 1.0 g TDS for 12 weeks	Febuxostat 40 mg daily from day 1 till end of 12 weeks[b]	No treatment from day 1 to 14, febuxostat 40 mg daily from day 15 till end of 12 weeks[b]	VAS for pain Recurrent gout flare	Serum urate level CRP/ESR IL-1β TNF-α Adverse events
Jia 2021 [17]	Single-blind	140	121	28 days	Diclofenac 150 mg daily, reduced to 75 mg daily once remission achieved	Febuxostat 40 mg daily from day 1 to 28	Placebo from day 1 to 7, then febuxostat 40 mg daily from day 8 to 28	Time to resolution	Recurrent gout flare Joint pain score Joint swelling score Joint tenderness score Joint erythema score Serum urate level ESR/CRP Adverse events
Satpanich 2021 [14]	Open-label	117	115	28 days	Ibuprofen 1200 mg daily for the acute flare[a], standard prophylaxis with colchicine from day 6	Allopurinol 100 mg daily from day 1 to 14, then allopurinol 200 mg daily from day 14 to 28[c]	No treatment from day 1 to 14, then allopurinol 100 mg daily from day 14 to 28[c]	Time to complete resolution	Time to clinical resolution VAS for pain Recurrent gout flare Serum urate level CRP/ESR eGFR Adverse events
Yang 2023 [15]	Double-blind	40	35	15 days	Aceclofenac 100 mg PRN and colchicine 0.5 mg BD	Probenecid 500 mg daily (contained in hybrid pill with colchicine)	Placebo (colchicine)	VAS for pain	Serum urate level CRP Complete blood count Creatinine Liver function

[a] Patients with contraindications to NSAIDs were given colchicine (if onset of gout flare was <36 h) or oral prednisolone (if onset of gout flare was ≥36 h) for management of the gout flare.
[b] During the study, febuxostat dose was adjusted according to patients' serum urate level.
[c] Patients with eGFR <50 ml/min/1.73m^2 received allopurinol 50 mg daily for 14 days, then 100 mg daily for the next 14 days.

Fig. 2. Assessment of the methodological quality of the included studies using the Cochrane Risk of Bias Tool (RoB 2.0).

Table 2
Participant characteristics.

Study	Country	Inpatients vs Outpatients	Male (%)	Age (years), mean	Baseline serum urate level (mg/dL), mean	Gout disease duration (years), mean	Number of previous attacks, mean	Patients with tophi (%)
Taylor 2012 [12]	USA	Outpatients	100	E: 57 C: 61	E: 7.8 C: 7.6	Not reported	Not reported	E:0 C: 0
Hill 2015 [16]	USA	Outpatients	94	E: 61 C: 53	E: 8.2 C: 8.0	E: 5.5 C: 5	E: 3.7 C: 6.6	E: 38. C: 32
Sun 2020 [13]	China	Outpatients	100	E: 41 C: 44.5	E: 8.8 C: 8.4	E: 3 C: 4	E: 2.8 C: 2.7	Not reported
Jia 2021 [17]	China	Not reported	97.1	E: 42 C: 41	E: 8.7 C: 9.1	E: 4 C: 3	Not reported	E: 13 C: 10
Satpanich 2021 [14]	Thailand	Both	83.5	E: 58[a] C: 66[a]	E: 7.9 C: 7.3	E: 3 C: 3	E: 3.0 C: 2.8	E: 29 C: 30
Yang 2023 [15]	Taiwan	Not reported	95	E: 34.5[a] C: 39[a]	E: 7.2 C: 7.0	Not reported	Not reported	Not reported

E – Experimental group (early initiation of ULT); C – Control group (placebo or delayed initiation of ULT)
[a]Median values for age reported in study

0.57) (Fig. 3).

Duration of gout flare

Three studies ($n = 267$) assessed the effect of early initiation of ULT on the duration of the gout flare [14,16,17]. Meta-analysis demonstrated no difference in the time to flare resolution between the experimental and control groups (SMD 0.77 days; 95 % CI −0.26 to 1.79; I^2=0 %; $p = 0.14$) (Fig. 4).

Recurrent gout flare

Five studies assessed the risk of recurrent gout flare over the study period [12–14,16,17]. Four studies ($n = 318$) were included in the meta-analysis as they had a similar duration of follow-up (28 to 30 days) [12,14,16,17]. There was no difference in the risk of recurrent gout flare within the subsequent 28 to 30 days (RR 1.06; 95 % CI 0.59 to 1.92; I^2=0 %; $p = 0.84$) (Fig. 5).

Other outcomes

The included studies reported similar levels of compliance and drop-out in the experimental and control groups. However, long-term adherence to ULT could not be assessed due to their relatively short follow-up periods (15 days to 12 weeks, median 28 days). The time to achieve target serum urate and patient satisfaction with treatment were not reported in the included studies.

Adverse events

Adverse events were reported in five studies and were similar between the experimental and control groups [12–14,16,17]. These included renal impairment, elevated liver enzymes, gastrointestinal symptoms and mild hypersensitivity reactions (Supplementary Table 1).

Subgroup analyses

Subgroup analysis by ULT type (allopurinol, febuxostat, probenecid) was performed for patient-rated pain scores. There was no significant difference in pain scores between experimental and control groups at baseline, days 3–4 and days 7–8 for different ULT types (Supplementary Fig. 1–3). It was not possible to perform subgroup analyses by gout severity or healthcare setting as none of the included studies reported outcomes according to these variables. Subgroup analyses for other outcomes of interest were not possible due to the smaller number of studies available for meta-analysis.

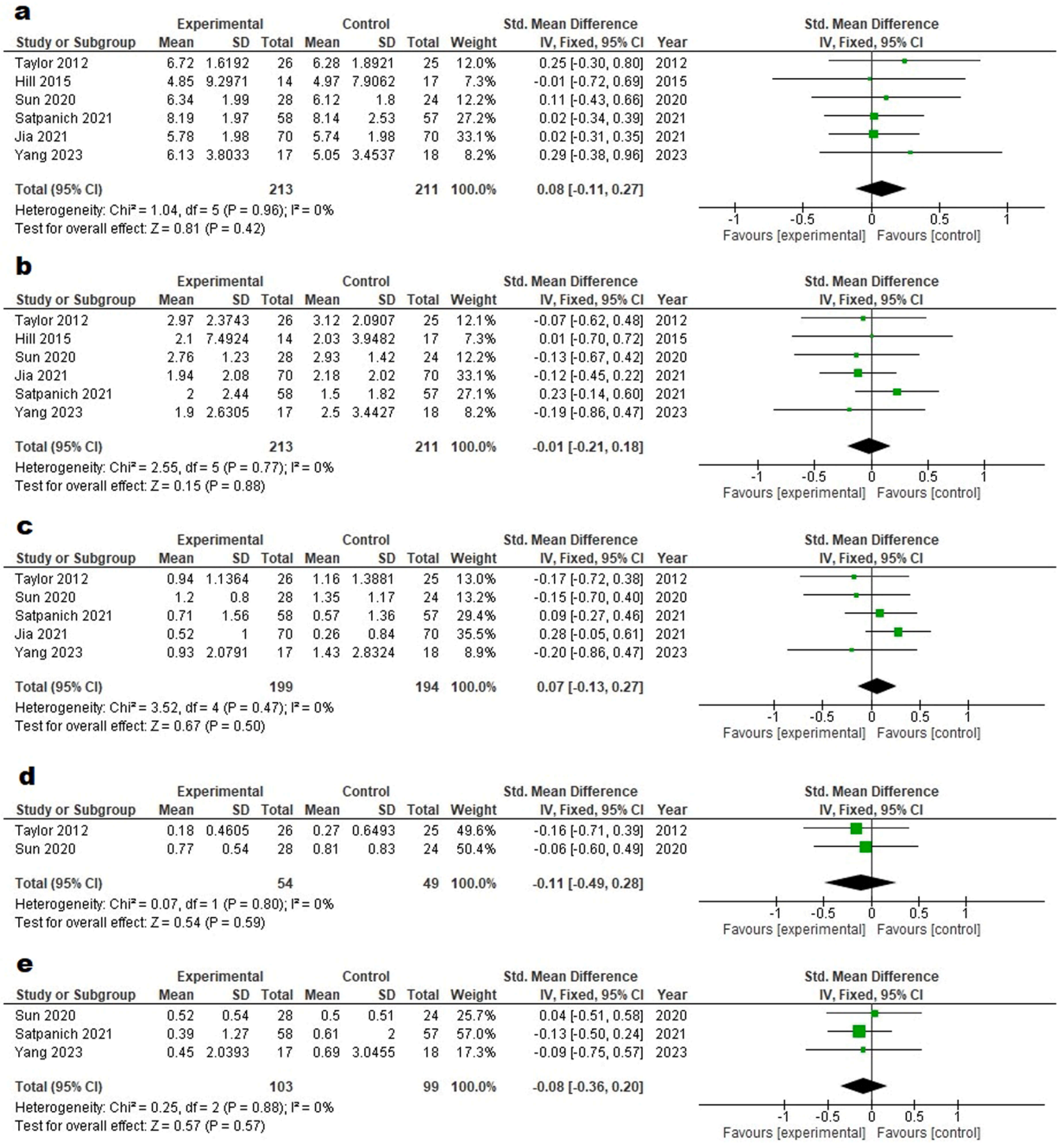

Fig. 3. Forest plots of patient-rated pain scores between the experimental group (early initiation of ULT) and the control group (placebo or delayed initiation of ULT) at baseline (a), days 3–4 (b), days 7–8 (c), day 10 (d) and days 14–15 (e). The 'total number of participants analysed' in each study was used for the meta-analyses. However, the 'total number of participants randomised' ($n = 70$ in each of the experimental and control groups) was used for the Jia 2021 study as this trial presented their intention-to-treat analysis for pain scores in the main text of the paper.

Discussion

Principal findings

Compared to placebo or delayed initiation of ULT, early initiation of ULT was not associated with differences in pain scores over 14–15 days, the duration of gout flare or risk of recurrent gout flare in the subsequent 28 to 30 days, or adverse event outcomes. The included studies did not report time to achieve target serum urate, long-term adherence to ULT, or patient satisfaction with treatment.

Strengths and limitations

The strength of this systematic review and meta-analysis is its comprehensive nature. We have included the latest RCTs examining the initiation of ULT during a gout flare. Participants from various

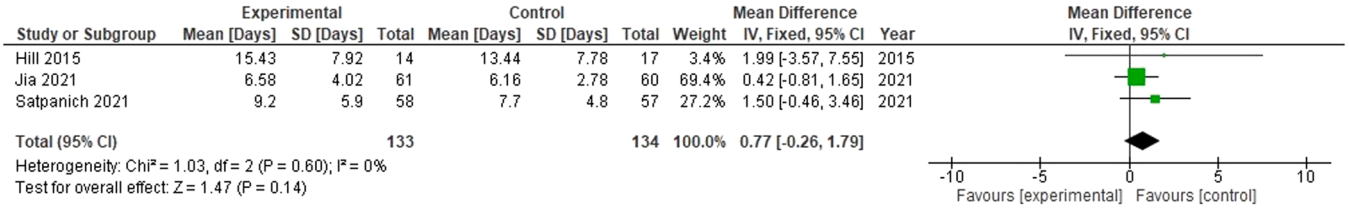

Fig. 4. Forest plot of the days to gout flare resolution between the experimental group (early initiation of ULT) and control group (placebo or delayed initiation of ULT). The 'total number of participants analysed' in each study was used for the meta-analysis.

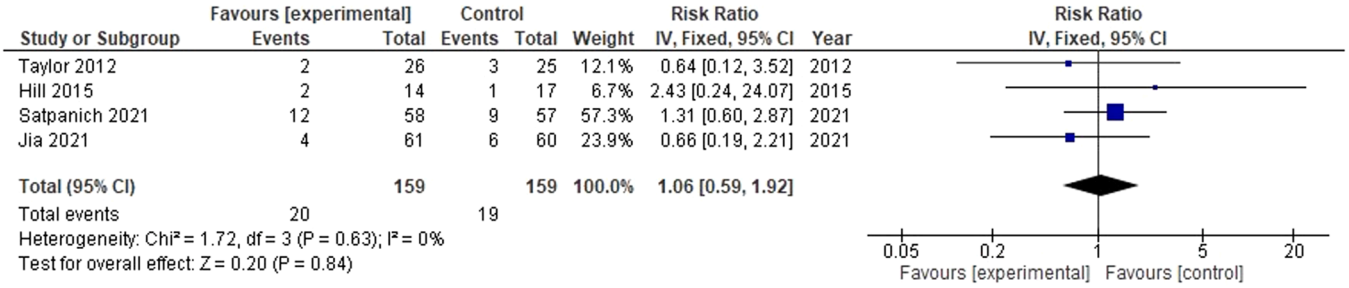

Fig. 5. Forest plot of the risk of recurrent gout flare within the subsequent 28 to 30 days between the experimental group (early initiation of ULT) and the control group (placebo or delayed initiation of ULT). The 'total number of participants analysed' in each study was used for the meta-analysis.

geographical locations including the US, China, Thailand and Taiwan were included. Additionally, commonly used ULT medications (allopurinol, febuxostat and probenecid) have been assessed. Previous meta-analyses have only reported pain scores on day 10, whereas our study has assessed pain scores at additional time points (days 3–4, days 7–8, days 14–15), further supporting that early initiation of ULT during a gout flare may not affect the severity of the flare.

Limitations of this study include its small size (total of 445 participants). Most of the included studies were small, with <100 participants, which increases the risk of Type II error. The meta-analysis of three studies on duration of gout flare ($n = 267$) demonstrated a trend towards shorter duration of gout flare (by 0.77 days) in the control group (placebo or delayed initiation of ULT), however, it did not reach statistical significance, possibly owing to the small size of the individual studies.

Another important limitation is that the included studies are of moderate to low quality. In our risk of bias assessment, three studies were assessed as high risk of bias. Two of these studies were not blinded and therefore participants and investigators were at risk of bias in the measurement of outcomes including pain score rating and assessments of gout flare resolution or recurrence [13,14]. The other study was a double-blinded, placebo-controlled RCT, however, unmasking occurred during the follow-up period as investigators were not blinded to participants' laboratory results [16]. Additionally, the majority of included studies only reported per-protocol or modified ITT analyses in the main text of the paper (the results of which were used for our meta-analyses). Per-protocol and modified ITT analyses may be prone to attrition bias.

Other limitations include the short duration of the included trials, with five studies having a follow-up period of ≤1 month [12,14–17]. These studies were unable to assess long-term adherence to ULT, nor the risk of recurrent gout flare in the subsequent months. Additionally, two studies allowed the investigators to determine initial therapy for the gout flare [14,16]. The resultant heterogeneity in initial treatment may have impacted outcomes including patient-rated pain scores and the duration of the gout flare. None of the studies reported on patients' quality of life.

Finally, participants from the included studies were predominantly outpatients with a mean of 3 to 4 previous flares, suggesting that they had early or milder disease. Few participants had tophaceous gout. In addition, participants with renal impairment were excluded from most studies. This limits the generalisability of our findings to patients with more advanced gout or comorbid renal disease.

Implications of findings

Our review has found no evidence for benefit or for harm to the early initiation of ULT during a gout flare. However, these findings may not be applicable to patients with more severe gout, particularly tophaceous gout, or in those with renal impairment – further studies are required in these groups of patients. Guidelines on gout management have suggested that patients may be more motivated to initiate and persist with ULT when experiencing a gout flare [4]; however, long-term adherence to ULT and patient satisfaction with treatment were not reported in the RCTs. A retrospective study comparing early vs delayed initiation of ULT found that early initiation of ULT reduced the time to achieve target serum urate by approximately one month (2.5 ± 0.6 vs 3.8 ± 1.2 months, $p = 0.004$) but this has not been assessed in RCTs [18]. Given these uncertainties, the timing of ULT initiation in relation to a gout flare should remain individualised, taking into account the patient's preferences, severity of gout, comorbidities and likelihood of returning for follow-up.

Conclusions

Our updated systematic review and meta-analysis of RCTs suggests that initiation of ULT during a gout flare does not affect the severity of the flare, nor the duration of the flare or risk of recurrence in the subsequent 28 to 30 days. However, important caveats include the small sample size and the low to moderate quality of included studies. Additionally, our findings may not be applicable to patients with tophaceous gout or comorbid renal disease. Therefore, an individualised approach to patient management is recommended.

Declaration of competing interest

ND has received consulting fees, speaker fees or grants from AstraZeneca, Novartis, Horizon, Selecta, Arthrosi, JW Pharmaceutical Corporation, PK Med, LG Chem, JPI, PTC Therapeutics, Protalix, Unlocked Labs, Hikma outside the submitted work. AA has received institutional research grants from AstraZeneca and Oxford Immunotech; and personal fees from UpToDate (royalty), Springer (royalty), Cadilla

Pharmaceuticals (lecture fees), NGM Bio (consulting), Limbic (consulting) and personal fees from Inflazome (consulting) unrelated to the work. VT, PG, SS, PS and CL do not have conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2024.152367.

References

[1] Dalbeth N, Gosling AL, Gaffo A, Abhishek A. Gout. Lancet 2021;397:1843–55.
[2] Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. Nat Rev Rheumatol 2020;16:380–90.
[3] Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castañeda-Sanabria J, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017;76:29–42.
[4] FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, et al. 2020 American College of rheumatology guideline for the management of gout. Arthritis Care Res (Hoboken) 2020;72:744–60.
[5] Hui M, Carr A, Cameron S, Davenport G, Doherty M, Forrester H, et al. The British Society for rheumatology guideline for the management of gout. Rheumatology (Oxford) 2017;56:1056–9.
[6] Becker MA, MacDonald PA, Hunt BJ, Lademacher C, Joseph-Ridge N. Determinants of the clinical outcomes of gout during the first year of urate-lowering therapy. Nucleosides Nucleotides Nucleic Acids 2008;27:585–91.
[7] Eminaga F, La-Crette J, Jones A, Abhishek A. Does the initiation of urate-lowering treatment during an acute gout attack prolong the current episode and precipitate recurrent attacks: a systematic literature review. Rheumatol Int 2016;36:1747–52.
[8] Zhang X, Tang Y, Wang M, Wang D, Li Q. The clinical efficacy of urate-lowering therapy in acute gout: a meta-analysis of randomized controlled trials. Clin Rheumatol 2021;40:701–10.
[9] Jia E, Yao X, Geng H, Zhong L, Xie J, Xiao Y, et al. The effect of initiation of urate-lowering treatment during a gout flare on the current episode: a meta-analysis of randomized controlled trials. Adv Rheumatol 2022;62:5.
[10] Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160.
[11] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
[12] Taylor TH, Mecchella JN, Larson RJ, Kerin KD, Mackenzie TA. Initiation of allopurinol at first medical contact for acute attacks of gout: a randomized clinical trial. Am J Med 2012;125:1126–34.
[13] Sun R, Lu J, Li H, Cheng X, Xin Y, Li C. Evaluation of febuxostat initiation during an acute gout attack: a prospective, randomized clinical trial. Joint Bone Spine 2020;87:461–6.
[14] Satpanich P, Pongsittisak W, Manavathongchai S. Early versus late allopurinol initiation in acute gout flare (ELAG): a randomized controlled trial. Clin Rheumatol 2022;41:213–21.
[15] Yang D, Chen H, Wei JC. Early urate-lowering therapy in gouty arthritis with acute flares: a double-blind placebo controlled clinical trial. Eur J Med Res 2023;28:10–8.
[16] Hill EM, Sky K, Sit M, Collamer A, Higgs J. Does starting allopurinol prolong acute treated gout? A randomized clinical trial. J Clin Rheumatol 2015;21:120–5.
[17] Jia E, Zhang Y, Ma W, Li B, Geng H, Zhong L, et al. Initiation of febuxostat for acute gout flare does not prolong the current episode: a randomized clinical trial. Rheumatology (Oxford) 2021;60:4199–204.
[18] Feng X, Li Y, Gao W. Significance of the initiation time of urate-lowering therapy in gout patients: a retrospective research. Joint Bone Spine 2015;82:428–31.