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Urate-Lowering Drugs and Muscle Injury: A Systematic Review and Network Meta-Analysis

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Abstract

Several urate-lowering drugs have been linked to muscle injury. This study investigated the association of oral urate-lowering drugs with the risk of muscle injury by performing a network meta-analysis of randomized and non-randomized controlled trials. A systematic search of MEDLINE, via PubMed, the ClinicalTrials.gov website, and the Cochrane Central Register of Controlled Trials was conducted to identify relevant studies with a primary outcome of "all muscle injuries." A random-effects model was used to perform a frequentist network meta-analysis to estimate whether there was significant heterogeneity among the studies. In total, 32 studies including 28,327 participants with 2694 (9.5%) "all muscle injuries" were assessed, and the overall risk of bias was judged to be low to moderate. No statistically significant differences were found between placebo and 6 urate-lowering therapies: allopurinol (risk ratio, RR, 1.05; 95% confidence interval, 95%CI, 0.63-1.73), febuxostat (RR 1.10, 95%CI 0.71-1.70), lesinurad (RR 7.00, 95%CI 0.31-160.36), lesinurad concomitant with allopurinol (RR 0.85, 95%CI 0.34-2.11), lesinurad concomitant with febuxostat (RR 1.97, 95%CI 0.55-7.03), and topiroxostat (RR 0.99, 95%CI 0.37-2.65). The findings suggest that there is little need to consider the risk of muscle injury when using urate-lowering drugs in the clinical setting.

Keywords

allopurinol, febuxostat, lesinurad, muscle injury, network meta-analysis, topiroxostat

Gout is the most common type of joint inflammation and its prevalence continues to grow worldwide, with more than 9 million people affected in the USA.[1] Oral urate-lowering therapy is typically used to prevent flares of gout,[2] and the number of patients receiving these drugs has steadily increased.[3] Although xanthine oxidase inhibitors, such as allopurinol or febuxostat, are generally used as urate-lowering therapy, the guidelines also suggest administering uric acid reabsorption inhibitors, such as lesinurad or benzbromarone, in patients with high serum uric acid levels despite the administration of xanthine oxidase inhibitors.[4,5]

These urate-lowering therapies are important in the treatment of patients with gout, but there is concern about the association between the excessive lowering of urate and adverse outcomes.[6,7] Given that uric acid is a strong free-radical scavenger, lowering the serum uric acid level may reduce antioxidant capacity, resulting in damage to various organs. Indeed, a number of studies suggest that reducing serum uric acid levels may lead to worse outcomes, including an increased risk of cardiovascular disease or mortality.[6–11] Interestingly, high oxidative stress in muscle cells may cause muscle injury, such as rhabdomyolysis, via a decrease in the production of adenosine triphosphate.[12] Skeletal muscle contraction generates free radicals, and prolonged and intense exercise can contribute to oxidative damage in active myofibers. Urate could potentially act as an antioxidant scavenger in muscle fibers during exercise, implying that lower uric acid levels might increase the risk of muscle injury.[13] In particular, rhabdomyolysis is an important adverse event and is fatal in 8%-10% of patients.[14] Moreover, these patients often have the complication of acute kidney injury,[15] for which the mortality rate is as high as 42%.[16]

It has been reported that some urate-lowering drugs have the potential to cause muscle injuries. For example, a link between febuxostat and rhabdomyolysis was suggested in 3 case reports,[17–19] and a retrospective cohort study reported an increased risk of myopa-

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thy in patients with chronic kidney disease who used febuxostat.[20] Moreover, 2 randomized controlled trials (RCTs) of lesinurad reported each case of rhabdomyolysis as an adverse event.[21,22] On the other hand, our previous meta-analysis of RCTs found no increased risk of muscle injury associated with febuxostat compared with placebo or allopurinol,[23] and allopurinol reduces oxidative stress in damaged muscle, attenuates muscle inflammation, and accelerates muscular recovery in rats.[24] Nevertheless, the number of patients investigated was limited by the inclusion of only RCTs, and the effect of selective uric acid reabsorption inhibitors has not been investigated. Clarification of the risk of muscular injury would aid in the selection of urate-lowering medications. Therefore, this study investigated the association of oral urate-lowering drugs with the risk of muscle injury by performing a network meta-analysis of RCTs and non-RCTs.

Methods

Study Design

A systematic review/network meta-analysis of RCTs and non-RCTs was performed to investigate the risk of muscle injury in patients who use oral urate-lowering drugs. This method can merge and compare direct and indirect evidence and help in selection between the various medications.

Search Strategy and Selection of Studies

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol.[25] The study included all RCTs, regardless of whether they had a cluster- or crossover-randomized design, as well as non-RCTs. The study cohorts comprised adults with either hyperuricemia or gout. The intervention involved treatment with urate-lowering drugs, including allopurinol benzbromarone, dotinurad, febuxostat, lesinurad, and topiroxostat. The analysis protocol was not registered in advance.

We applied the following exclusion criteria: a study population comprising individuals who do not have gout or hyperuricemia; a study population comprising individuals with serious underlying conditions, such as cancer, or individuals who need organ transplantation; no assessment of adverse events; and published in a language other than English. No limitations were applied in terms of drug dose or follow-up period. Authors of studies that did not cover all outcomes were contacted to gather additional data that had not yet been published.

We conducted a comprehensive search of MEDLINE via PubMed, the ClinicalTrials.gov website, and the Cochrane Central Register of Controlled Trials (CENTRAL)to identify all relevant studies. The search methodology was as follows: ((“hyperuricemia”[MeSH Terms] OR “gout”[MeSH Terms]) AND (“allopurinol”[MeSH Terms] OR “febuxostat”[MeSH Terms] OR “benzbromarone”[MeSH Terms] OR (“topiroxostat”[Title/Abstract] OR “lesinurad”[Title/Abstract] OR “dotinurad”[Title/Abstract])). The search strategy used for CENTRAL was (MeSH descriptor: [Hyperuricemia] explode all trees OR MeSH descriptor: [Gout] explode all trees) AND (MeSH descriptor: [Allopurinol] explode all trees OR MeSH descriptor: [Febuxostat] explode all trees OR MeSH descriptor: [benzbromarone] explode all trees OR MeSH descriptor: [topiroxostat] explode all trees OR MeSH descriptor: [lesinurad] explode all trees OR MeSH descriptor: [dotinurad] explode all trees). The search strategy used for ClinicalTrials.gov was (other terms: allopurinol, benzbromarone, dotinurad, febuxostat, lesinurad, or topiroxostat).

The titles and abstracts of the articles identified were evaluated in accordance with the inclusion and exclusion criteria, and a full-text review was conducted when deemed appropriate. Then, outcome measurement, data extraction, data synthesis, statistical analysis, and quality assessment were performed. Two of the 3 researchers (S.M., M.M., or K.K.) performed these tasks independent of one another. Any discrepancies in the results of assessments were resolved through discussion until a consensus was reached among the 3 researchers.

Outcome Definition and Measures

“All muscle injuries” was selected as the primary outcome, and “severe muscle injuries” and “mild muscle injuries” were selected as secondary outcomes. These 3 outcomes were extracted directly from the results of the retrieved articles or from the ClinicalTrials.gov website. Muscle injuries were defined as muscle-related adverse events, including rhabdomyolysis, myopathy, increased blood creatine phosphokinase, muscle damage, and muscle pain, and their severity was judged by the investigators in each study. When there was no description of severity, the injury was classified as “mild.” “All muscle injuries” were calculated as the sum of “severe” and “mild” muscle injuries.

Data Extraction and Quality Assessment

The following data were extracted from each study: author names, country, publication status, study design, details of interventions, inclusion and exclusion criteria, diagnostic criteria for hyperuricemia, study period, population size, mean age, sex, comorbidity, number of outcomes, and number of dropouts. If mean values and standard deviations were unavailable, medians were assumed to be equal to mean values.

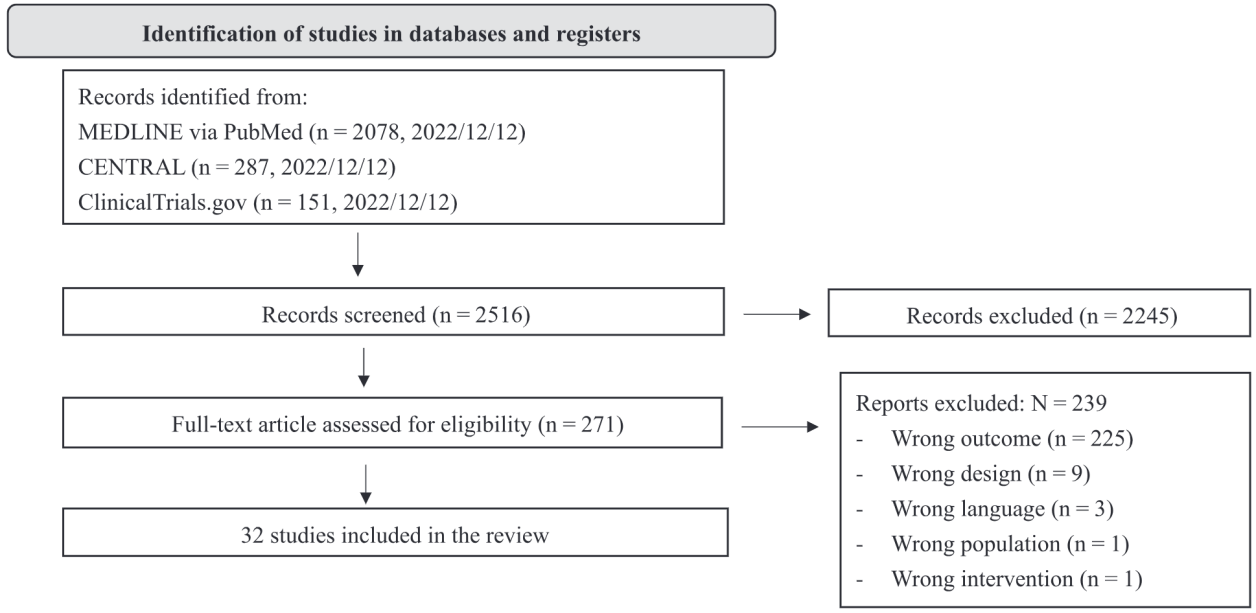

Figure 1. PRISMA flow diagram. CENTRAL, Cochrane Central Register of Controlled Trials; MEDLINE, Medical Literature Analysis and Retrieval System Online; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

The risk of bias for all outcomes in each study was assessed using version 2 of the Cochrane risk-of-bias tool for randomized trials and the ROBINS-I (risk of bias in non-randomized studies – of interventions) for non-RCTs.[26,27]

Statistical Analysis

First, a meta-analysis of studies that included direct treatment comparisons was performed using the DerSimonian–Laird random-effects model, and muscle injuries were visually assessed in each study.

Second, a frequentist network meta-analysis was performed using a random-effects model to take into account any significant heterogeneity among the included studies. The risk ratios (RRs) and 95% confidence intervals (95%CIs) for muscle injuries that occurred with each urate-lowering drug in comparison with the placebo were computed based on the size of the intention-to-treat population, after which the difference between direct and indirect treatment comparisons was calculated. The degree of heterogeneity among the studies was evaluated using the I^2 statistic, which is typically interpreted as follows: 0%-40%, likely not important; 30%-60%, moderate heterogeneity; 50%-90%, substantial heterogeneity; and 75%-100%, considerable heterogeneity.[26] To assess the potential for publication bias, a funnel plot was visually inspected and Harbord's regression modification of Egger's test was performed.[28]

Statistical differences were evaluated using R 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) and MetaInsight 4.0.0. (https://crsu.shinyapps.io/MetaInsight/) [29] $P < .05$ was taken to indicate significance.

Sensitivity Analysis

A sensitivity analysis was performed, using a frequentist network meta-analysis with a random-effects model, on the sum of "myopathy or increased creatine kinase" that was extracted from "all muscle injuries." This was performed to extract only objective events from muscle injuries and to avoid any bias stemming from the subjective opinions of patients.

Subgroup Analysis

Two types of subgroup analyses for "all muscle injuries" were performed in this study. A meta-analysis of studies that included direct treatment comparisons was performed using the DerSimonian-Laird random-effects model, and muscle injuries were assessed in each study.

First, because chronic kidney disease and heart disease increase the risk of muscle injuries.[17,18,20,30] studies that included patients with these diseases were analyzed. Second, because likely unimportant heterogeneity was detected in the study of allopurinol versus placebo, and because substantial heterogeneity was detected in the study of febuxostat versus allopurinol, the type of study (whether or not gout was present), study period, and patient age were all analyzed.

Results

We identified 2078 studies in PubMed, 287 in CENTRAL, and 151 on the ClinicalTrials.gov website. After the initial screening process, 271 articles were evaluated

for eligibility. Additional details on adverse events not reported in 2 studies were obtained directly from the respective corresponding authors, and one of these studies satisfied the inclusion criteria for the network meta-analysis.[31] Finally, 32 studies and 34 comparisons, with 1 study including a triple arm,[32] were included in the network meta-analysis (Figure 1). Table 1 shows the characteristics of the included studies, and Table S1 shows the details of the reported muscle injuries.

Of the 32 studies included in the analyses, allopurinol was evaluated in 20, febuxostat was evaluated in 23, topiroxostat was evaluated in 3, lesinurad was evaluated in 1, lesinurad concomitant with febuxostat was evaluated in 1, and lesinurad concomitant with allopurinol was evaluated in 1. No studies that evaluated benzbromarone or dotinurad were found. All studies were reported between 2005 and 2022. The median study duration was 24 weeks. Eighteen studies (56%) included only patients with gout and the remaining 14 studies (44%) included patients with hyperuricemia only or with both hyperuricemia and gout. Thirty studies (94%) were RCTs and 2 studies (6%) were non-RCTs. Twenty-four (80%) of the 30 RCTs had a blinded design, and there were no cluster or crossover RCTs.

The results of the meta-analysis for studies that included direct treatment comparisons are shown in Figures S1- S4. No relationship was found between the use of any of the urate-lowering drugs and the incidence of each muscle injury.

Quality Assessment

The risk of bias was assessed for "all muscle injuries" and found to be "low" in 12 studies (38%), "of some concern" in 13 studies (41%), and "high" in 7 studies (22%) (Figures 2 and 3). Therefore, the overall risk of bias was considered to be low to moderate. The risk of bias was considered "high" for open-label RCTs and non-RCTs. Although the risks of bias for "severe muscle injuries," "mild muscle injuries," and "myopathy or increased creatine kinase" were also assessed, the results were determined to be the same as those for "all muscle injuries."

The results of the assessment of inconsistency for "all muscle injuries" are shown in Table 2. No difference between direct and indirect effects were found for each comparison. Statistical tests of "all muscle injuries" found low heterogeneity in the comparison between febuxostat and placebo ($I^2 = 0\%$), likely unimportant heterogeneity in the comparison between allopurinol and placebo ($I^2 = 47\%$), and substantial heterogeneity in the comparison between allopurinol and febuxostat ($I^2 = 90\%$). It was not possible to identify the heterogeneity of the other comparisons because the number of studies was limited.

The league table for risk of "all muscle injuries" with urate-lowering drugs is shown in Table 3. Data were available for 9 of 21 possible results by pairwise meta-analysis, and no conflicting results were identified between pairwise and network meta-analysis.

Publication bias could be assessed only in the studies of allopurinol and febuxostat, and was not apparent in the funnel plot (Figure S5) or Egger's test ($P = .75$).

Primary Outcome of all Muscle Injuries

A total of 32 studies including 28,327 participants with 2694 (9.5%) "all muscle injuries" were assessed in the network meta-analysis. No significant differences were found between the 6 urate-lowering therapies and the placebo (Figure 4): allopurinol (RR 1.05, 95%CI 0.63-1.73), febuxostat (RR 1.10, 95%CI 0.71-1.70), lesinurad (RR 7.00, 95%CI 0.31-160.36), lesinurad concomitant with allopurinol (RR 0.85, 95%CI 0.34-2.11), lesinurad concomitant with febuxostat (RR 1.97, 95%CI 0.55-7.03), and topiroxostat (RR 0.99, 95%CI 0.37-2.65).

Secondary Outcomes

A total of 12 RCTs including 19,194 participants with 72 (0.4%) "severe muscle injuries" were assessed in the network meta-analysis. This analysis included only RCTs because the non-RCTs did not report these events. Only 3 arms (allopurinol, febuxostat, and topiroxostat) could be assessed, and no significant differences were found between the 3 urate-lowering therapies and the placebo (Figure S6): allopurinol (RR 1.09, 95%CI 0.39-3.05), febuxostat (RR 1.08, 95%CI 0.45-2.59), and topiroxostat (RR 0.38, 95%CI 0.01-10.85).

A total of 30 studies including 27,234 participants with 2603 (9.6%) "mild muscle injuries" were assessed in the network meta-analysis. All 6 arms were included in the analysis, and no significant differences were found between the 6 urate-lowering therapies and the placebo (Figure S6): allopurinol (RR 1.07, 95%CI 0.64-1.81), febuxostat (RR 1.11, 95%CI 0.70-1.75), lesinurad (RR 7.00, 95%CI 0.30-162.73), lesinurad concomitant with allopurinol (RR 1.14, 95%CI 0.39-3.29), lesinurad concomitant with febuxostat (RR 1.99, 95%CI 0.54-7.40), and topiroxostat (RR 1.00, 95%CI 0.37-2.74).

Sensitivity Analysis

A total of 18 studies including 15,535 participants with 876 (5.6%) cases of "myopathy or increased creatine kinase" were assessed in the network meta-analysis. Five arms were included, and no significant differences were found between the 5 urate-lowering therapies and the placebo (Figure S6): allopurinol (RR 1.20, 95%CI 0.48-3.01), febuxostat (RR 0.92, 95%CI 0.41-2.07), lesinurad concomitant with allopurinol (RR 1.27, 95%CI 0.32-5.16), lesinurad concomitant with febuxostat (RR 1.87,

Table 1. Characteristics of the Included Studies

Reference	Country (study type and design)	Patients (n)	Intervention and comparison	Study duration (weeks)	Main population, comorbidity included
Bardin et al 2017[33]	Multinational (RCT, blinded)	610	Lesinurad (200-400 mg/day) + allopurinol (>200 mg/day) Placebo + allopurinol (>200 mg/day)	52	Gout, none
Becker et al 2005[34]	North America (RCT, blinded)	153	Febuxostat (40-120 mg/day)Placebo	4	Gout, none
Becker et al 2005[35]	North America (RCT, blinded)	760	Allopurinol (300 mg/day) Febuxostat (80-120 mg/day)	52	Gout, none
Becker et al 2010[36]	North America (RCT, blinded)	2269	Allopurinol (200-300 mg/day) Febuxostat (40-80 mg/day)	24	Gout, none
Dalbeth et al 2017[37]	North America(RCT, blinded)	314	Febuxostat (40-80 mg/day) Placebo	104	Gout, none
Dalbeth et al 2019[38]	North America (RCT, blinded)	324	Lesinurad (200-400 mg/day) + febuxostat (80 mg/day) Placebo + febuxostat (80 mg/day)	52	Gout, none
Desideri et al 2022[39]	Europe (RCT, open-label)	196	Allopurinol (100-600 mg/day) Febuxostat (80-120 mg/day)	38	Gout, none
Givertz et al 2015[40]	North America (RCT, blinded)	253	Allopurinol (300-600 mg/day) Placebo	24	Hyperuricemia (UA $\geq$ 9.5 mg/dL), heart failure
Goldfarb et al 2011[41]	North America (RCT, blinded)	153	Febuxostat (40 mg/day) Placebo	4	Gout, none
Hosoya et al 2016[42]	Asia (RCT, blinded)	205	Allopurinol (200 mg/day) Topiroxostat (120 mg/day)	16	Hyperuricemia (UA $\geq$ 7 mg/dL), none
Hosoya et al 2016[43]	Asia (RCT, blinded)	187	Topiroxostat (40-120 mg/day) Placebo	8	Hyperuricemia (UA $\geq$ 8 mg/dL), none
Kamatani et al 2011[44]	Asia (RCT, blinded)	102	Febuxostat (20-40 mg/day) Placebo	8	Hyperuricemia (UA > 8 mg/dL), none
Kamatani et al 2011[45]	Asia (RCT, blinded)	199	Febuxostat (20-80 mg/day) Placebo	16	Hyperuricemia (UA $\geq$ 7.0 mg/dL), none
Kamatani et al 2011[46]	Asia (RCT, open-label)	38	Allopurinol (300 mg/day) Febuxostat (40-60 mg/day)	16	Hyperuricemia (UA $\geq$ 7.0 mg/dL), none
Kamatani et al 2011[47]	Asia (RCT, blinded)	244	Allopurinol (200 mg/day) Febuxostat (40 mg/day)	8	Hyperuricemia (UA $\geq$ 8 mg/dL), none
Kario et al 2021[48]	Asia (RCT, open-label)	135	Febuxostat (10-60 mg/day) Topiroxostat (40-120 mg/day)	24	Hyperuricemia (UA > 7.0 mg/dL), none
Kimura et al 2018[49]	Asia (RCT, blinded)	441	Febuxostat (40 mg/day) Placebo	108	Hyperuricemia (UA 7.0-10.0 mg/dL), CKD
Mackenzie et al 2020[50]	Europe (RCT, open-label)	6128	Allopurinol (100-300 mg/day) Febuxostat (80-120 mg/day)	312	Gout, none
NCT02078219[51]	Asia (RCT, blinded)	81	Allopurinol (200 mg/day) Placebo	24	Hyperuricemia (UA > 8.0 mg/dL), none
YSO Hsu et al 2020[52]	Asia (non-RCT)	6057	Allopurinol (dose not reported) Febuxostat (dose not reported)	208	Hyperuricemia (UA > 7 mg/dL), CKD
O'Dell et al 2022[53]	North America (RCT, blinded)	940	Allopurinol (100-800 mg/day) Febuxostat (40-120 mg/day)	72	Gout, none

(*Continued*)

Table 1. Continued

Reference	Country (study type and design)	Patients (n)	Intervention and comparison	Study duration (weeks)	Main population, comorbidity included
Perez-Ruiz et al 2016[54]	Multinational (RCT, blinded)	208	Lesinurad (200-400 mg/day) + allopurinol (200-600 mg/day) Placebo + allopurinol (200-600 mg/day)	4	Gout, none
Poiley et al 2016[55]	North America (RCT, blinded)	83	Allopurinol (300 mg/day) Placebo	12	Gout, none
Saag et al 2016[56]	North America (RCT, blinded)	96	Febuxostat (40-80 mg/day) Placebo	56	Gout, CKD
Saag et al 2017[57]	North America (RCT, blinded)	603	Lesinurad (200-400 mg/day) + allopurinol (200-800 mg/day) Placebo + allopurinol (200-800 mg/day)	52	Gout, none
Schumacher et al 2008[32]	North America (RCT, blinded)	1072	Allopurinol (300 mg/day) Febuxostat (80-240 mg/day) Placebo	28	Gout, none
Suzuki et al 2021[31]	Asia (RCT, open-label)	263	Allopurinol (200 mg/day) Febuxostat (10 mg/day)	156	Hyperuricemia (UA > 7.0 mg/dL), heart failure
Tanaka et al 2020[58]	Asia (RCT, open-label)	483	Febuxostat (10-60 mg/day) Control (no placebo)	104	Hyperuricemia (UA > 7.0 mg/dL), none
Tausche et al 2017[59]	Europe (RCT, blinded)	214	Lesinurad (400 mg/day) Placebo	24	Gout, none
White et al 2018[60]	North America (RCT, blinded)	6190	Allopurinol (200-600 mg/day) Febuxostat (40-80 mg/day)	332	Gout, CVD
Xu et al 2015[61]	Asia (RCT, blinded)	504	Allopurinol (300 mg/day) Febuxostat (40-80 mg/day)	24	Gout, none
Yunhua et al 2020[62]	Asia (non-RCT)	96	Allopurinol (300 mg/day) Febuxostat (40-80 mg/day)	24	Hyperuricemia (UA > 8.0 mg/dL), none

CKD, chronic kidney disease; CVD, cardiovascular disease; RCT randomized controlled trial; UA, uric acid.

95%CI 0.28-12.60), and topiroxostat (RR 0.87, 95%CI 0.19-4.01).

Subgroup Analysis

The subgroup analysis results are shown in Figures S7-S9. First, studies that evaluated febuxostat versus placebo in patients with chronic kidney disease, studies that evaluated allopurinol versus febuxostat in patients with heart disease, and studies that evaluated allopurinol versus febuxostat in patients with chronic kidney disease or heart disease were assessed. The risk of "all muscle injuries" was not increased in any of these populations (Figure S7). Second, studies that evaluated allopurinol versus placebo could be assessed only by excluding 1 study in patients with heart disease, and heterogeneity was improved from 47% to 17% (Figure S8). Furthermore, the heterogeneity of studies that evaluated febuxostat versus allopurinol was improved from 90% to 0% by including only blinded RCTs, to 30% by including only trials in which the study period was <52 weeks, and to 3% by including only studies in which the mean patient age was <60 years (Figure S9).

Discussion

This systematic review and network meta-analysis of RCTs and non-RCTs assessed a total of 32 studies that included 28,327 participants with 2694 (9.5%) muscle injuries. The results did not show any evidence of an association between urate-lowering drugs and muscle injuries, which suggests that the risk of muscle injuries with the various urate-lowering drugs is no higher than that with placebo. A previous meta-analysis of RCTs found that febuxostat and allopurinol do not increase the risk of muscle injuries compared with placebo,[23] and there are no data on the association between the use of lesinurad and muscle injuries. This large-scale network meta-analysis, which included non-RCTs, reconfirms that the use of allopurinol and febuxostat do not increase the risk of muscle injury and shows that muscle injuries may be less of a concern when using lesinurad. Considering that the management of gout is suboptimal because of poor patient compliance with urate-lowering drugs,[63] this information is reassuring for patients and healthcare workers and may improve the management of gout.

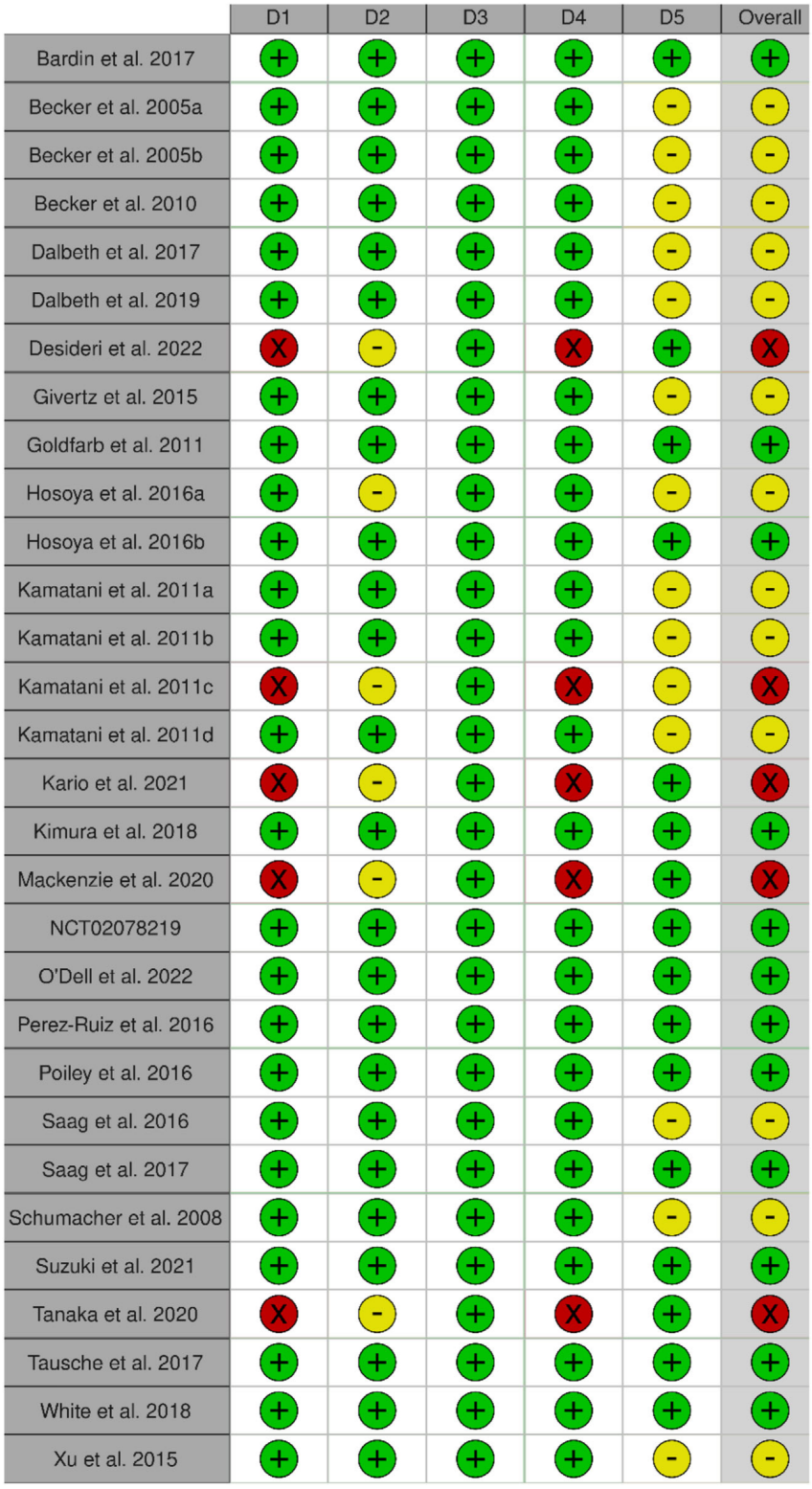

Figure 2. Risk-of-bias summary for randomized controlled trials: D1, bias arising from the randomization process; D2, bias arising from deviations from intended interventions; D3, bias arising from missing outcome data; D4, bias in measurement of the outcome; D5, bias in selection of results reported. ×, high risk of bias; −, some concerns; +, low risk of bias.

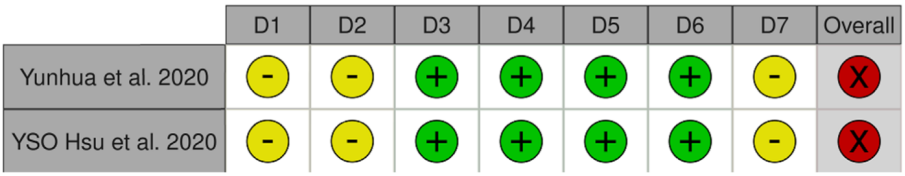

Figure 3. Risk-of-bias summary for non-randomized controlled trials: D1, bias caused by confounding; D2, bias in selection of study participants; D3, bias in classification of interventions; D4, bias arising from deviations from intended interventions; D5, bias stemming from missing data; D6, bias in measurements of outcomes; D7, bias in selection of results reported. ×, serious; −, moderate; +, low.

Table 2. Assessment of Inconsistency for "All Muscle Injuries"

Comparison	Studies (n)	Direct	Indirect	Difference (95%CI)	I^2 index
Allopurinol versus febuxostat	13	−0.07	0.10	−0.17 (−1.40-1.07)	90%
Febuxostat versus placebo	9	0.02	0.49	−0.47 (−1.69-0.76)	0%
Allopurinol versus placebo	4	0.14	0.02	0.12 (−1.03-1.27)	47%
Allopurinol versus lesinurad + allopurinol	3	0.25	NA	NA	NA
Allopurinol versus topiroxostat	1	−0.06	0.26	−0.32 (−2.48-1.85)	NA
Febuxostat versus lesinurad + febuxostat	1	−0.70	NA	NA	NA
Febuxostat versus topiroxostat	1	1.10	0.01	1.09 (−2.53-4.70)	NA
Lesinurad versus placebo	1	1.97	NA	NA	NA
Topiroxostat versus placebo	1	0.04	−0.04	0.08 (−2.18-2.34)	NA

Results listed only for combinations that were direct comparisons in the meta-analysis. CI, confidence interval; NA, not applicable.

Table 3. League Table for Risk of "All Muscle Injuries" with Each Urate-Lowering Drug

Pairwise meta-analysis						
Lesinurad + allopurinol	NA	NA	0.81 (0.38-1.74)	NA	NA	NA
0.85 (0.34-2.13)	**Placebo**	0.96 (0.19-4.75)	0.89 (0.40-1.98)	0.99 (0.60-1.62)	NA	0.14 (0.01-3.28)
0.85 (0.25-2.90)	1.01 (0.38-2.69)	**Topiroxostat**	1.05 (0.31-3.55)	0.34 (0.01-9.67)	NA	NA
0.81 (0.38-1.74)	0.95 (0.57-1.58)	0.95 (0.37-2.45)	**Allopurinol**	0.93 (0.63-1.39)	NA	NA
0.77 (0.33-1.81)	0.91 (0.58-1.41)	0.90 (0.34-2.39)	0.95 (0.66-1.38)	**Febuxostat**	0.56 (0.17-1.85)	NA
0.43 (0.10-1.87)	0.51 (0.14-1.81)	0.50 (0.11-2.35)	0.53 (0.15-1.86)	0.56 (0.17-1.85)	**Lesinurad + febuxostat**	NA
0.12 (0.00-3.18)	0.14 (0.01-3.28)	0.14 (0.01-3.79)	0.15 (0.01-3.58)	0.16 (0.01-3.73)	0.28 (0.01-8.32)	**Lesinurad**
Network meta-analysis						

Numbers indicate the relative risk and 95% confidence interval. NA, not applicable.

Although uric acid reabsorption inhibitors such as lesinurad have not been mentioned in terms of muscle injuries as adverse events, these types of drugs are sometimes used concomitantly with xanthine oxidase inhibitors. Therefore, there may be concerns about adverse events in view of their strong uric acid-lowering effect. However, this network meta-analysis found that lesinurad alone or concomitant with allopurinol or febuxostat did not increase the risk of muscle injuries in comparison with placebo. Unfortunately, we did not find any study that evaluated muscle injuries caused by benzbromarone or dotinurad. Further studies may be needed to obtain data on the association between muscle injuries and uric acid reabsorption inhibitors because of the lack or small number of studies overall.

There may be some ongoing concerns about the risk of muscle injury in patients with chronic kidney disease receiving febuxostat. Febuxostat is reported to increase the risk of myopathy and rhabdomyolysis in patients with chronic kidney disease.[20] Our previous meta-analysis of RCTs found that febuxostat did not increase the risk of muscle injury compared with placebo or allopurinol,[23] and similar results were also found in the present study. However, only 2 studies included in our meta-analysis evaluated a population with chronic kidney disease (Figure S7), and it was difficult to evaluate these associations.

The risk of bias in this study was generally considered to be low to moderate. One of the strengths of this research is that most of the included studies were RCTs, which can mitigate the biases associated with the use of summary statistics and allow for the adjustment of confounding factors. Thus, it may be useful when the RCTs available do not have sufficient

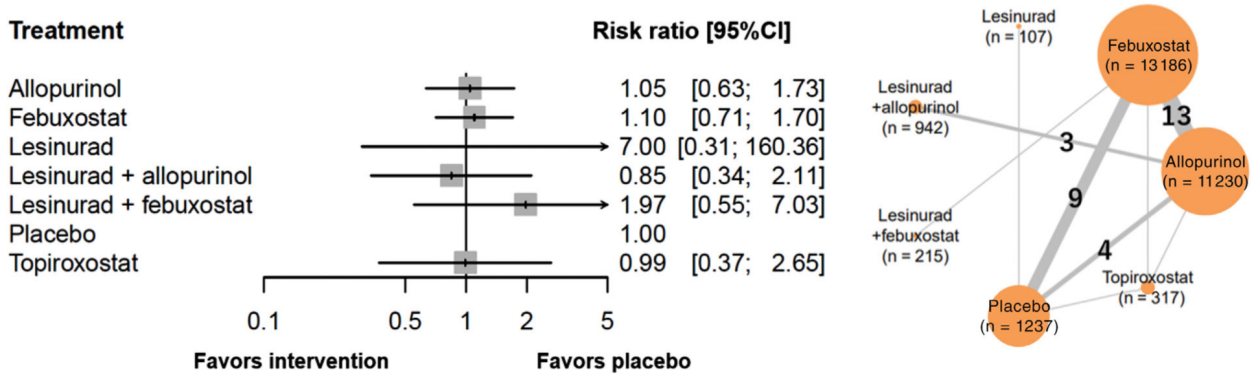

Figure 4. Forest plot and network plot of urate-lowering drugs versus placebo for the primary outcome of "all muscle injuries." Network meta-analysis estimates of treatment effect for each drug versus placebo are reported as RRs and 95%CIs. For the network plot, the numbers on the line indicate the number of studies conducted for the comparison; lines with no numbers indicate that there was only 1 study. CI, confidence interval; RR, risk ratio.

statistical power to address the outcome of interest.[64] Furthermore, the league table for risk of "all muscle injuries" does not show any conflicting results between pairwise and network meta-analysis (Table 3), and the results of "direct" and "indirect" comparisons are consistent. Moreover, the funnel plot did not show any publication bias in the studies between allopurinol and febuxostat. These findings suggest that the validity of the results of this network meta-analysis is likely to be high.

We identified likely unimportant heterogeneity in the comparison between allopurinol and placebo ($I^2 = 47\%$) and substantial heterogeneity in the comparison between allopurinol and febuxostat ($I^2 = 90\%$). These heterogeneities were improved by excluding studies that included patients aged ≥60 years, patients with comorbid heart disease, a study period of >52 weeks, or only blinded RCTs. Thus, a rigorous RCT study design considering the patient's age, study period, and comorbidities may contribute to obtaining study results with a low risk of bias for muscle injuries caused by urate-lowering drugs. In particular, muscle injuries may be caused by a decrease in antioxidant effects via hypouricemia,[8] and further studies with longer follow-up periods may be important.

This network meta-analysis has yielded results with important clinical implications but there are also some limitations that should be discussed. First, the muscle-related adverse events reported were likely derived from the subjective complaints of patients and the evaluation methods used to assess muscle injuries may have differed among the included studies. The definitions used to evaluate muscle injuries may also have differed among the studies and the severity of the injuries ranged from mild to severe (Table S1), although most of the adverse events were not serious. However, several factors that increased heterogeneity between the studies were identified, and differences in the methods used to assess muscle injuries may not be the primary cause of heterogeneity. Furthermore, the results of the sensitivity analysis consistently support the present findings. Second, this meta-analysis focused on studies that were designed primarily to evaluate treatment efficacy and thus may not have placed a strong emphasis on assessing adverse events. This means that their detection power may not be as strong as that in studies that focused on primary outcomes. Third, there was a wide range of 95%CIs in the results for lesinurad. The main reason may be the limited number of participants included in the trial, suggesting the need for further research. Fourth, approval for allopurinol was granted by the US Food and Drug Administration in 1966, whereas febuxostat and lesinurad were approved in 2009 and 2015, respectively.[65] Therefore, the nature and frequency of adverse events found in clinical studies may have been influenced by changes in clinical practices or by shifts in the perception of adverse events associated with urate-lowering drugs. Fifth, the median study period was 24 weeks, and this observation period may not have been long enough. Moreover, only 2 trials included in this meta-analysis evaluated populations with chronic kidney disease. Therefore, further high-quality studies that include longer-term observation periods and patients with chronic kidney disease may be needed.

Conclusions

In conclusion, this systematic review and network meta-analysis targeting RCTs and non-RCTs suggests that there may be little need to consider the risk of muscle injuries when using urate-lowering drugs in the clinical setting. Although further studies are needed, this finding may provide useful information for improving patient compliance with urate-lowering drugs.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by S.M., M.M., K.K., and R.K. The first draft of the article was written by S.M., and all authors commented on previous versions of the article. All authors read and approved the final version for publication.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

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Data Availability Statement

Data supporting the findings of this study are available from the author, upon reasonable request.

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