DR. LINAN ZENG (Orcid ID : 0000-0001-9892-2000)

DR. TUHINA NEOGI (Orcid ID : 0000-0002-9515-1711)

DR. JOHN D. FITZGERALD (Orcid ID : 0000-0002-8419-7538)

DR. NICOLA DALBETH (Orcid ID : 0000-0003-4632-4476)

DR. TED R MIKULS (Orcid ID : 0000-0002-0897-2272)

Article type : Original Article

Comparative efficacy and safety of pharmacological interventions in patients experiencing a gout flare: a systematic review and network meta-analysis

Linan Zeng PhD

Pharmacy Department/Evidence-based Pharmacy Center, West China Second University Hospital, Sichuan University and Key Laboratory of Birth Defects and Related Disease of Women and Children (Sichuan University), Ministry of Education, Chengdu, China

Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada

zengl15@mcmaster.ca

Anila Qasim HBSc, MSc

Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada

qasima@mcmaster.ca

Tuhina Neogi MD, PhD, FRCPC

Boston University, Boston, Massachusetts
tneogi@bu.edu

John D. Fitzgerald MD, PhD
University of California, Los Angeles and VA Greater Los Angeles Health Care System, Los Angeles, California
JFitzgerald@mednet.ucla.edu

Nicola Dalbeth MD, FRACP
Department of Medicine, University of Auckland, Auckland, New Zealand
n.dalbeth@auckland.ac.nz

Ted R. Mikuls MD, MSPH
Department of Internal Medicine, Division of Rheumatology, University of Nebraska Medical Center, Omaha, USA
Medicine, VA Nebraska-Western Iowa Health Care System, Omaha, USA
tmikuls@unmc.edu

Gordon H. Guyatt MD
Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada
guyatt@mcmaster.ca

Romina Brignardello-Petersen MD, PhD
Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada
brignarr@mcmaster.ca

Corresponding author

Romina Brignardello-Petersen

1280 Main St West, Hamilton, ON, L8S 4L8, Canada

brignarr@mcmaster.ca

ABSTRACT

Objective. To compare the relative efficacy and safety of pharmacological anti-inflammatory interventions for gout flares.

Methods. We searched Ovid Medline, Embase and Cochrane library for randomized controlled trials (RCTs) that compared pharmacological anti-inflammatory treatment of gout flares. We conducted a network meta-analysis (NMA) using a frequentist framework, and assessed the certainty of evidence and made conclusions using the GRADE for NMA.

Results. In the 30 eligible RCTs, canakinumab provided the highest pain reduction at day two and at longest follow-up (Mean difference [MD] relative to acetic acid derivative non-steroidal anti-inflammatory drugs [NSAIDs] -41.12, 95% confidence interval [CI] -53.36 to -29.11 on a 0 to 100 scale at day two; MD -12.84, 95% CI -20.76 to -4.91 at longest follow-up; both moderate certainty; MID -19). Intravenous or intramuscular corticosteroids was inferior to canakinumab but may be better than the other commonly used interventions (low to very low certainty). For joint tenderness, canakinumab may be the most effective intervention at day two. Acetic acid

derivative NSAIDs improved joint swelling better than profen NSAIDs at day two (MD -0.29, 95% CI -0.56 to -0.02 on a 0 to 4 scale; moderate certainty) and improved patient global assessment (PGA) greater than profen NSAIDs at the longest follow-up (MD -0.44, 95% CI -0.86 to -0.02; moderate).

Conclusion. Canakinumab may be superior to other alternatives and intravenous or intramuscular corticosteroids may be the second best in pain reduction. Acetic acid derivative NSAIDs may be superior to profen NSAIDs in improving joint swelling and patient global assessment.

Significance & Innovations

- Despite consistent recommendations of first-line options for gout flare from guidelines, uncertainty of the efficacy and safety of pharmacological interventions remains.
- This systematic review identifies, in patients with gout flares, a potential advantage of canakinumab versus other anti-inflammatory interventions in pain reduction at day two and longest follow-up, and in improvement of joint tenderness at day two.
- Among commonly used interventions, intravenous or intramuscular corticosteroids may be superior to COX-2 highly selective NSAIDs, profen NSAIDs, colchicine and oral corticosteroids in pain reduction at day two. Acetic acid derivative NSAIDs are probably superior to profen NSAIDs in reducing joint swelling at day two and patient global assessment at longest follow-up.
- This review highlights the need for further evaluation of the comparative efficacy and safety of interventions used commonly in practice but not yet tested in RCTs (e.g. colchicine, pyrazolidine derivative NSAIDs, COX-2 selective NSAIDs and fenamate NSAIDs), and of multiple-drug treatments (e.g. interleukin-1 inhibitor plus acetic acid derivative NSAIDs) for gout flares.

INTRODUCTION

Gout is the most common inflammatory arthritis worldwide, caused by deposition of monosodium urate crystals in joint structures, and other sites (1).Despite advances in

understanding of the pathophysiology and therapy, gout continues to impair individual's health-related quality of life (HRQoL) and consume healthcare resources (2). For management of gout flares, pharmacologic therapies focus on rapid and effective control of the inflammatory response to monosodium urate crystals, thereby reducing joint pain and inflammation (3). Despite the consistent recommendations of first-line options for gout flare from the American College of Rheumatology (ACR), the American College of Physicians (ACP), the British Society for Rheumatology (BSR), and the European League Against Rheumatism (EULAR), uncertainty of the efficacy and safety of many pharmacological interventions remains (1, 4-6). Moreover, due to lack of evidence on comparative efficacy and safety, guidelines do not prioritize between these pharmacological options (4).

The comparative efficacy between current first-line options, e.g., non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or colchicine, and other pharmacological interventions, e.g., interleukin-1 (IL-1) inhibitors, remains unclear. Network meta-analysis (NMA) could help improve the precision by combining direct and indirect evidence, an approach that to date has not been performed to assess the comparative efficacy and safety of pharmacological anti-inflammatory interventions for gout flares. We therefore conducted this NMA considering both direct and indirect comparison to address the relative efficacy and safety of pharmacological anti-inflammatory interventions for gout flares based on evidence from randomized controlled trials (RCTs).

MATERIALS AND METHODS

Our systematic review was proposed by the ACR as one of the systematic reviews supporting its 2020 guideline of management of patients with gout (7). We did not register a protocol but followed the methodology established by the ACR to conduct systematic reviews to inform their guidelines. This report adheres to the PRISMA (Preferred Reporting items for Systematic Reviews and Meta-Analyses) statement (8).

Data source and searches

A research librarian conducted a single literature search for evidence pertaining to 57 questions in support of the 2020 guideline simultaneously in Ovid Medline, Embase and Cochrane library on September 24th, 2018. We updated the search for this specific question through December, 2019. Appendix 1 outlines the search strategies for each database.

Study selection

We made decisions with regards to eligibility criteria for patients, interventions, outcomes, and types of studies based on the needs of the ACR guidelines. We included RCTs that enrolled adult patients with gout flares and compared two or more anti-inflammatory pharmacological interventions, or compared pharmacological intervention(s) with placebo. Eligible trials reported at least one of the following outcomes: pain, joint tenderness, joint swelling, patient global assessment (PGA), or serious adverse events (SAE) with any duration of follow-up. Based on input of the guideline panel, we grouped interventions according to pharmacological mechanism of action and route of administration (Table 1). We excluded trials that compared interventions from the same intervention node (e.g. both arms in the trial used profen NSAIDs) and trials not published in the English language, or published as conference abstracts only.

Reviewers, working in pairs, screened titles and abstracts to determine potential eligibility for all guideline questions, and entries identified by at least one reviewer proceeded to full-text eligibility review, which was also conducted in duplicate. A pair of reviewers (LZN, AQ) confirmed eligibility of the studies addressing this systematic review question. A third adjudicator (RBP) helped to resolve any disagreement through consensus.

Data abstraction

One reviewer (LNZ) used standardized forms to extract data of study design, characteristics of participants, regimens of pharmacological interventions, and relevant outcomes. Another reviewer (AQ) checked the data. A third adjudicator (RBP) reviewed disagreements, and the

three reviewers reached consensus through discussion.

The guideline panel prioritized methods for measurement for the outcomes that were endorsed by the Outcome Measures in Rheumatology (OMERACT) (9), and time points of interest (day two or the day closest to day two, and longest available follow-up). We abstracted data from the following outcomes:

1) Mean change in pain score: The prioritized instrument was the 100-mm visual analogue scale (VAS) (0 mm=no pain, 100 mm=unbearable pain) in which the minimally important difference (MID) for gout patients is a 19 point reduction (10).
2) Mean change in joint tenderness and mean change in joint swelling: The prioritized instrument was the 4-point Likert scale (0=no pain, 3=pain, winces and withdraws; 0=no swelling, 3=bulging beyond the joint margins) where the MID is a one point reduction for join tenderness, and an one point reduction for joint swelling (10).
3) Mean change in patient global assessment (PGA): The prioritized instrument was the 5-point Likert scale (0 = excellent, 4 = poor). A MID for this 5-point Likert scale has not been established for gout patients.
4) Serious adverse event (SAE): We counted any adverse event that was classified as serious by the authors. When the authors did not report any SAE, we assumed none had occurred.

When the primary trials did not report standard deviation (SD), we imputed SD by using the median of SDs from other included trials that applied the same instrument in similar population during similar follow-up period.

Risk of bias and certainty of evidence

One reviewer (LNZ) assessed the risk of bias of individual studies using the Cochrane risk of bias tool, and another reviewer (AQ) cross-checked the judgments. A third adjudicator (RBP) reviewed disagreements not resolved by discussion.

Using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) for

NMA, we chose a null effect as a threshold and assessed the certainty that a particular intervention has an effect (i.e. improve a particular outcome) compared with another. The certainty of the evidence can be high, moderate, low, or very low. The assessment of this body of evidence from randomized trials started as high and was rated down based on limitation of risk of bias, inconsistency, indirectness, publication bias, intransitivity, incoherence, and imprecision. The steps of the GRADE assessment for each comparison and outcome included: 1) Rating the certainty of both of direct and indirect evidence contributing to the network estimate. For rating certainty in indirect evidence, we focused on the dominant first order loop. The certainty of the indirect evidence depends on the lowest certainty rating of the direct comparisons in the loop and intransitivity (i.e. extent of similarity of direct comparisons forming the indirect comparison) (11). 2) Rating the certainty of the network estimate: when the network estimate was based on only direct or indirect evidence, the network certainty rating was based on the certainty of that estimate (11). When both direct and indirect estimates were available, the rating of the network estimate was based on the dominant evidence. To determine the final rating, we considered incoherence (i.e. extent of similarity of direct and indirect estimates) and imprecision (11).

Data synthesis and analysis

To calculate direct estimates of effect for each paired comparison, we performed a frequentist random-effects pairwise meta-analysis using Review Manager 5.3 (Nordic Cochrane Centre; http://ims.cochrane.org/revman/download). For continuous outcomes, we used the standardized mean differences (SMDs) and corresponding 95% confidence intervals (CIs). For dichotomous outcomes, considering many trials had zero events in one or two arms, we used risk differences (RDs) and corresponding 95% CIs as the measure of effect. We quantified statistical heterogeneity by estimating the variance between trials using chi-square test and I^2 statistic.

We conducted the NMA using a frequentist framework and a random-effects model by the package netmeta in R (Version 1.1.463) (12). For continuous outcomes, we first calculated SMDs and corresponding 95% CIs, and then converted the SMDs into MDs in the natural units of

prioritized standard scales by multiplying the SMDs by an estimate of the SD associated with the standard scales. We used RDs and 95% CIs for dichotomous outcomes as the measure of pooled effect.

Data interpretation

To make conclusions from the NMA we used a novel methodology developed by the GRADE working group in which interventions are classified in groups from the most to the least efficacious or safe for each outcome (13). The approach begins by choosing an intervention that has the most direct comparisons with other interventions as the reference intervention. Second is choosing a decision threshold to categorize the interventions as not convincingly different, better or worse than the reference. We chose a null effect as the decision threshold. Using the same decision threshold we differentiated among interventions from categories that were better or worse than the reference. We then identified interventions within each category as those with high or moderate certainty relative to the reference standard, and those with low or very low certainty (13).

To facilitate the interpretation of the comparative efficacy and safety of each interventions in relation to the reference, we assumed an effect of the reference and calculated the difference between each intervention when compared to this reference. For continuous outcome, we estimated the effect of the reference was the weighted average of the mean change from baseline in the reference arm across all studies. For dichotomous outcomes, we used an inverse-variance fixed-effects model and meta-analysis of proportions based on a generalized linear mixed model. We assessed the certainty of evidence by using GRADE for observational studies (treating the single arm from RCT as before-after study).

RESULTS

The initial search for all 57 questions in support of the guideline yielded 3,337 citations; 466 proved potentially eligible after reviewing abstracts for the systematic reviews. Twenty-nine RCTs

(30 articles) proved eligible for this particular systematic review focused on gout flare management following full text review. The updated search until December 2019 found one new trial. We finally included 30 RCTs (31 articles) with 4,268 patients. We did not provide the specific reasons for exclusion of studies for this systematic review because we simultaneously screened studies for all of the systematic reviews for the broader needs of the full guideline.

Characteristic of the included studies

The eligible trials studied several anti-inflammatory interventions and their combinations for gout flare management including oral corticosteroids, intravenous or intramuscular corticosteroids, acetic acid derivative NSAIDs, profen NSAIDs, fenamate NSAIDs, pyrazolidine derivative NSAIDs, cyclooxygenase (COX)-2 selective NSAIDs, COX-2 highly selective NSAIDs, adrenocorticotropic hormone (ACTH), rilonacept, canakinumab, anakinra, colchicine, IL-1 inhibitor plus acetic acid derivative, and a free choice of colchicine, naproxen or prednisolone (Table 2, Appendix 2). Risk of bias of individual RCTs was mainly due to inadequate or unclear reporting of random sequence generation (46.7%, 14/30) or of allocation concealment (63.3%, 19/30), incomplete outcome including high proportion of lost to follow-up or unbalanced proportion of lost to follow-up between groups (43.3%, 13/30), and selective reporting including incomplete reporting of important outcomes or of means or standard deviations (46.7%, 14/30) (Appendix 3).

Effects of the interventions

We chose acetic acid derivative NSAIDs as the reference intervention for all outcomes as it has the most direct comparisons with other interventions. Because one RCT that compared anakinra with a free choice of colchicine or naproxen or prednisolone did not have interventions connected to the network by any node, we did not include this RCT in the NMA (14). In the results from NMA for the effectiveness outcomes (i.e. pain, joint tenderness, joint swelling, PGA), a negative number indicates better result with the intervention (i.e. greater pain reduction, better joint tenderness or joint swelling resolution, better PGA improvement) whereas a positive

number indicates better result with the comparison. Appendix 4 presents network plots illustrating the interventions and whether they have been compared directly in RCTs for each outcome.

Pain

Nineteen RCTs (3,560 patients, 9 interventions) reported on the change in pain from baseline at day two (15-32). The reference (i.e. acetic acid derivative NSAIDs) showed an important average reduction in pain from baseline to day two (MD -30.67, 95% CI -31.89 to -29.45 on a 0 to 100 VAS; very low certainty; MID -19) (Table 3). Of the 36 pairwise comparisons between interventions, direct evidence was available for 12. Canakinumab proved probably the most effective intervention for reducing pain at day two (MD relative to acetic acid derivative NSAIDs -41.12, 95% CI -53.36 to -29.11; moderate certainty). Intravenous or intramuscular corticosteroids may be superior to other interventions but inferior to canakinumab (Appendix 5). Rilonacept was probably better than acetic acid derivative NSAIDs but inferior to intravenous or intramuscular corticosteroids and canakinumab (Appendix 5). There were no convincing differences between COX-2 highly selective NSAIDs, profen NSAIDs, acetic acid derivative NSAIDs, colchicine, oral corticosteroids, or IL-1 inhibition plus acetic acid derivative NSAIDs (Appendix 5).

The NMA for change in pain at the longest follow-up (median: 7 days, range: 3 to 28 days) included 16 RCTs (2,384 patients, 9 interventions) (16-19,21-26,28-32). Of the 36 pairwise comparisons between interventions, direct evidence was available for 11. Acetic acid derivative NSAIDs showed an important average reduction in pain from baseline to the longest follow-up (MD -40.09, 95% CI -42.25 to -39.61; very low certainty). Canakinumab was probably the most effective intervention at the longest follow-up (MD relative to acetic acid derivative NSAIDs -12.84, 95% CI -20.76 to -4.91; moderate certainty). There were no convincing differences between acetic acid derivative NSAIDs, COX-2 highly selective NSAIDs, profen NSAIDs, colchicine, intravenous or intramuscular corticosteroids, oral corticosteroids, or rilonacept or IL-1 inhibition plus acetic acid derivative NSAIDs (Appendix 5).

Joint tenderness

Eight RCTs (1308 patients; six interventions) reported on the change of joint tenderness from baseline on day two (16,18,20,25,31-33). The reference (i.e. acetic acid derivative NSAIDs) showed an important average improvement relative to baseline on joint tenderness at day two (MD -1.29, 95% -1.38 to -1.21 on a 0 to 3 scale; very low certainty; MID -1) (Table 3). Of the 15 pairwise comparisons between interventions, direct evidence proved available for six. Canakinumab was probably the most effective intervention at day two (MD relative to acetic acid derivative NSAIDs -0.67, 95% CI -1.03 to -0.30; moderate certainty). However, the difference between canakinumab and acetic acid derivative NSAIDs was unimportant to gout patients (smaller than the MID of one point reduction). There were no convincing differences between COX-2 highly selective NSAIDs, profen NSAIDs, intravenous or intramuscular corticosteroids, oral corticosteroids and the reference standard, acetic acid derivative NSAIDs (Appendix 5).

For the longest follow-up (median: seven days, range: five to 14 days), the NMA included 10 RCTs (1,731 patients, six interventions) (16-18,21,23,26,27,31-33). From the 15 pairwise comparisons between interventions, direct comparisons proved available for six. Acetic acid derivative NSAIDs showed an important average improvement relative to baseline on joint tenderness at the longest follow-up (MD -1.77, 95% -1.83 to -1.71; very low certainty; MID -1). There were no convincing differences between any of the interventions and the reference standard, acetic acid derivative NSAIDs (Appendix 5).

Joint swelling

Seven RCTs (969 patients; six interventions) reported on the change of joint swelling from baseline on day two (16,18,25,31,32,33). The reference (i.e. acetic acid derivative NSAIDs) showed an important average improvement relative to baseline on joint swelling at day two (MD -0.89, 95% -1.02 to -0.76 on a 0 to 3 scale; very low certainty; MID -1) (Table 3). Of the 15 pairwise comparisons between interventions, direct evidence proved available for six.

Canakinumab was the only intervention that may be better than acetic acid derivative NSAIDs for improving joint swelling at day two (MD -0.61, 95% CI -1.01, -0.21; low certainty; MID -1), but the difference between canakinumab and acetic acid derivative NSAIDs was unimportant (smaller than the MID of one point reduction). Acetic acid derivative NSAIDs were probably superior to profen NSAIDs in joint swelling at day two (MD -0.29, 95% CI -0.56 to -0.02; moderate certainty). There were no convincing differences between intravenous or intramuscular corticosteroids, oral corticosteroids, COX-2 highly selective NSAIDs and the reference standard, acetic acid derivative NSAIDs (Appendix 5).

The NMA for change in joint swelling at the longest follow-up (median: seven days, range: five to 14 days) included 11 RCTs (1,741 patients, six interventions) (16-18,23,25-27,31-33) including direct evidence for six of 15 pairwise comparisons. Acetic acid derivative NSAIDs showed an important average improvement relative to baseline on joint swelling at the longest follow-up (MD -1.63, 95% CI -1.70 to -1.56; very low certainty; MID -1). There were no convincing differences between the reference standard and any of the other interventions (Appendix 5).

Patient global assessment (PGA)

Three RCTs reported PGA of change from baseline at day two (16,18,20). The reference (i.e. acetic acid derivative NSAIDs) showed an important average improvement relative to baseline on PGA at day two (MD -1.47, 95% CI -1.60 to -1.34 on a 0 to 4 scale; very low certainty) (Table 3). The NMA for change in PGA at day two included three RCTs (460 patients, three interventions). Of the four pairwise comparisons between intervention, direct evidence proved available for only one. There were no convincing differences between any of the interventions (Appendix 5).

The NMA for change in PGA at the longest follow-up (median: seven days, range: five to eight days) included five RCTs (638 patients, three interventions) (16-18,23,26) including direct evidence for one of three pairwise comparisons. Acetic acid derivative NSAIDs showed an important average improvement relative to baseline on PGA at the longest follow-up (MD -1.64,

95% -1.74 to -1.53; very low certainty). Profen NSAIDs were probably worse than acetic acid derivative NSAIDs (MD 0.44, 95% CI 0.02 to 0.86; moderate certainty). There were no convincing differences between COX-2 highly selective NSAIDs and acetic acid derivative NSAIDs (Appendix 5).

Serious adverse events (SAE)

The NMA for SAEs included 29 RCTs (4,248 patients; 13 interventions) (15-23,26-44), and 78 paired estimates of which 15 had both direct and indirect evidence and 58 had only indirect evidence. The median duration of available follow-up was eight days (range: five to 365 days). Oral corticosteroids were the only intervention that may be safer than acetic acid derivative NSAIDs (RD -0.03, 95%CI -0.05 to -0.01; very low certainty). There were no convincing differences between any of the other interventions (Appendix 5).

The only SAE reported in oral corticosteroids group was a case of low potassium associated with prednisolone. Main SAEs associated with acetic acid derivative NSAIDs were gastrointestinal events including gastric or gastroduodenal ulcers, abdominal pain, and vomiting. SAEs reported in COX-2 highly selective NSAIDs group were mainly in the urinary system and included renal calculi, uronephrosis, and renal failure. Serious infections, and cardiovascular events were reported in canakinumab group. However, the causality between the SAE and canakinumab was not reported. Among the three canakinumab trials, two trials found increased risk of infection associated with canakinumab during a 6-month follow-up (incidence of infection: 18.8% and 22.1% in canakinumab groups, 8.8% and 15.7% in triamcinolone groups), while the other small trial failed to find any difference in a follow-up of 8 weeks (incidence of infection: 7% in both groups) (25,33,44).

One trial not included in the NMA reported no significant difference between anakinra versus a free choice of colchicine or naproxen or prednisolone in pain reduction, joint tenderness improvement, joint swelling improvement, PGA or SAE (Appendix 5) (14).

DISCUSSION

The results of this NMA highlight a potential advantage of canakinumab versus other anti-inflammatory interventions for gout flares in pain reduction at day two and the longest follow-up (moderate certainty). Canakinumab also showed larger effects on joint tenderness and joint swelling over day two (moderate certainty; low certainty), but the differences were unimportant (smaller than the MIDs) (Table 3). Among the commonly used therapies for gout flares (i.e. NSAIDs, colchicine and corticosteroids), intravenous or intramuscular corticosteroids may be more effective than COX-2 highly selective NSAIDs, profen NSAIDs, acetic acid derivative NSAIDs and oral corticosteroids on pain reduction at short-term (low certainty) (Appendix 5). Profen NSAIDs were probably worse than acetic acid derivative NSAIDs in joint swelling at day two and PGA at the longest follow-up (moderate certainty) (Table 3). For the safety evaluation, oral corticosteroids may cause fewer SAEs than acetic acid derivative NSAIDs (very low certainty) (Table 3). Results showed no convincing differences in safety among the other pharmacological interventions.

Our study has several strengths. Using rigorous NMA methods, we incorporated direct and indirect evidence of the comparative efficacy and safety of anti-inflammatory treatment for gout flares. We used the GRADE approach to assess the certainty of evidence informing the estimates. The outcomes evaluated in this review are important from both patient and provider points of view (45). For enhancing the interpretability of results, we converted the SMDs from NMA into MDs in the natural units of standard instruments, and compared the MDs to the MIDs. We estimated the efficacy or baseline risk of the reference group (i.e. acetic acid derivative NSAIDs) facilitating the interpretation of comparative efficacy and safety of other pharmacological interventions in relation to the reference. Moreover, the approach of making conclusion from NMA enabled a transparent, straightforward process of classifying interventions according to their relative benefit and harm. Our review also includes recently published studies that were not included in prior reviews, and summarizes all the available RCT evidence.

In terms of limitations, to deal with the large number of interventions and relatively small number of trials for each intervention, we created clusters of interventions, taking the risk that effects would differ across treatments within clusters. Second, the effect of the reference treatment was based on a before-after comparison in the included RCTs and how much of the apparent improvement is due to natural history or placebo effects is uncertain. Third, three of the RCTs enrolling patients with difficult-to-treat gouty arthritis might cause heterogeneity and intransitivity (24,25,33,44). We planned to conduct subgroup analyses based on the number of joints involved, pain levels, duration of the flare at presentation, duration of anti-inflammatory therapy, and dose of the agent. Few trials, however, assessed differences in the relative effects of the interventions by patient characteristics. Information to inform subgroup analysis based on patient characteristics was therefore unavailable. As there were multiple interventions in some categories, we are unable to compare efficacy and safety between different dosing. Furthermore, evaluation of rare event adverse effects would be underpowered in RCTs.

Previous systematic reviews evaluating only direct estimates did not report important differences in pain reduction between canakinumab and intravenous or intramuscular corticosteroids versus other pharmaceutical interventions (46-48). The difference is likely due to the enhanced precision of estimates that, through including more studies and considering both direct and indirect evidence, this NMA provides.

A Cochrane systematic review and a systematic review in support of the ACP guideline found no difference between NSAIDs and oral glucocorticoids in pain relief (48). The Cochrane systematic review also indicated no difference between conventional NSAIDs and selective COX-2 inhibitor in pain relief, swelling and global improvement (49). In our systematic review, we categorized NSAIDs into sub-groups according to the pharmacological mechanism of action, that enables the comparison within NSAIDs and the comparison between sub-category of NSAIDs and other interventions. We found consistent result that NSAIDs were not different with oral glucocorticoids in effectiveness outcomes (Appendix 5). However, profen NSAIDs was inferior to

acetic acid derivative NSAIDs in resolution of joint swelling at day two and improvement of PGA at longest follow-up (Table 3). Another Cochrane systematic review of colchicine for acute gout identified no studies comparing colchicine to any other active treatment (50). In our NMA, colchicine compared indirectly with other interventions through profen NSAIDs showed inferior to canakinumab, rilonacept and intravenous or intramuscular corticosteroids but no difference with other interventions (Appendix 5).

Cost or financial barriers to medications are not considered in this systematic review. However, although our review highlights potential advantages of canakinumab in terms of effectiveness, cost and the administration route have limited its use (51). Inherent delays with prior authorization requirements likely limits the practical use of canakinumab for management of gout flare. These issues have been explicitly considered and addressed in the 2020 American College of Rheumatology Guideline for the Management of Gout (52). In our review, among the three canakinumab trials, two trials found increased risk of infection associated with canakinumab while the other one small trial failed to find any difference (25,33,44). Future RCTs and observational studies are needed to evaluate the safety of canakinumab in this regard.

Future studies need to evaluate the comparative efficacy and safety of pharmacological interventions used commonly in practice but not yet tested in RCTs (e.g. colchicine, pyrazolidine derivative NSAIDs, COX-2 selective NSAIDs and fenamate NSAIDs). RCTs are also needed to evaluate IL-inhibitors other than canakinumab. Experts writing in prior guidelines have suggested evaluating the efficacy and safety of combination-drug treatments for gout flares (e.g., IL-1 inhibitor plus acetic acid derivative) (6). Future studies should report data for relevant patient subgroups (e.g., those with polyarticular gout or subgroups based on flare severity), thus enabling, in subsequent systematic reviews, subgroup analysis of patients with different characteristics.

In summary, this systematic review provides a current, comprehensive summary of the

comparative efficacy and safety of pharmacological interventions used in clinical practice for anti-inflammatory treatment in patients with gout flare. Canakinumab may be superior to other alternatives and intravenous or intramuscular corticosteroids may be the second best in terms of pain reduction at day two. Acetic acid derivative NSAIDs may be superior to profen NSAIDs on the improvement of joint swelling at day two and patient global assessment at the longest follow-up.

AUTHORS CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

Study conception and design: Romina Brignardello-Petersen, Tuhina Neogi, John Fitzgerald, Nicola Dalbeth, Ted Mikuls, Gordon H Guyatt

Acquisition of data: Linan Zeng, Anila Qasim, Romina Brignardello-Petersen

Analysis and interpretation of data: Linan Zeng, Anila Qasim, Romina Brignardello-Petersen, Tuhina Neogi, John Fitzgerald, Nicola Dalbeth, Ted Mikuls, Gordon H Guyatt

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Table 1 Pharmacological interventions included in each intervention node

Category of pharmacological mechanism	Intervention node	Pharmacological interventions included in each node
Corticosteroids	corticosteroids-po	prednisolone
	corticosteroids-im or iv	compound betamethasone, methylprednisolone, triamcinolone acetonide
Colchicine	colchicine	colchicine
ACTH	ACTH	ACTH
NSAIDs	acetic acid derivative NSAIDs	etodolac, indomethacin, diclofenac
	profen NSAIDs	ketoprofen, naproxen, flurbiprofen
	pyrazolidine derivative NSAIDs	phenylbutazone, azapropazone
	fenamate NSAIDs	meclofenamate sodium, flufenamic acid
Selective NSAIDs	COX-2 selective NSAIDs	meloxicam
	COX-2 highly selective NSAIDs	etoricoxib, celecoxib, rofecoxib, lumiracoxib
IL-inhibitors	rilonacept	rilonacept
	canakinumab	canakinumab
	anakinra	anakinra
Acetaminophen	acetaminophen	acetaminophen
Combinations	IL-1 inhibitor plus acetic acid derivative NSAIDs	rilonacept plus indomethacin

ACTH = adrenocorticotropic hormone; COX = cyclo-oxygenase; IL = Interleukin; NSAIDs = nonsteroidal anti-inflammatory drugs.

Table 2 Characteristics of included RCTs

Characteristic	**Total (n=30)**
No. of patients randomized, median (range)	91.5 (20-416)
No. of multi-arm trials, n (%)	4(13.3)
Duration of treatment, weeks, median (range)	1.0 (0.1-52.1)
Intervention evaluated (No. of patients randomized/ No. of trials)	
Acetic acid derivative NSAIDs	1112/17
COX-2 highly selective NSAIDs	753/11
Corticosteroids-im or iv	394/7
Corticosteroids-po	312/3

Canakinumab	270/3
Profen NSAIDs	367/6
Colchicine	199/1
Rilonacept	75/1
IL-1 inhibitor plus acetic acid derivative NSAIDs	75/1
ACTH	53/2
Acetic acid derivative NSAIDs plus acetaminophen	45/1
Corticosteroids-po plus acetaminophen	45/1
Colchicine, or naproxen, or prednisone	44/1
Pyrazolidine derivative NSAIDs	44/3
COX-2 selective NSAIDs	31/1
Fenamate NSAIDs	13/1
Outcome analyzed (No. of patients analyzed/ No. of trials)	
Serious adverse events	4266/30
Pain	3961/23
Joint tenderness	2928/17
Joint swelling	2173/16
Patient global assessment	2154/15
Methodological characteristics, No. of trials (%)	
Adequate generation of random sequence	16 (53.3%)
Adequate allocation concealment	11 (36.7%)
Adequate blinding of outcome assessors	23 (76.7%)
Characteristics of patients	
Percentage of males, median (range)	92.1 (68.4-100)
Average age, years, median (range)	53 (43.8-69.6)
Report of gout duration, No. of trials (%)	10 (33.3)

ACTH = adrenocorticotropic hormone; COX = cyclo-oxygenase; IL = Interleukin; NSAIDs = nonsteroidal anti-inflammatory drugs; RCT = randomized controlled trial.

Table 3 Most and least efficacious or safe treatment for all the outcomes*

Intervention	Effectiveness outcome								Safety outcome
	Pain score-mean change MD (95% CI) Standard scale:100-mm VAS (0mm=no pain, 100mm=unbearable pain) MID=-19		Joint tenderness-mean reduction MD (95% CI) Standard scale: 4-point Likert scale (0=no pain ,pain, 3=pain, winces and withdraws) MID= -1		Joint swelling-mean reduction MD (95% CI) Standard scale: 4-point Likert scale (0=no swelling, 3=bulging beyond the joint margins) MID= -1		Patient global assessment-mean change MD (95% CI) Standard scale: 5-point Likert scale (0 = excellent, 4 = poor)		Serious adverse event RD (95%CI)
	Day 2	Longest follow-up	Day 2	Longest follow-up	Day 2	Longest follow-up	Day 2	Longest follow-up	Longest follow-up
Change from baseline or baseline risk in reference group (acetic acid derivative NSAIDs)†									
Acetic acid derivative NSAIDs	-30.67 (-31.89, -29.45)	-40.09 (-42.25, -39.61)	-1.29 (-1.38, -1.21)	-1.77 (-1.83, -1.71)	-0.89 (-1.02, -0.76)	-1.63 (-1.70, -1.56)	-1.47 (-1.60, -1.34)	-1.64 (-1.74, -1.53)	0.025 (0.018, 0.035)
Relative effect in relative to reference (acetic acid derivative NSAIDs) ‡									
Canakinumab	-41.12 (-53.36, -29.11)	-12.84 (-20.76, -4.91)	-0.67 (-1.03, -0.3)	-0.42 (-0.86, 0.03)	-0.61 (-1.01, -0.21)	-0.28 (-0.71, 0.16)	-	-	0.03 (-0.01. 0.06)
Corticosteroids-im or iv	-30.72 (-40.89, -20.79)	-5.71 (-12.36, 0.79)	-0.33 (-0.68, 0.01)	0 (-0.33, 0.33)	-0.3 (-0.67, 0.08)	-0.03 (-0.44, 0.37)	-	-	0 (-0.03, 0.02)
COX-2 highly selective NSAIDs	1.85 (-2.31, 6.01)	0.32 (-3.01, 3.65)	--0.05 (-0.18, 0.08)	-0.01 (-0.1, 0.08)	0.1 (-0.23, 0.43)	-0.07 (-0.19, 0.05)	-0.01 (-1, 0.98)	0.095 (-0.08, 0.27)	0 (-0.01, 0)
Corticosteroids-po	4.62 (-1.39, 10.63)	-0.32 (-4.91, 4.12)	-0.19 (-0.48, 0.1)	-0.03 (-0.14, 0.08)	-0.1 (-0.45, 0.25)	-0.21 (-0.56, 0.12)	-	-	-0.03 (-0.05, -0.01)
Profen NSAIDs	6.24 (-2.08, 14.78)	3.8 (-4.12, 11.73)	0.16 (-0.08, 0.41)	0.19 (-0.08, 0.46)	0.29 (0.02, 0.56)	-0.04 (-0.36, 0.29)	0.21 (-0.56, 0.98)	0.44 (0.02, 0.86)	-0.02 (-0.04, 0.01)
Rilonacept	-11.78 (-23.56, 0)	-3.17 (-10.94, 4.6)	-	-	-	-	-	-	0 (-0.03, 0.03)
IL-1 inhibition + acetic acid derivative NSAIDs	-6.47 (-18.02, 5.31)	-1.59 (-9.35, 6.18)	-	-	-	-	-	-	0.04 (-0.01, 0.09)
Colchicine	10.63 (-2.54, 24.02)	4.91 (-5.39, 15.37)	-	-	-	-	-	-	-0.02 (-0.04, 0.01)
Pyrazolidine derivative NSAIDs	-	-	-	-	-	-	-	-	0 (-0.04, 0.03)
ACTH	-	-	-	-	-	-	-	-	0 (-0.05, 0.05)
COX-2 selective NSAIDs	-	-	-	-	-	-	-	-	0 (-0.08, 0.08)
Fenamate NSAIDs	-	-	-	-	-	-	-	-	0 (-0.11, 0.11)
Cell color pattern‡‡									-
Category	Most effectivenes/safety high/moderate certainty of evidence	Most effectivenes/safety low/very low certainty of evidence					Least effectiveness/safety high/moderate certainty of evidence	Least effectivenes/safety low/very low certainty of evidence	No study for that outcome

ACTH = adrenocorticotropic hormone; COX = cyclo-oxygenase; IL = Interleukin; MID = minimally important difference; MD = mean difference; NSAIDs = nonsteroidal anti-inflammatory drugs; RD = risk difference.

* We present mean differences (MDs) in the natural units of standard scales for continuous outcomes, and risk differences (RDs) for dichotomous outcome.

† The reference was acetic acid derivative NSAIDs for all the outcomes (pain, patient global assessment, joint tenderness, joint swelling and serious adverse event). For continuous outcomes, the effect of the reference was the change from baseline at a particular timepoint in acetic acid derivative NSAIDs arm across trials; for dichotomous outcomes, the effect was the risk of the outcome in acetic acid derivative NSAIDs arm across trials (the baseline risk).

‡ The values in each cell represent the effect of the treatment in each row when compared to the reference. For example, canakinumab resulted in a reduction in pain 41.12 units greater than acetic acid derivative NSAIDs or a reduction from baseline of 71.79 units.

‡‡ Interventions depicted with the same color belong to the same category. Green represents the most effective/safe interventions, while red represents the least effective/safe. Yellow and orange represents intermediate efficacy/safety. "Green" designates 'good' patient outcomes, while "red" designates 'inferior' patient outcomes (including for the serious adverse event).