Title

Efficacy and Safety of Pharmacologic Interventions in Patients Experiencing a Gout Flare: A Systematic Review and Network Meta-Analysis.

Journal

Arthritis Care & Research, 73(5)

Authors

Zeng, Linan
Qasim, Anila
Neogi, Tuhina
et al.

Publication Date

2021-05-01

DOI

10.1002/acr.24402

Peer reviewed

HHS Public Access

Author manuscript

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2023 October 13.

Published in final edited form as:

Arthritis Care Res (Hoboken). 2021 May ; 73(5): 755–764. doi:10.1002/acr.24402.

Efficacy and Safety of Pharmacologic Interventions in Patients Experiencing a Gout Flare: A Systematic Review and Network Meta-Analysis

Linan Zeng, PhD[1], **Anila Qasim, HBSc, MSc**[2], **Tuhina Neogi, MD, PhD, FRCPC**[3], **John D. Fitzgerald, MD, PhD**[4], **Nicola Dalbeth, MD, FRACP**[5], **Ted R. Mikuls, MD, MSPH**[6], **Gordon H. Guyatt, MD**[2], **Romina Brignardello-Petersen, MD, PhD**[2]

[1]West China Second University Hospital, Sichuan University, Chengdu, China, and McMaster University, Hamilton, Ontario, Canada

[2]McMaster University, Hamilton, Ontario, Canada

[3]Boston University, Boston, Massachusetts

[4]University of California, Los Angeles and VA Greater Los Angeles Health Care System, Los Angeles, California

[5]University of Auckland, Auckland, New Zealand

[6]University of Nebraska Medical Center and VA Nebraska-Western Iowa Health Care System, Omaha.

Abstract

Objective.—To compare the relative efficacy and safety of pharmacologic antiinflammatory interventions for gout flares.

Methods.—We searched Ovid Medline, Embase, and Cochrane library for randomized controlled trials (RCTs) that compared pharmacologic antiinflammatory 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 Grading of Recommendations Assessment, Development, and Evaluation for NMA.

Results.—In the 30 eligible RCTs, canakinumab provided the highest pain reduction at day 2 and at longest follow-up (mean difference relative to acetic acid derivative nonsteroidal antiinflammatory drugs [NSAIDs] −41.12 [95% confidence interval (95% CI) −53.36, −29.11] on a 0–100 scale at day 2, and mean difference −12.84 [95% CI −20.76, −4.91] at longest follow-

Address correspondence to Romina Brignardello-Petersen, MD, PhD, 1280 Main Street West, Hamilton, ON, L8S 4L8, Canada. brignarr@mcmaster.ca.

AUTHOR 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 submitted for publication. Dr. Brignardello-Petersen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Neogi, Fitzgerald, Dalbeth, Mikuls, Guyatt, Brignardello-Petersen.

Acquisition of data. Zeng, Qasim, Brignardello-Petersen.

Analysis and interpretation of data. Zeng, Qasim, Neogi, Fitzgerald, Dalbeth, Mikuls, Guyatt, Brignardello-Petersen.

No potential conflicts of interest relevant to this article were reported.

up; both moderate certainty; minimum important difference −19). Intravenous or intramuscular corticosteroids were 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 2. Acetic acid derivative NSAIDs improved joint swelling better than ibuprofen NSAIDs at day 2 (mean difference −0.29 [95% CI −0.56, −0.02] on a 0–4 scale; moderate certainty) and improved patient global assessment (PtGA) greater than ibuprofen NSAIDs at the longest follow-up (mean difference −0.44 [95% CI −0.86, −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 ibuprofen NSAIDs in improving joint swelling and PtGA.

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 and consume health care 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, and the European Alliance of Associations for Rheumatology, uncertainty of the efficacy and safety of many pharmacologic interventions remains (1,4–6). Moreover, due to lack of evidence on comparative efficacy and safety, guidelines do not prioritize between these pharmacologic options (4).

The comparative efficacy between current first-line options, e.g., nonsteroidal antiinflammatory drugs (NSAIDs), corticosteroids, or colchicine, and other pharmacologic 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 pharmacologic antiinflammatory interventions for gout flares. We therefore conducted this NMA considering both direct and indirect comparison to address the relative efficacy and safety of pharmacologic antiinflammatory 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 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 ACR 2020 guidelines simultaneously in Ovid Medline, Embase, and Cochrane library on September 24, 2018. We updated the search for this specific question through December of 2019. The search strategies for each database are outlined (see Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24402/abstract).

Study selection.

We made decisions about 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 ≥2 anti-inflammatory pharmacologic interventions or compared pharmacologic interventions with placebo. Eligible trials reported at least 1 outcome, including pain, joint tenderness, joint swelling, patient global assessment (PtGA), or serious adverse events (SAE) with any duration of follow-up. Based on input of the guideline panel, we grouped interventions according to pharmacologic 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 ibuprofen NSAIDs) and those not published in the English or 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 1 reviewer proceeded to full-text eligibility review, which was also conducted in duplicate. A pair of reviewers (LZ and AQ) confirmed eligibility of the studies addressing this systematic review question. A third adjudicator (RB-P) helped to resolve any disagreement, through consensus.

Data abstraction.

One reviewer (LZ) used standardized forms to extract data of study design, characteristics of participants, regimens of pharmacologic interventions, and relevant outcomes. Another reviewer (AQ) checked the data. A third adjudicator (RB-P) reviewed disagreements, and the 3 reviewers reached consensus through discussion.

The guideline panel prioritized methods for measurement for the outcomes that were endorsed by the Outcome Measures in Rheumatology (9), and time points of interest (day 2 or the day closest to day 2, 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 analog scale (VAS) (0 mm = no pain, 100 mm = unbearable pain) in which the minimum 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 (for joint tenderness: 0 = no pain, 3 = pain, winces, and withdraws; for joint swelling: 0 = no swelling, 3 =

bulging beyond the joint margins), where the MID is a 1-point reduction for joint tenderness and a 1-point reduction for joint swelling (10).

3. Mean change in PtGA. 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. 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 the SD, we imputed the SD by using the median of SDs from other included trials that applied the same instrument in similar populations during similar follow-up periods.

Risk of bias and certainty of evidence.

One reviewer (LZ) 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 (RB-P) 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., improves 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 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., the 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., the 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 (95% CIs). For dichotomous outcomes, considering many trials had 0 events in 1 or 2 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. The next step in the approach is to choose 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 that 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 guidelines yielded 3,337 citations; after reviewing abstracts for the systematic reviews, 466 proved potentially eligible. Twenty-nine RCTs (30 articles) proved eligible for this particular systematic review, which, following full text review, was focused on gout flare management. The updated search, which included dates until December 2019, found 1 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 guidelines.

Characteristic of the included studies.

The eligible trials studied several antiinflammatory interventions and their combinations for gout flare management, including oral corticosteroids, intravenous or intramuscular

corticosteroids, acetic acid derivative NSAIDs, ibuprofen NSAIDs, fenamate NSAIDs, pyrazolidine derivative NSAIDs, cyclooxygenase 2 (COX-2) selective NSAIDs, COX-2 highly selective NSAIDs, adrenocorticotropic hormone, rilonacept, canakinumab, anakinra, colchicine, IL-1 inhibitor plus acetic acid derivative, and a free choice of colchicine, naproxen, or prednisolone (Table 2) (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24402/abstract). Risk of bias of individual RCTs was mainly due to inadequate or unclear reporting of random sequence generation (46.7% [14 of 30]) or of allocation concealment (63.3% [19 of 30]), incomplete outcome including high proportion of lost to follow-up or unbalanced proportion of lost to follow-up between groups (43.3% [13 of 30]), and selective reporting including incomplete reporting of important outcomes or of mean or SDs (46.7% [14 of 30]) (see Supplementary Figure 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24402/abstract).

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 1 RCT that compared anakinra with a free choice of colchicine, 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, PtGA), a negative number indicates a better result with the intervention (i.e., greater pain reduction, better joint tenderness or joint swelling resolution, better PtGA improvement), whereas a positive number indicates a better result with the comparison. Network plots illustrating the interventions and whether they have been compared directly in RCTs for each outcome are presented (see Supplementary Figure 2A–I, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24402/abstract).

Pain.—Nineteen RCTs (3,560 patients, 9 interventions) described the change in pain from baseline at day 2 (15–32). The reference (i.e., acetic acid derivative NSAIDs) showed an important average reduction in pain from baseline to day 2 (MD −30.67 [95% CI −31.89, −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 2 (MD relative to acetic acid derivative NSAIDs −41.12 [95% CI −53.36, −29.11]; moderate certainty). Intravenous or intramuscular corticosteroids may be superior to other interventions but inferior to canakinumab (see Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24402/abstract). Rilonacept was probably better than acetic acid derivative NSAIDs but inferior to intravenous or intramuscular corticosteroids and canakinumab (see Supplementary Table 2). There were no convincing differences between COX-2 highly selective NSAIDs, ibuprofen NSAIDs, acetic acid derivative NSAIDs, colchicine, oral corticosteroids, or IL-1 inhibition plus acetic acid derivative NSAIDs (see Supplementary Table 2).

The NMA for change in pain at the longest follow-up (median 7 days, range 3–28 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, −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, −4.91], moderate certainty). There were no convincing differences between acetic acid derivative NSAIDs, COX-2 highly selective NSAIDs, ibuprofen NSAIDs, colchicine, intravenous or intramuscular corticosteroids, oral corticosteroids, or rilonacept or IL-1 inhibition plus acetic acid derivative NSAIDs (see Supplementary Table 2).

Joint tenderness.—Eight RCTs (1,308 patients; 6 interventions) reported on the change of joint tenderness from baseline on day 2 (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 2 (MD −1.29 [95% CI −1.38, −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 6. Canakinumab was probably the most effective intervention at day 2 (MD relative to acetic acid derivative NSAIDs −0.67 [95% CI −1.03, −0.30], moderate certainty). However, the difference between canakinumab and acetic acid derivative NSAIDs was unimportant to gout patients (smaller than the MID of 1 point reduction). There were no convincing differences between COX-2 highly selective NSAIDs, ibuprofen NSAIDs, intravenous or intramuscular corticosteroids, oral corticosteroids, and the reference standard, acetic acid derivative NSAIDs (see Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24402/abstract).

For the longest follow-up (median 7 days, range 5–14 days), the NMA included 10 RCTs (1,731 patients, 6 interventions) (16–18,21,23,26,27,31–33). From the 15 pairwise comparisons between interventions, direct comparisons proved available for 6. Acetic acid derivative NSAIDs showed an important average improvement relative to baseline on joint tenderness at the longest follow-up (MD −1.77 [95% CI −1.83, −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 (see Supplementary Table 2).

Joint swelling.—Seven RCTs (969 patients, 6 interventions) described the change of joint swelling from baseline on day 2 (16,18,25,31–33). The reference (i.e., acetic acid derivative NSAIDs) showed an important average improvement relative to baseline on joint swelling at day 2 (MD −0.89 [95% CI −1.02, −0.76] on a 0–3 scale, very low certainty; MID −1) (Table 3). Of the 15 pairwise comparisons between interventions, direct evidence proved available for 6. Canakinumab was the only intervention that may be better than acetic acid derivative NSAIDs for improving joint swelling at day 2 (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 1 point reduction). Acetic acid derivative NSAIDs were probably superior to ibuprofen NSAIDs in joint swelling at day 2 (MD −0.29 [95% CI −0.56, −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 (see Supplementary Table 2).

The NMA for change in joint swelling at the longest follow-up (median 7 days, range 5–14 days) comprised 11 RCTs (1,741 patients, 6 interventions) (16–18,23,25–27,31–33), including direct evidence for 6 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, −1.56], very low certainty; MID −1). There were no convincing differences between the reference standard and any of the other interventions (see Supplementary Table 2).

PtGA.—Three RCTs reported PtGA of change from baseline at day 2 (16,18,20). The reference (i.e., acetic acid derivative NSAIDs) showed an important average improvement relative to baseline on PtGA at day 2 (MD −1.47 [95% CI −1.60, −1.34] on a 0–4 scale, very low certainty) (Table 3). The NMA for change in PtGA at day 2 included 3 RCTs (460 patients, 3 interventions). Of the 4 pairwise comparisons between intervention, direct evidence proved available for only 1 comparison. There were no convincing differences between any of the interventions (see Supplementary Table 2).

The NMA for change in PtGA at the longest follow–up (median 7 days, range 5–8 days) included 5 RCTs (638 patients, 3 interventions) (16–18,23,26) including direct evidence for 1 of 3 pairwise comparisons. Acetic acid derivative NSAIDs showed an important average improvement relative to baseline on PtGA at the longest follow-up (MD −1.64 [95% CI −1.74, −1.53], very low certainty). Ibuprofen NSAIDs were probably worse than acetic acid derivative NSAIDs (MD 0.44 [95% CI 0.02, 0.86], moderate certainty). There were no convincing differences between COX-2 highly selective NSAIDs and acetic acid derivative NSAIDs (see Supplementary Table 2).

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 8 days (range 5–365 days). Oral corticosteroids were the only intervention that may be safer than acetic acid derivative NSAIDs (RD −0.03 [95% CI −0.05, −0.01], very low certainty). There were no convincing differences between any of the other interventions (see Supplementary Table 2).

The only SAE reported in the oral corticosteroids group was a case of low potassium associated with prednisolone. The main SAEs associated with acetic acid derivative NSAIDs were gastrointestinal events, including gastric or gastroduodenal ulcers, abdominal pain, and vomiting. SAEs reported in the 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 the canakinumab group. However, the causality between the SAE and canakinumab was not reported. Among the 3 canakinumab trials, 2 trials found increased risk of infection associated with canakinumab during a 6-month follow-up (incidence of infection of 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 of 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, naproxen, or prednisolone in pain reduction, joint tenderness improvement, joint swelling improvement, PtGA, or SAE (14) (for details on the effects of each intervention see Supplementary Table 2).

DISCUSSION

The results of this NMA highlight a potential advantage of canakinumab versus other antiinflammatory interventions for gout flares in pain reduction at day 2 and the longest follow-up (moderate certainty). Canakinumab also showed larger effects on joint tenderness and joint swelling at day 2 (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, ibuprofen NSAIDs, acetic acid derivative NSAIDs, and oral corticosteroids on pain reduction at short-term (low certainty) (see Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24402/abstract). Ibuprofen NSAIDs were probably worse than acetic acid derivative NSAIDs in joint swelling at day 2 and PtGA 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 pharmacologic interventions.

Our study has several strengths. Using rigorous NMA methods, we incorporated direct and indirect evidence of the comparative efficacy and safety of antiinflammatory 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 pharmacologic interventions in relation to the reference. Moreover, the approach of making a conclusion from an 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 of the present review, in order 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. Another limitation is that the degree to which the apparent improvement is due to natural history or placebo effects is uncertain, because the effect of the reference treatment was based on a before–after comparison in the included RCTs. A third limitation is that 3 of the RCTs that enrolled patients with difficult-to-treat gouty arthritis might cause heterogeneity

and intransitivity (24,25,33,44). Additionally, we planned to conduct subgroup analyses based on the number of joints involved, pain levels, duration of the flare at presentation, duration of antiinflammatory 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 AEs would be underpowered in RCTs.

Previous systematic reviews that evaluated 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 this NMA provides, through inclusion of more studies and consideration of both direct and indirect evidence.

A Cochrane systematic review and a systematic review in support of the ACP guidelines found no difference in pain relief between NSAIDs and oral glucocorticoids (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 the present systematic review, we categorized NSAIDs into subgroups according to the pharmacologic mechanism of action, which enabled the comparison within NSAIDs and the comparison between subcategory of NSAIDs and other interventions. We found consistent results that NSAIDs were not different with oral glucocorticoids in effectiveness outcomes (see Supplementary Table 2). However, ibuprofen NSAIDs were inferior to acetic acid derivative NSAIDs in resolution of joint swelling at day 2 and improvement of PtGA 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, although ibuprofen NSAIDs were shown to be inferior to canakinumab, rilonacept, and intravenous or intramuscular corticosteroids, but showed no difference with other interventions (see Supplementary Table 2).

Cost or financial barriers to medications are not considered in this systematic review. 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 limit the practical use of canakinumab for management of gout flare. These issues have been explicitly considered and addressed in the 2020 ACR Guideline for the Management of Gout (7). In the present review, among the 3 canakinumab trials, 2 trials found increased risk of infection associated with canakinumab while the other 1 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 pharmacologic 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 subgroup analysis of patients with different characteristics in subsequent systematic reviews.

In summary, the present systematic review provides a current, comprehensive summary of the comparative efficacy and safety of pharmacologic interventions used in clinical practice for antiinflammatory treatment in patients with gout flare. Canakinumab may be superior to other alternatives and intravenous or intramuscular corticosteroids may be the second-best treatment in terms of pain reduction at day 2. Acetic acid derivative NSAIDs may be superior to ibuprofen NSAIDs on the improvement of joint swelling at day 2 and PtGA at the longest follow-up.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

REFERENCES

1. Qaseem A, Harris RP, Forciea MA. Management of acute and recurrent gout: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2017;166:58–68. [PubMed: 27802508]
2. Bardin T, Voshaar MA, van de Laar MA. The human and economic burden of difficult-to-treat gouty arthritis. Joint Bone Spine 2015;82(Suppl 1):eS2–8. [PubMed: 26717799]
3. Dalbeth N, Merriman TR, Stamp LK. Gout. Lancet 2016;388:2039–52. [PubMed: 27112094]
4. 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. [PubMed: 27457514]
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 2017;56:e1–20. [PubMed: 28549177]
6. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 2012;64:1431–46. [PubMed: 23024028]
7. FitzGerald J, 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;72:744–760. [PubMed: 32391934]
8. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777–84. [PubMed: 26030634]
9. Schumacher HR, Taylor W, Edwards L, Grainger R, Schlesinger N, Dalbeth N, et al. Outcome domains for studies of acute and chronic gout. J Rheumatol 2009;36:2342–5. [PubMed: 19820223]
10. Taylor WJ, Redden D, Dalbeth N, Schumacher HR, Edwards NL, Simon LS, et al. Application of the OMERACT filter to measures of core outcome domains in recent clinical studies of acute gout. J Rheumatol 2014;41:574–80. [PubMed: 24429178]
11. Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. J Clin Epidemiol 2018;93:36–44. [PubMed: 29051107]

12. R Development Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2005. URL: http://www.R-project.org.
13. Brignardello-Petersen R, Florez ID, Izcovich A, Santesso N, Hazlewood G, Alhazanni W, et al. GRADE approach to drawing conclusions from a network meta-analysis using a minimally contextualised framework BMJ 2020;371:m3900. [PubMed: 33177059]
14. Janssen CA, Oude Voshaar MA, Vonkeman HE, Jansen TL, Janssen M, Kok MR, et al. Anakinra for the treatment of acute gout flares: a randomized, double-blind, placebo-controlled, active-comparator, non-inferiority trial. Rheumatology 2019;58:1344–52.
15. Janssens HJ, Janssen M, Van de Lisdonk EH, Van Riel PL, Van Weel C. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. Lancet 2008;371:1854–60. [PubMed: 18514729]
16. Lederman R A double-blind comparison of etodolac (Lodine) and high doses of naproxen in the treatment of acute gout. Adv Ther 1990;7:344–54.
17. Li T, Chen SL, Dai Q, Han XH, Li ZG, Wu DH, et al. Etoricoxib versus indometacin in the treatment of Chinese patients with acute gouty arthritis: a randomized double-blind trial. Chin Med J 2013;126:1867–71. [PubMed: 23673101]
18. Maccagno A, Di Giorgio E, Romanowicz A. Effectiveness of etodolac ('Lodine') compared with naproxen in patients with acute gout. Curr Med Res Opin 1991;12:423–9. [PubMed: 1838075]
19. Man CY, Cheung IT, Cameron PA, Rainer TH. Comparison of oral prednisolone/paracetamol and oral indomethacin/paracetamol combination therapy in the treatment of acute goutlike arthritis: a double-blind, randomized, controlled trial. Ann Emerg Med 2007;49:670–7. [PubMed: 17276548]
20. Navarra S, Rubin BR, Yu Q, Smugar SS, Tershakovec AM. Association of baseline disease and patient characteristics with response to etoricoxib and indomethacin for acute gout. Curr Med Res Opin 2007;23:1685–91. [PubMed: 17588299]
21. Rainer TH, Cheng CH, Janssens HJ, Man CY, Tam LS, Choi YF, et al. Oral prednisolone in the treatment of acute gout: a pragmatic, multicenter, double-blind, randomized trial. Ann Intern Med 2016;164:464–71. [PubMed: 26903390]
22. Roddy E, Clarkson K, Blagojevic-Buchnall M, Mehta R, Oppong R, Avery A, et al. Open-label randomised pragmatic trial (CONTACT) comparing naproxen and low-dose colchicine for the treatment of gout flares in primary care. Ann Rheum Dis 2020;79:276–84. [PubMed: 31666237]
23. Rubin BR, Burton R, Navarra S, Antigua J, Londoño J, Pryhuber KG, et al. Efficacy and safety profile of treatment with etoricoxib 120 mg once daily compared with indomethacin 50 mg three times daily in acute gout: a randomized controlled trial. Arthritis Rheum 2004;50:598–606. [PubMed: 14872504]
24. So A, De Meulemeester M, Pikhlak A, Yücel AE, Richard D, Murphy V, et al. Canakinumab for the treatment of acute flares in difficult-to-treat gouty arthritis: results of a multicenter, phase II, dose-ranging study. Arthritis Rheum 2010;62:3064–76. [PubMed: 20533546]
25. Schlesinger N, Alten RE, Bardin T, Schumacher HR, Bloch M, Gimona A, et al. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. Ann Rheum Dis 2012;71:1839–48. [PubMed: 22586173]
26. Schumacher HR Jr, Boice JA, Daikh DI, Mukhopadhyay S, Malmstrom K, Ng J, et al. Randomised double blind trial of etoricoxib and indometacin in treatment of acute gouty arthritis. BMJ 2002;324:1488–92. [PubMed: 12077033]
27. Schumacher HR, Berger MF, Li-Yu J, Perez-Ruiz F, Burgos-Vargas R, Li C. Efficacy and tolerability of celecoxib in the treatment of acute gouty arthritis: a randomized controlled trial. J Rheumatol 2012;39:1859–66. [PubMed: 22859357]
28. Terkeltaub RA, Schumacher HR, Carter JD, Baraf HS, Evans RR, Wang J, et al. Rilonacept in the treatment of acute gouty arthritis: a randomized, controlled clinical trial using indomethacin as the active comparator. Arthritis Res Ther 2013;15:R25. [PubMed: 23375025]
29. Willburger RE, Mysler E, Derbot J, Jung T, Thurston H, Kreiss A, et al. Lumiracoxib 400 mg once daily is comparable to indomethacin 50 mg three times daily for the treatment of acute flares of gout. Rheumatology (Oxford) 2007;46:1126–32. [PubMed: 17478464]

30. Xu Z, Zhang R, Zhang D, Yao J, Shi R, Tang Q, et al. Peptic ulcer hemorrhage combined with acute gout: analyses of treatment in 136 cases. Int J Clin Exp Med 2015;8:6193–9. [PubMed: 26131224]
31. Xu L, Liu S, Guan M, Xue Y. Comparison of prednisolone, etoricoxib, and indomethacin in treatment of acute gouty arthritis: an open-label, randomized, controlled trial. Med Sci Monit 2016;22:810–7. [PubMed: 26965791]
32. Zhang YK, Yang H, Zhang JY, Song LJ, Fan YC. Comparison of intramuscular compound betamethasone and oral diclofenac sodium in the treatment of acute attacks of gout. Int J Clin Pract 2014;68:633–8. [PubMed: 24472084]
33. Schlesinger N, De Meulemeester M, Pikhlak A, Yücel AE, Richard D, Murphy V, et al. Canakinumab relieves symptoms of acute flares and improves health-related quality of life in patients with difficult-to-treat gouty arthritis by suppressing inflammation: results of a randomized, dose-ranging study. Arthritis Res Ther 2011;13:R53. [PubMed: 21439048]
34. Alloway JA, Moriarty MJ, Hoogland YT, Nashel DJ. Comparison of triamcinolone acetonide with indomethacin in the treatment of acute gouty arthritis. J Rheumatol 1993;20:111–3. [PubMed: 8441139]
35. Altman RD, Honig S, Levin JM, Lightfoot RW. Ketoprofen versus indomethacin in patients with acute gouty arthritis: a multicenter, double blind comparative study. J Rheumatol 1988;15:1422–6. [PubMed: 3058974]
36. Axelrod D, Preston S. Comparison of parenteral adrenocorticotropic hormone with oral indomethacin in the treatment of acute gout. Arthritis Rheum 1988;31:803–5. [PubMed: 2454635]
37. Butler RC, Goddard DH, Higgens CS, Hollingworth F, Pease CT, Stodell MA, et al. Double-blind trial of flurbiprofen and phenylbutazone in acute gouty arthritis. Br J Clin Pharmacol 1985;20:511–3. [PubMed: 3907678]
38. Cheng TT, Lai HM, Chiu CK, Chen YC. A single-blind, randomized, controlled trial to assess the efficacy and tolerability of rofecoxib, diclofenac sodium, and meloxicam in patients with acute gouty arthritis. Clin Ther 2004;26:399–406. [PubMed: 15110132]
39. Douglas G, Thompson M. A comparison of phenylbutazone and flufenamic acid in the treatment of acute gout. Rheumatology 1970;10:275–80.
40. Eberl R, Dunky A. Meclofenamate sodium in the treatment of acute gout. Results of a double-blind study. Arzneimittelforschung 1983;33:641–3. [PubMed: 6349648]
41. Fraser RC, Davis RH, Walker FS. Comparative trial of azapropazone and indomethacin plus allopurinol in acute gout and hyperuricaemia. J R Coll Gen Pract 1987;37:409–11. [PubMed: 3330140]
42. Siegel LB, Alloway JA, Nashel DJ. Comparison of adrenocorticotropic hormone and triamcinolone acetonide in the treatment of acute gouty arthritis. J Rheumatol 1994;21:1325–7. [PubMed: 7966077]
43. Smyth CJ, Percy JS. Comparison of indomethacin and phenylbutazone in acute gout. Ann Rheum Dis 1973;32:351–3. [PubMed: 4726072]
44. Hirsch JD, Gnanasakthy A, Lale R, Choi K, Sarkin AJ. Efficacy of canakinumab vs. triamcinolone acetonide according to multiple gouty arthritis-related health outcomes measures. Int J Clin Pract 2014;68:1503–7. [PubMed: 25298264]
45. Dalbeth N, Zhong CS, Grainger R, Khanna D, Khanna PP, Singh JA, et al. Outcome measures in acute gout: a systematic literature review. J Rheumatol 2014;41:558–68. [PubMed: 24334652]
46. Sivera F, Wechalekar MD, Andrés M, Buchbinder R, Carmona L. Interleukin-1 inhibitors for acute gout. Cochrane Database Syst Rev 2014:CD009993. [PubMed: 25177840]
47. Janssens HJ, Lucassen PL, Van de Laar FA, Janssen M, Van de Lisdonk EH. Systemic corticosteroids for acute gout. Cochrane Database Syst Rev 2008:CD005521.
48. Shekelle PG, Newberry SJ, FitzGerald JD, Motala A, O'Hanlon CE, Tariq A, et al. Management of gout: a systematic review in support of an American College of Physicians clinical practice guideline. Ann Intern Med 2017;166:37–51. [PubMed: 27802478]
49. Van Durme CM, Wechalekar MD, Buchbinder R, Schlesinger N, van der Heijde D, Landewé RB. Non-steroidal anti-inflammatory drugs for acute gout. Cochrane Database Syst Rev 2014:CD010120.

50. Van Echteld I, Wechalekar MD, Schlesinger N, Buchbinder R, Aletaha D. Colchicine for acute gout. Cochrane Database Syst Rev 2014:CD006190.

51. National Institute of Clinical Excellence. Gouty arthritis: canakinumab. Evidence summary ESNM23 2013. URL: https://www.nice.org.uk/advice/esnm23/chapter/Keypoints-from-the-evidence

SIGNIFICANCE & INNOVATIONS

- Despite consistent recommendations of first-line options for gout flare from guidelines, uncertainty of the efficacy and safety of pharmacologic interventions remains.
- This systematic review identifies, in patients with gout flares, a potential advantage of canakinumab versus other antiinflammatory interventions in pain reduction at day 2 and longest follow-up, and in improvement of joint tenderness at day 2.
- Among commonly used interventions, intravenous or intramuscular corticosteroids may be superior to cyclooxygenase 2 (COX-2) highly selective non-steroidal antiinflammatory drugs (NSAIDs), ibuprofen NSAIDs, colchicine, and oral corticosteroids in pain reduction at day 2. Acetic acid derivative NSAIDs are probably superior to ibuprofen NSAIDs in reducing joint swelling at day 2 and patient global assessment at longest follow-up
- This systematic review highlights the need for further evaluation of the comparative efficacy and safety of interventions used commonly in practice but not yet tested in randomized controlled trials (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.

Table 1.

Pharmacologic interventions included in each intervention node*

Category of pharmacologic mechanism, intervention node	Pharmacologic interventions included in each node
Corticosteroids	
Oral	Prednisolone
IM or IV	Compound betamethasone, methylprednisolone, triamcinolone acetonide
Colchicine	Colchicine
ACTH	ACTH
NSAIDs	
Acetic acid derivative	Etodolac, indomethacin, diclofenac
Ibuprofen	Ketoprofen, naproxen, flurbiprofen
Pyrazolidine derivative	Phenylbutazone, azapropazone
Fenamate	Meclofenamate sodium, flufenamic acid
Selective NSAIDs	
COX-2 selective	Meloxicam
COX-2 highly selective	Etoricoxib, celecoxib, rofecoxib, lumiracoxib
IL inhibitors	
Rilonacept	Rilonacept
Canakinumab	Canakinumab
Anakinra	Anakinra
Acetaminophen	Acetaminophen
Combinations	Rilonacept plus indomethacin
IL-1 inhibitors plus acetic acid derivative NSAIDs	

*ACTH = adrenocorticotropic hormone; COX-2 = cyclooxygenase 2; IL-1 = interleukin-1; IM = intramuscular; IV = intravenous; NSAIDs = nonsteroidal antiinflammatory drugs.

Table 2.

Characteristics of included RCTs (n = 30)*

Characteristic	Value
No. of patients randomized, median (range)	91.5 (20–416)
No. of multi-arm trials, %	4 (13.3)
Weeks of treatment duration, median (range)	1.0 (0.1–52.1)
Intervention evaluated	
Acetic acid derivative NSAIDs	1,112/17
COX-2 highly selective NSAIDs	753/11
Corticosteroids, IM or IV	394/7
Corticosteroids, oral	312/3
Canakinumab	270/3
Ibuprofen 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
Oral corticosteroids 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	4,266/30
Pain	3,961/23
Joint tenderness	2,928/17
Joint swelling	2,173/16
Patient global assessment	2,154/15
Methodologic 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 men, median (range)	92.1 (68.4–100)
Age, median (range) years	53 (43.8–69.6)
Report of gout duration, no. of trials (%)	10 (33.3)

* Values are the number of patients randomized/number of trials, unless indicated otherwise. ACTH = adrenocorticotropic hormone; COX-2 = cyclooxygenase 2; IL-1 = interleukin-1; IM = intramuscular; IV = intravenous; NSAIDs = nonsteroidal antiinflammatory drugs; RCT = randomized controlled trial.

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2023 October 13.

Table 3.

Most and least efficacious or safe treatment for all the outcomes [*]

Intervention	Pain score[†]		Joint tenderness[‡]		Joint swelling[§]		Patient global assessment[¶]		SAE 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 ref. group[#]									
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 ref.[§§]									
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: oral	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) [††]
Ibuprofen 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) [**]

[*] Values are the mean difference (MD) (95% confidence interval [95% CI]) unless indicated otherwise. MDs in the natural units of standard scales for continuous outcomes and risk differences (RDs) for dichotomous outcome are shown. Effectiveness outcomes included pain score, joint tenderness, joint swelling, and patient global assessment, and safety outcomes included serious adverse events

(SAEs). ACTH = adrenocorticotropic hormone; cox-2 = cyclooxygenase 2; IL-1 = interleukin-1; IM = intramuscular; IV = intravenous; MID = minimum important difference; NSAIDs = nonsteroidal antiinflammatory drugs; ref. = reference; VAS = visual analog scale.

† Mean change, 100-mm VAS for pain, where 0 mm = no pain, 100 mm = unbearable pain; MID = −19.

‡ Mean reduction, 4-point standard Likert scale for joint tenderness, where 0 = no pain, 3 = pain, winces, and withdraws; MID = −1.

§ Mean reduction, 4-point standard Likert scale for joint swelling, where 0 = no swelling, 3 = bulging beyond the joint margins; MID = −1.

¶ Mean change, 5-point standard Likert scale for patient global assessment, where 0 = excellent, 4 = poor.

The reference was acetic acid derivative NSAIDs for all the outcomes. For continuous outcomes, the effect of the reference was the change from baseline at a particular time point in the acetic acid derivative NSAIDs arm across trials; for dichotomous outcomes, the effect was the risk of the outcome in the acetic acid derivative NSAIDs arm across trials (the baseline risk).

** Interventions showing least effectiveness and safety.

†† Interventions showing most effectiveness and safety.

‡‡ Interventions showing intermediate effectiveness and safety.

§§ Cell values represent the effect of the treatment in each row when compared to the reference (e.g., canakinumab resulted in pain reduction 41.12 units greater than acetic acid derivative NSAIDs, or a 71.79-unit reduction from baseline).

¶¶ Interventions showing good patient outcomes.

Interventions showing inferior patient outcomes, including SAEs.

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2023 October 13.