



Treatment of acute gout: A systematic review

Puja P. Khanna, MD, MPH^{a,*}, Heather S. Gladue, DO^c, Manjit K. Singh, MD^d, John D. FitzGerald, MD, PhD^{e,2}, Sangmee Bae, MD^e, Shraddha Prakash, MD^e, Marian Kaldas, MD^e, Maneesh Gogia, MD^e, Veronica Berrocal, PhD^a, Whitney Townsend, MLIS^{a,b}, Robert Terkeltaub, MD^{f,3}, Dinesh Khanna, MD, MS^{a,4}



^a Division of Rheumatology, University of Michigan, 300 North Ingalls, 7D13, Ann Arbor, MI 48109-5422

^b Taubman Health Science Library, University of Michigan, 300 North Ingalls, 7D13, Ann Arbor, MI 48109-5422

^c Emory University, Atlanta, GA

^d Rochester General Health System, Rochester, NY

^e David Geffen School of Medicine, UCLA, Los Angeles, CA

^f VAMC/UCSD, La Jolla, CA

ARTICLE INFO

Keywords:
Systematic review
Acute gout

ABSTRACT

Objective: Acute gout is traditionally treated with NSAIDs, corticosteroids, and colchicine; however, subjects have multiple comorbidities that limit the use of some conventional therapies. We systematically reviewed the published data on the pharmacologic and non-pharmacologic agents used for the treatment of acute gouty arthritis.

Methods: A systematic search was performed using PubMed and Cochrane database through May 2013. We included only randomized controlled trials (RCTs) that included NSAIDs, corticosteroids, colchicine, adrenocorticotropic hormone (ACTH), interleukin-1 (IL-1) inhibitors, topical ice, or herbal supplements.

Results: Thirty articles were selected for systematic review. The results show that NSAIDs and COX-2 inhibitors are effective agents for the treatment of acute gout attacks. Systemic corticosteroids have similar efficacy to therapeutic doses of NSAIDs, with studies supporting oral and intramuscular use. ACTH is suggested to be efficacious in acute gout. Oral colchicine demonstrated to be effective, with low-dose colchicine demonstrating a comparable tolerability profile as placebo and a significantly lower side effect profile to high-dose colchicine. The IL-1 β inhibitory antibody, canakinumab, was effective for the treatment of acute attacks in subjects refractory to and in those with contraindications to NSAIDs and/or colchicine. However, rilonacept was demonstrated to be not as effective, and there are no RCTs for the use of anakinra. **Conclusion:** NSAIDs, COX-2 selective inhibitors, corticosteroids, colchicine, ACTH, and canakinumab have evidence to suggest efficacy in treatment of acute gout.

Published by Elsevier Inc.

Introduction

Acute gout is a common inflammatory arthritis in the adult US population [1,2] and presents as self-limiting flares of synovitis that occur due to deposits of monosodium urate crystals [1]. Epidemiologic evidence suggests that the prevalence of gout is on a steady rise and attributed to longevity, obesity, coexisting comorbidities, and iatrogenic causes contributing to hyperuricemia such as diuretic use [3]. Recent prevalence estimates from NHANES III showed that 3.9% of adults in the United States suffer from gout [2]. Acute gouty arthritis flares are characterized by the rapid onset of severe pain, swelling, warmth, erythema, and decreased range of motion in the affected joint [1,4,5]. Untreated flares can last from hours to weeks, resulting in missed work, and become chronic, which lead to joint destruction [6]. The frequency of flares generally increases over time in subjects whose risk factors for acute gout attacks are not adequately addressed [1,2]. Although

This work was supported in part by the American College of Rheumatology Gout Guidelines Grant.

* Corresponding author.

E-mail address: pkhanna@umich.edu (P.P. Khanna).

¹ P.P.K. is supported by NIAMS/NIH 5 U01 AR057936-02; a member of the taskforce panel of the American College of Rheumatology's Guidelines Committee to develop Quality Measures in Gout (FitzGerald, J [PI]); Coordinating Investigator on VA cooperative study, CRYSTAL; affiliated with the Ann Arbor VA Health System and University of Michigan; and has received consultant fees from Takeda.

² Supported by the American College of Rheumatology Gout Guidelines Grant and principal investigator of the taskforce panel to develop Quality Measures in Gout.

³ R.T. has received consultant fees from Regeneron, Novartis, Pfizer, Takeda, ARDEA/AstraZeneca, BioCryst, Metabolex, and Mallinckrodt.

⁴ Supported by NIH/NIAMS K24 Grant K24AR063120-02; National PI on VA cooperative study, CRYSTAL; and is a consultant to AstraZeneca and Takeda.

pain is the primary symptom, effective treatment of acute gouty arthritis must target both the pain and underlying inflammation. Acute gout is frequently treated with non-steroidal anti-inflammatory agents (NSAIDs), colchicine, or corticosteroids [1,4,7].

A systematic review of the literature was originally performed in 2010 as part of the initiative funded by the American College of Rheumatology to develop recommendations for the management of gout (including but not limited to management of acute attacks of gouty arthritis). The guidelines were published in 2012 [8]. Since the initial systematic review effort, there have been new publications on the management of acute gout. Therefore, for this article, we performed an updated systematic review focused specifically on the pharmacologic and non-pharmacologic agents used for the treatment of acute gouty arthritis.

Methods

Literature search

Structured search strategy

PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) were searched using a hedge based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials that was expanded to include articles discussing research design, cohort, case-control, and cross-sectional studies. A hedge is a search strategy that employs specific terminology to identify pertinent publications. We did not limit the search terms to RCTs and included cohort and case-control studies to be inclusive. Limits added to the hedge included English language, the exclusion of “animal only” studies and publication date between 1946 and the May 5, 2013. The exact hedge used was as follows: ((acute[All Fields] OR severe[All Fields] OR flare[All Fields] OR “acute disease”[mesh]) AND (“gout”[mh] OR gout*[tw] OR “Hyperuricemia”[mh] OR hyperuricemia[tw] OR hyperuricaemia[tw] OR toph*[tw] OR arthritis uric*[tw] OR arthriti uric*[tw] OR uric acid dis*[tw])) AND English[lang] NOT (“Animals”[Mesh] NOT (“Animals”[Mesh] AND “Humans”[Mesh])). Again, the Mesh terms included hyperuricemia and tophi, since we wanted to be inclusive of all studies on acute gout therapy. A total of 2291 articles were retrieved from PubMed and CENTRAL.

Selection of acute gout articles

P.K. and H.G. reviewed the citations generated from the search, and the review was divided into 3 stages: titles, abstracts, and articles. Titles were assessed by H.G. and P.K. for relevancy and rejected if they met any of the explicit exclusion criteria (Fig.): (1) not written in English, concerned with human subjects, or pertaining to adult studies; (2) not pertaining to gout or hyperuricemia or hypouricemia or tophi or tophi; (3) not pertaining to pharmacologic modalities; (4) not pertaining to non-pharmacological modalities, i.e., foods, diet, lifestyle, supplements related to urate/uric acid/hypo- or hyper-uricemia/gout; and (5) editorials, review articles, letters, case reports, opinions, author reply, or comments. Discordant assessments between reviewers were resolved with direct discussion and uncertainty overseen by a third party arbitrator (D.K.). We were inclusive by accepting a title if there was an uncertainty about how best to deliberate.

Of 2291 titles on acute gout, 70 were duplicates, 8 non-English, and 2056 met exclusion criteria, leaving 157 titles for abstract review. Application of the exclusion criteria outlined above to these remaining 157 abstracts (Fig.) and only 47 articles were included, which were then reviewed. We also searched for recent meeting abstracts from the American College of Rheumatology and EULAR for any randomized controlled trials from 2012 that were

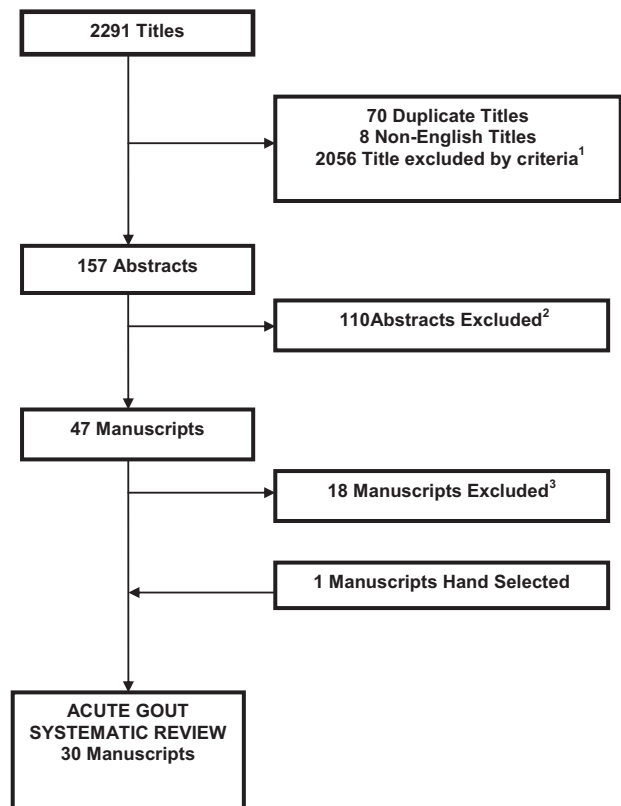


Fig. Literature search strategy.

not yet published, and handpicked 1 randomized controlled trial [9]. The 47 articles were next reviewed for another additional exclusion criterion; not a randomized clinical trial, leaving a total of 30 articles for the systematic review.

Qualitative review of articles

The methodological quality of the included studies was first assessed by assigning a Jadad score to each study [10]. The Jadad score is based on a 3-point questionnaire assessing whether the study was randomized, double-blinded or if a description of withdrawals and dropouts was given. Two additional points were given if the method of randomization and blinding was appropriate for a total of 5 possible points, 0–1 being poor, 2–3 moderate, and ≥ 4 is good. We arbitrarily assigned Level A evidence to studies with more than 1 published RCT for an agent and B for agents with 1 RCT. Although the majority of studies assessed pain as the primary outcome of acute gout trials, there was a lack of a single uniform measure that precluded meta-analysis. Furthermore, there was a lack of consensus on what time period after initiation of therapy constitutes a primary response, since trials ranged from a few hours to 10 days.

Results

Description and quality of studies

Of the 30 articles, 28 were active comparator studies, while the remaining 2 studies had a placebo-controlled group. All 30 were RCTs, 21 were double blind, 5 single blind, 3 blinding not described, and 1 non-blinded. The pooled mean age in years for all trials was 54.14 (SD = 11.94), and 89.7% were male.

Table 1
Summary of the trials and strength of evidence for currently available therapies

	No of trials ^a	Strength of evidence	Jadad score (median)	Comparator (no. of studies if > 1)	Primary end point	Time at evaluation of end point	Urate-lowering therapy (ULT) allowed?
NSAIDs							
Indomethacin [13–16,18,19,22–27,29,31]	14	A	3.5	NSAIDs (4), ACTH, COX-2 (2), oral steroids, IM TA, rilonacept, DGNTT, and Simiao pill ^b	Variable end points—see comparators	Variable	NR (8), stable ULT (5), and excluded ULT (1)
Naproxen [9,21,28]	3	A	3	Etodolac (2) and prednisolone	1. Percentage decrease in pain compared to baseline (1–5 scale) (2 trials) 2. Decreased pain after 90 h on VAS	1. Day 7 2. 90 h	Stable ULT (2) and NR (1)
Etodolac [9,28]	2	A	3	Naproxen (2)	Percentage decrease in pain compared to baseline (1–5 scale) (2 trials)	Day 7	Stable ULT (1) and NR (1)
Diclofenac [4]	1	B	4	Rofecoxib	Patient pain score	12 h	NR
Fenoprofen [45]	1	B	5	Phenylbutazone	Percentage reduction of total daily score	Days 1–4	Stable ULT
Feprazone [46]	1	B	4	Phenylbutazone	Mean time to end of attack		NR
Flufenamic acid [47]	1	B	4	Phenylbutazone	Number of days until pain relief		Stable ULT
Flurbiprofen [48]	1	B	4	Phenylbutazone	Time to resolution of symptoms		NR
Ketoprofen [14]	1	B	3	Indomethacin	Relative rate of pain reduction compared to baseline (0–3 scale)	Day 8	NR
Ketorolac [13]	1	B	5	Indomethacin	Mean decrease in pain (0–5 Wong–Baker scale)	2 h	NR
Meloxicam [4]	1	B	4	Rofecoxib	Patient pain score (5-point verbal score)	12 h	NR
Meclofenamate sodium [15]	1	B	3	Indomethacin	Percentage pain improvement (0–3 scale)	Day 7	NR
Tenoxicam [40]	1	B	1	Indomethacin	Speed of improvement of pain	Day 6	NR
COX-2 inhibitors							
Celecoxib [29]	1	B	5	Indomethacin	Pain on VAS (0–10)	Day 2	Stable ULT
Etoricoxib [18]	2	A	4.5	Indomethacin (2)	Likert scale of pain assessment (0–4)	Days 2–5	Stable ULT
Corticosteroids/ACTH							
Oral steroids [21,22]	2	A	5	Naproxen and indomethacin	1. Pain on VAS 2. Mean rate of decrease in pain on VAS (0–10)	1. 90 h 2. Variable	Stable ULT (1) and NR (1)
Intramuscular triamcinolone acetate (IM TA) [5,23,30,31]	5	A	3	ACTH, indomethacin, and canakinumab (3)	1. Mean time to resolution of symptoms (2 trials) 2. Mean interval to relief of pain 3. Percentage change in pain intensity	1. Variable 2. Variable 3. 72 h	Stable ULT (5)
IM ACTH [24,30]	2	A	2	Indomethacin and IM TA	1. Mean interval to pain relief 2. Mean time to resolution	Variable	Stable ULT (1) and excluded ULT (1)
Oral colchicine [11,12]	2	A	2.5	Placebo (2)	50% improvement on VAS (2 trials)	1. 48 h 2. 24 h	Stable ULT (1) and NR (1)

Table 1 (continued)

	No of trials ^a	Strength of evidence	Jadad score (median)	Comparator (no. of studies if > 1)	Primary end point	Time at evaluation of end point	Urate-lowering therapy (ULT) allowed?
IL-1 inhibitors							
Canakinumab [5,31]	3	A	5	IM, TA (3)	Difference in reducing VAS pain score	72 h	Stable ULT (3)
Rilonacept [25]	1	B	5	Indomethacin	Reduction of pain on Likert scale (5 point)	Day 3	Stable ULT
[33]	1	B	2	Colchicine and steroids	Relative rate of pain reduction on VAS	Day 7	Stable ULT
Simiao pill [27]	1	B	2	Indomethacin	Clinical efficacy	Day 7	NR
DGNTT [26]	1	B	1	Indomethacin	Pain score	Days 2–3	NR
ICE [33]	1	B	2	Colchicine and steroids	Relative rate of pain reduction on VAS	Day 7	Stable ULT

NSAIDs = Non-steroidal anti-inflammatory drugs; COX-2 = cyclo-oxygenase-2 inhibitors;

ACTH = Adrenocorticotropic hormone; DGNNT = Danggui-Nian-Tong-Tang; IL = Interleukin; IM = Intramuscular; TA = Triamcinolone.

Trials reported in the Table included more than 30 subjects; all trials except colchicine were active comparator studies.

NR—not reported.

^b Three studies not included in the Table—no longer on the market.

Symptom duration at time of therapy

The studies had a broad range for time after onset of an acute attack until initiation of therapy. Almost one-third (30%) of studies treated subjects within 48 h, 17% within 24 h, 1 study within 12 h, and the remaining studies ranged from 3 to 10 days of symptoms prior to initiation of therapy; 23% did not report the duration of symptoms prior to initiation of therapy. Within the various types of medications, such as NSAIDs, corticosteroids, and colchicine, there was a great variability (hours to 10 days) in the duration of symptoms before initiation of therapy.

For the 30 studies, the median Jadad score was 4.0 suggesting a good quality for the study design [10]. Studies that assessed efficacy of IL-1 inhibitors ($n = 4$, median score = 5) and corticosteroids ($n = 7$, median score = 5) had a higher Jadad score compared to studies of NSAIDs ($n = 20$, median score = 4). Studies of colchicine ($n = 2$) had Jadad scores of 4.0 [11] and 2.0 [12], and topical ice ($n = 1$) had a Jadad score of 2.0 (Table 1).

Types of studies/active comparators

The following sections provide brief overview of the various studies. Detailed information is included in Tables A1 to A3 in the Supplementary Material. Table 1 provides a summary of the trials and strength of evidence (Level A assigned for > 1 RCT for an agent and B for 1 RCT for an agent) for currently available therapies.

NSAIDs: Indomethacin, naproxen, and cyclooxygenase-2 inhibitors

Twenty-three studies (77%) (19 double-blind RCT's, 2 single-blind RCT, and 2 blinding not reported) assessed the use of NSAIDs for the treatment of acute gout, all which were active comparator studies, none were placebo controlled. There were 15 studies that evaluated the efficacy of indomethacin compared to other active agents. Of the indomethacin studies, 4 studies were compared to other active NSAID treatments [13–16], 4 studies to COX-2 selective inhibitors [17–20], 3 to corticosteroids [21–23], 1 each to ACTH, IL-inhibitor, and 2 to Chinese herbs (Danggui-Nian-Tong-Tang and the Simiao pill) [24–27]. There were no placebo-controlled trials, and all the 14 studies showed an improvement in pain in the indomethacin-treated subjects compared to baseline. Three studies compared naproxen to other active medications. Two explored the efficacy of naproxen compared to etodolac [9,28] and found that there was no statistical difference between them, and that both had a statistical improvement in pain compared to baseline. One compared naproxen to prednisolone [21] and showed a similar decrease in pain with both treatments. Five studies [4,17–20] assessed the efficacy of COX-2 selective inhibitors for the treatment of acute gouty arthritis. Of these, 4 used indomethacin as a comparator all showing similar efficacy to indomethacin except low-dose celecoxib was statistically less effective than indomethacin [17–20]. Schumacher et al. [20,29] recently compared the efficacy of high-dose celecoxib vs. low-dose celecoxib compared to indomethacin in the treatment of moderate to severe pain and inflammation associated with an acute gouty arthritis attack. This double-blind, double-dummy, active control, randomized trial randomized subjects to receive celecoxib 50 mg twice a day, celecoxib 400 mg (followed by 200 mg later on Day 1 and 200 mg twice a day for 7 days), celecoxib 800 mg (followed by 400 mg later on Day 1 and then 400 mg twice a day for 7 days), or indomethacin 50 mg 3 times a day. Subjects in the high-dose celecoxib groups (800 mg and 400 mg) had a greater reduction in pain intensity on Day 2 compared to low-dose celecoxib. However, the reduction in pain intensity on Day 2 was similar between high-dose celecoxib and indomethacin 3 times a day. Of the 5 studies, 4 of the studies assessed COX-2 inhibitors that are not available in

the United States, and 2 studies assessed COX-2 inhibitors that are no longer on the market (rofecoxib) and lumiracoxib, which is available in Mexico, Ecuador, and Dominican Republic.

Corticosteroids

Seven studies assessed the use of corticosteroids for the treatment of acute gout. Two compared oral corticosteroids to NSAIDs [21,22] and 5 compared intramuscular triamcinolone to an active comparator [5,23,30,31]. All the 7 studies showed efficacy for the use of corticosteroids in the treatment of acute gout when compared to NSAIDs, IL-1 inhibition, and ACTH.

ACTH

Two studies (1 single-blind RCT and 1 RCT where blinding was not described) assessed the use of intramuscular ACTH injection to an active comparator [24,30] and suggest a quicker resolution of pain when compared to indomethacin ($p < 0.0001$) and similar when compared to intramuscular triamcinolone acetate ($p = 0.89$). Another retrospective cohort study supports the safety and efficacy of ACTH for the treatment of acute gout [32].

Colchicine

Two studies assessed the efficacy of colchicine, both using a placebo-controlled group, both showing a statistical decrease in pain at 24 or 48 h [11,12] that showed oral colchicine as an effective treatment for an acute attack and had greater efficacy in treating pain compared to placebo when administered within first 12 h of an acute attack. Although low-dose (1.2 mg, followed by 0.6 mg 1 h later) and high-dose colchicine (4.8 mg total over 6 h) have comparable efficacy, low-dose colchicine dosing has a significantly and markedly greater tolerability profile in the AGREE trial. In this study, 77% of subjects on high-dose colchicine developed diarrhea compared to 23% in the low-dose group vs. 14% in placebo group (p value statistically significant in high-dose vs. low-dose colchicine and placebo, but no statistical significance between low-dose colchicine and placebo) [11]. The duration of treatment with oral colchicine for an acute gout attack was not assessed in these RCTs.

IL-1 inhibitors

Four RCTs assessed the efficacy of IL-1 inhibitors in the treatment of an acute gout attack compared to an active comparator [5,25,31]. Three studies evaluating canakinumab found that it was efficacious in the treatment of acute gout when compared to intramuscular triamcinolone acetate. The fourth study looked at rilonacept compared to indomethacin and suggested that rilonacept alone or in combination with indomethacin did not provide any additional pain relief at 72 h as compared to indomethacin alone.

Topical ice

One study evaluated local ice as a complementary modality and showed statistical improvement in pain on a visual analog scale ($p = 0.021$) when ice treatment was added to the corticosteroid and colchicine regimen [33].

Chinese herbs

One RCT evaluated a traditional Chinese herb used to decrease joint inflammation, the Simiao pill [27] and showed that it was more efficacious than indomethacin at Day 7. Another study compared Danggui-Nian-Tong-Tang (DGNTT) to indomethacin and found that DGNTT was not effective in treating acute gout [26].

Combination therapy

No data was found for combination of 2 pharmacologic therapies for treatment of acute gout. Two studies used combination of

pharmacologic and non-pharmacologic therapies. The first with oral steroid taper and colchicine compared to oral steroid taper, colchicine, and ice combination, which had a significant decrease in pain on a VAS with the addition of ice [33]. The second study compared acetaminophen/prednisone to acetaminophen/indomethacin and showed a statistical difference in the mean decrease in pain in the acetaminophen/prednisone group as compared to the acetaminophen/indomethacin group during the follow-up phase, but no significant difference during the emergency department phase [22].

Discussion

Guidelines for the management of gout have been published by the rheumatologic societies around the world including the European League against rheumatism (EULAR) [34], the British Society of Rheumatology (BSR) [35], the American College of Rheumatology (ACR) [8], and an international effort (the 3e initiative) [36] (Table 2). These recommendations range from treatment of acute gout to chronic management of gout. For treatment of acute gout, all guidelines recommend NSAIDs, corticosteroids, or oral colchicine. The ACR, BSR, and 3e initiative do not differentiate between NSAIDs, corticosteroids, or oral colchicine and leave the judgment on the prescribing physician depending on the comorbidities and patient preferences; the EULAR [34] recommends oral colchicine and/or NSAID as first-line agents for systemic treatment of acute attacks. All guidelines recommend low-dose colchicine—1.8 mg on first day followed by 0.6 mg once or twice a day by the ACR, 0.5 mg 3 times daily by the EULAR, or a maximum of 2.0 mg/day by the 3e initiative recommendations [36]. Only ACR recommends combination pharmacologic therapy for treatment of severe attacks (arbitrarily defined as > 7 of 10 pain on a 0–10 VAS and/or acute polyarticular gout attack, or an attack involving at least 1–2 large joints) and use of IL-1 inhibition in subjects with refractory attacks of acute gout or contraindications to all 3 agents above. The EULAR and BSR recommend a combination of pharmacological and non-pharmacological treatments such as rest or ice as add-on to single-drug treatment for acute gouty episodes. In addition, the ACR and BSR recommend initiating therapy as close to onset of attack with an assumption that earlier treatment will lead to better patient-reported outcome measures with ACR recommending with 24 h of onset.

In contrast to published guidelines, which are both data driven and consensus based, our systematic review provides evidence for only monotherapy for the treatment of acute gout and not combination therapy. All therapies were found to be effective and there are no head-to-head trials comparing NSAIDs, glucocorticosteroids, and colchicine to distinguish superiority of 1 agent over the other. In addition, apart from colchicine, none of the other therapies have been compared to placebo in a RCT. Therefore, interpretation is limited to before and after change or in comparison to another active comparator (such as NSAID, COX-2 inhibitor, and ACTH). The head-to-head trials between NSAIDs and COX-2 inhibitors showed equivalent efficacy at regulatory-approved doses (except celecoxib that required higher doses). In addition, IL-1 inhibition was found to be effective for subjects with contraindications to the traditional therapies. Although the current studies only support the use of canakinumab, open-label pilot studies have suggested a class effect and efficacy of anakinra [3] as suggested in the pathophysiology studies. In addition, there is no RCT to evaluate intra-articular corticosteroids in acute gout, but their effectiveness is published in a small case series [37]. All trials have only studied monotherapy with pharmacologic agents, whereas only 2 studies used combination of pharmacologic and non-pharmacologic therapies. No data was found for combination of 2 pharmacologic therapies for treatment of acute gout.

Table 2
Summary of recommendations and evidence on management of acute gout

Therapy for acute gout	BSR	EULAR	ACR	3e initiative	Findings from the systematic review
When to start Rx	Immediately after initiation of acute attack	Not addressed	Within 24 h of initiation of attack	Not addressed	Wide range without consensus
Monotherapy	NSAIDs are the drugs of choice followed by colchicine	first-line oral low-dose colchicine or NSAIDs	No preference and can be colchicine, NSAIDs, or corticosteroids	No preference and can be colchicine, NSAIDs, or corticosteroids	Equivalent efficacy of NSAIDs and corticosteroids; no head-to-head study with colchicine
Oral colchicine	0.5 mg 2–4 times daily	0.5 mg 3 times a day	1.8 mg first day followed by 0.6 mg once or twice daily until end of attack	Low-dose colchicine (up to 2 mg daily)	Low-dose colchicine is effective as high-dose colchicine; no RCT evidence for duration of therapy
NSAIDs and coxibs	Fast-acting NSAIDs at maximum dose are the drugs of choice; duration of therapy not addressed	Different NSAIDs are similarly effective; duration of therapy not addressed	NSAIDs or COX-2 is effective at FDA/EMA-approved doses; duration for 1 week	NSAIDs or COX-2 is effective; duration of therapy not addressed	NSAIDs have the majority of RCTs showing efficacy; RCTs support the use of coxibs; lack of placebo-controlled trials for NSAIDs and coxibs
Intra-articular steroids	IA steroids for acute monoarticular gouty arthritis	Effective and safe for acute gout	Recommends for acute gout in 1–2 large joints with acute gout	Effective for acute gout	No RCT to support use of IA steroids
Oral steroids	Effective if unable to tolerate NSAIDs or refractory gout; duration of therapy not addressed	Not addressed	Recommends oral steroids at 0.5 mg/kg for 5–10 days, or 2–5 days of full dose tapered over 7–10 days	Effective for acute gout; duration of therapy not addressed	Support for efficacy in acute gout; lack of placebo-controlled trials
IM steroids	Effective if unable to tolerate NSAIDs or refractory gout	Not addressed	Triamcinolone acetonide 60 mg once followed by oral prednisone. In patients who are NPO, initial methylprednisolone is 0.5–2 mg/kg and repeated, as needed	Effective for acute gout	Support for efficacy in acute gout 40–60 mg IM once; lack of placebo-controlled trials
Combination therapy: with 2 pharmacologic agents	Not addressed	Not addressed	When the acute attack was characterized by severe pain; acute polyarticular gout attack or an attack involving 1–2 large joints	Not addressed	Not addressed in a RCT
Non-pharmacologic	Recommends lifestyle modifications as well as ice in combination with pharmacologic therapy	Should be used in combination with pharmacologic therapy (i.e., ice)	Supplement first-line therapy with topical ice as needed	Not addressed	Ice did not provide benefit in addition to colchicine and prednisone in one RCT.

IA = intrarticular; PO = oral; IM = intramuscular; BSR = British Society of Rheumatology; EULAR = European League against Rheumatism; ACR = American College of Rheumatology; NSAIDs = Non-steroidal anti-inflammatory drugs; COX-2 = Cyclo-oxygenase-2 inhibitors.

Despite that, survey data from the US and New Zealand suggest widespread use of combination pharmacologic therapies [38,39].

This review also provided an insight on the outcome measures and trial design. We found significant heterogeneity in the trial designs. The majority of the studies ($n = 27$) appeared to be designed as non-inferiority studies although it was not explicitly stated, 2 colchicine studies [11,12] were designed as active comparator studies, and it was not clear in the remaining colchicine study [40]. In addition, end points were variable with 5 studies evaluating the time for resolution of symptoms as the primary end point, while the majority of the remaining studies evaluating the decrease in pain compared to baseline at varying follow-up times from 2 h to 8 days. A variety of patient assessment tools were used including pain scores on a 1–5 Likert score, visual analog scales (VAS), the Wong–Baker scale, and (0–4) Likert scale of pain assessment. Two studies looked at the percentage of subjects with 50% improvement on VAS at either 24 or 48 h. Although pain was the primary outcome in majority of the studies, lack of single validated uniform measures precludes meta-analysis of this systematic review. A more standardized trial design with similar primary end points for evaluation of agents in the treatment of acute gout is necessary. For future trial design, uniform definitions of primary and secondary outcome measures need to be agreed on [41].

In addition, the inclusion/exclusion criteria should provide information on: (a) severity of the flare; (b) agreement on which joints to evaluate and report number of joints involved; and (c) additional acute therapies allowed/contraindicated for rebound flares, i.e., prophylaxis when initiating and maintaining ULT. Our review suggests utilizing a more standardized RCT algorithm to initiate acute therapy within 24–48 h of a flare due to its natural course of subsiding over a short duration. In addition, it would be important to have a common end point across future trials—particularly a quick reduction in pain in order to allow subjects undergoing attacks to resume their daily activities faster and result in fewer days missed from work.

Finally, the data on cost-effectiveness of acute gout pharmacologic therapies is minimal. There are 2 studies looking at cost-effectiveness of treatment of acute gout—one in an emergency room setting [42], that showed treatment with a 5-day course of prednisolone was more cost effective than indomethacin, and the other study showed colchicine to be more cost effective than NSAIDs due to higher incidence of serious adverse effects with NSAIDs [43]. With the evolution of biologics for the treatment of acute gout, cost-effective studies are needed to determine if biologics, despite their initial upfront costs, might prove to be cost effective in the long term if their use would reduce emergency room visits or other health expenditures. Barring cost-effectiveness studies, their current use is limited to only subjects with contraindications to alternative therapies.

Conclusion

In conclusion, the current armamentarium for treatment of acute gout includes NSAIDs (oral and IM), oral colchicine, corticosteroids (oral or intramuscular), and IL-1 β antagonists. All treatments appear to be effective in controlling or abating an acute gout attack. However, the treatment choice depends on multiple factors, such as comorbidities that a patient may have, their response to previous therapies, and the cost associated with these therapies. NSAIDs continue to be the most widely studied pharmacologic agents for acute gout. Oral colchicine is an effective agent for treatment of acute gout, but the duration of treatment still needs to be determined in a RCT. Corticosteroids and probably

ACTH may be a good therapeutic alternative in subjects with acute gouty arthritis, especially in subjects with contraindications to NSAIDs or colchicine therapy. IL-1 β inhibition with canakinumab is a promising therapeutic option for acute gout that is refractory or has contraindications to conventional therapies but approved only in Europe and yet to be approved by the FDA. In addition, large, well-powered RCTs are needed with upfront or sequential combination therapies to better understand management for severe gout attacks. There are ongoing efforts by the international community and OMERACT to provide uniform definitions for clinical trials in gout and should be a step forward to conduct standardized RCTs [41,44].

Appendix A. Supporting Information

Supplementary material cited in this article is available online at <http://dx.doi.org/10.1016/j.semarthrit.2014.02.003>.

References

- [1] Neogi T. Gout. *N Engl J Med* 2011;364:443–52.
- [2] Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. *Arthritis Rheum* 2011;63:3136–41.
- [3] So A, De Smedt T, Revaz S, Tschopp J. A pilot study of IL-1 inhibition by anakinra in acute gout. *Arthritis Res Ther* 2007;9:R28.
- [4] 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.
- [5] So A, De Meulemeester M, Pikhak A, Yucel 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.
- [6] Sarawate CA, Patel PA, Schumacher HR, Yang W, Brewer KK, Bakst AW. Serum urate levels and gout flares: analysis from managed care data. *J Clin Rheumatol* 2006;12:61–5.
- [7] Terkeltaub R. Clinical practice gout. *N Engl J Med* 2003;349:1647–55.
- [8] Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res (Hoboken)* 2012;64:1447–61.
- [9] Lederman R. A double-blind comparison of etodolac and high doses of naproxen in the treatment of acute gout. *Adv Ther* 1990;7:344–54.
- [10] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12.
- [11] Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett RS, Davis MW. High versus low dosing of oral colchicine for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum* 2010;62:1060–8.
- [12] Ahern MJ, Reid C, Gordon TP, McCredie M, Brooks PM, Jones M. Does colchicine work? The results of the first controlled study in acute gout. *Aust N Z J Med* 1987;17:301–4.
- [13] Shrestha M, Morgan DL, Moreden JM, Singh R, Nelson M, Hayes JE. Randomized double-blind comparison of the analgesic efficacy of intramuscular ketorolac and oral indomethacin in the treatment of acute gouty arthritis. *Ann Emerg Med* 1995;12:682–6.
- [14] 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.
- [15] Eberl R, Dunky A. Meclofenamate sodium in the treatment of acute gout. Results of a double-blind study. *Arzneimittelforschung* 1983;33:641–3.
- [16] Ruotsi A, Vainio U. Treatment of acute gouty arthritis with proquazone and indomethacin. A comparative, double-blind trial. *Scand J Rheumatol Suppl* 1978;7:15–7.
- [17] Schumacher HR, 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. *Br Med J* 2002;324:1488–92.
- [18] Rubin BR, Burton R, Navarra S, Antigua J, Londono 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.
- [19] 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.

- [20] Schumacher HR, Berger MF, Li-Yu J, Perez-Ruiz F, Burgos-Vargas R, Li C, et al. Efficacy and tolerability of celecoxib in the treatment of moderate to extreme pain associated with acute gouty arthritis: a randomized controlled trial. *Arthritis Rheum* 2010;56:3–4.
- [21] 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.
- [22] 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.
- [23] 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.
- [24] Axelrod D, Preston S. Comparison of parenteral adrenocorticotropic hormone with oral indomethacin in the treatment of acute gout. *Arthritis Rheum* 1988;31:803–5.
- [25] Terkeltaub RA, Schumacher HR, Carter JD, Baraf HS, Evans RR, Wang J, et al. Riloncept in the treatment of acute gouty arthritis: a randomized, controlled clinical trial using indomethacin as the active comparator. *Arthritis Res Ther* 2013;15:R25.
- [26] Chou CT, Kuo SC. The anti-inflammatory and anti-hyperuricemic effects of Chinese herbal formula danggui-nian-tong-tang on acute gouty arthritis: a comparative study with indomethacin and allopurinol. *Am J Chin Med* 1995;23:261–71.
- [27] Shi XD, Li GC, Qian ZX, Jin ZQ, Song Y. Randomized and controlled clinical study of modified prescriptions of Simiao Pill in the treatment of acute gouty arthritis. *Chin J Integr Med* 2008;14:17–22.
- [28] 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.
- [29] 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.
- [30] 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.
- [31] 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.
- [32] Daoussis D, Antonopoulos I, Yiannopoulos G, Andonopoulos AP. ACTH as first line treatment for acute gout in 181 hospitalized patients. *Joint Bone Spine* 2012;80:291–4.
- [33] Schlesinger N, Detry MA, Holland BK, Baker DG, Beutler AM, Rull M, et al. Local ice therapy during bouts of acute gouty arthritis. *J Rheumatol* 2002;29:331–4.
- [34] Zhang W, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P, et al. EULAR evidence based recommendations for gout. Part II: management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCIIT). *Ann Rheum Dis* 2006;65:1312–24.
- [35] Jordan KM, Cameron JS, Snaith M, Zhang W, Doherty M, Seckl J, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatology (Oxford)* 2007;46:1372–4.
- [36] Sivera F, Andres M, Carmona L, Kydd AS, Moi J, Seth R, et al. Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative. *Ann Rheum Dis* 2013;73:328–35.
- [37] Fernandez C, Noguera R, Gonzalez JA, Pascual E. Treatment of acute attacks of gout with a small dose of intraarticular triamcinolone acetonide. *J Rheumatol* 1999;26:2285–6.
- [38] Schlesinger N, Moore DF, Sun JD, Schumacher HR Jr. A survey of current evaluation and treatment of gout. *J Rheumatol* 2006;33:2050–2.
- [39] Stuart RA, Gow PJ, Bellamy N, Campbell J, Grigor R. A survey of current prescribing practices of antiinflammatory and urate-lowering drugs in gouty arthritis. *N Z Med J* 1991;104:115–7.
- [40] Valdes EF. Use of tenoxicam in patients with acute gouty arthritis. *Eur J Rheumatol Inflamm* 1987;9:133–6.
- [41] Khanna P, Khanna D. Quality of life and outcome measures. In: Terkeltaub R, editor. *Gout & Other Crystal Arthropathies*. 1st ed. Elsevier; 2012. p. 217–24.
- [42] Cattermole GN, Man CY, Cheng CH, Graham CA, Rainer TH. Oral prednisolone is more cost-effective than oral indomethacin for treating patients with acute gout-like arthritis. *Eur J Emerg Med* 2009;16:261–6.
- [43] Wertheimer AI, Davis MW, Lauterio TJ. A new perspective on the pharmacoeconomics of colchicine. *Curr Med Res Opin* 2011;27:931–7.
- [44] Singh JA, Taylor WJ, Simon LS, Khanna PP, Stamp LK, McQueen FM, et al. Patient-reported outcomes in chronic gout: a report from OMERACT 10. *J Rheumatol* 2011;38:1452–7.
- [45] Weiner GI, White SR, Weitzner RI, Rubinstein HM. Double-blind study of fenopropfen versus phenylbutazone in acute gouty arthritis. *Arthritis Rheum* 1979;22:425–6.
- [46] Reardon JA, Stockman A, Darlington LG, Scott JT. Double-blind trial of feprazone and phenylbutazone in acute gout. *Curr Med Res Opin* 1980;6:445–8.
- [47] Douglas G, Thompson M. A comparison of phenylbutazone and flufenamic acid in the treatment of acute gout. *Ann Phys Med* 1970;10:275–80.
- [48] Butler RC, Goddard DH, Higgins CS, Hollingworth P, 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.