Interventions for Tophi in Gout: A Cochrane Systematic Literature Review

Melonie K. Sriranganathan, Ophir Vinik, Louise Falzon, Claire Bombardier, Desiree M. van der Heijde, and Christopher J. Edwards

ABSTRACT. ***Objective.*** To systematically review the available literature on the management of tophi in gout. This article is based on the Cochrane Review Interventions for Tophi in Gout published in the Cochrane Database of Systematic Reviews.

Methods. Medline, Embase, and The Cochrane Library were searched using a strategy developed with an experienced librarian. We also searched American College of Rheumatology and European League Against Rheumatism conference abstracts from 2010-2011. Included articles were reviewed in detail and a risk of bias (using the Cochrane tool) and quality assessment were performed.

Results. In total, 3206 references were recovered. Of these, 72 articles were selected based on our inclusion criteria. This included 1 report of 2 randomized controlled trials, 2 nonrandomized studies, and 69 case series and reports. The study with 2 randomized controlled trials looked at pegloticase. This showed improvement in tophi with treatment. One observational prospective trial looked at allopurinol and benzbromarone individually and in combination. It noted that achieving lower serum urate levels was associated with a faster reduction of tophi. An open-label extension trial noted that longterm maintenance of serum uric acid < 6.0 mg/dl with febuxostat led to a reduction in tophi. The case series and reports looked at surgical, pharmacological, and other interventions, as well as combination therapies. All surgical interventions reported improvement in pain and/or function. No report had objective measures of outcome.

Conclusion. Treatment with urate-lowering therapy such as allopurinol, benzbromarone, allopurinol + benzbromarone in combination, febuxostat, or pegloticase can lead to reduction in tophi. There is some evidence that achieving a lower serum urate level leads to a faster rate of tophi reduction. (J Rheumatol Suppl. 2014 Sept; 92:63–9; doi:10.3899/jrheum.140464)

Key Indexing Terms:
GOUT TOPHI

This article is part of the 3e (Evidence, Expertise, Exchange) Initiative on Diagnosis and Management of Gout. The objective of the current work was to systematically review the available literature concerning 1 of the 10 selected questions as an evidence base for generating the recommendations. The question was: How should tophi be managed? This review is also reported in the Cochrane review entitled "Interventions for Tophi in Gout."

Gout affects at least 1% of the population in Western countries[1]. It is characterized by the formation of

From the Rheumatology Department, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom; Division of Rheumatology, University of Toronto, Toronto, Ontario, Canada; Center for Behavioral Cardiovascular Health, Columbia University Medical Center, New York, NY, USA; Division of Rheumatology and Institute of Health Policy, Management, and Evaluation, University of Toronto; and Toronto General Research Institute, University Health Network; Institute for Work and Health, Mount Sinai Hospital, Toronto, Ontario, Canada; Rheumatology Department, Leiden University Medical Center, Leiden, The Netherlands; and the Department of Rheumatology and NIHR Wellcome Trust Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom.

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M.K. Sriranganathan, MBBS, MRCP, Specialist Registrar in Rheumatology and General Internal Medicine, Rheumatology Department, University Hospital Southampton NHS Foundation Trust; O. Vinik, MD, FRCPC, Division of Rheumatology, University of Toronto; L. Falzon, PGDipInf, Center for Behavioral Cardiovascular Health, Columbia University Medical Center; C. Bombardier, MD, FRCPC, Professor, Division of Rheumatology and Institute of Health Policy, Management, and Evaluation, University of Toronto; and Toronto General Research Institute, University Health Network; Institute for Work and Health, Mount Sinai Hospital; D.M. van der Heijde, MD, PhD, Professor of Rheumatology, Rheumatology Department, Leiden University Medical Center; C.J. Edwards, MBBS, MD, FRCP, Department of Rheumatology and NIHR Wellcome Trust Clinical Research Facility, University Hospital Southampton NHS Foundation Trust.

Address correspondence to Dr. M.K. Sriranganathan, Department of Rheumatology, University Hospital Southampton NHS Foundation Trust, Southhampton, UK. E-mail: melonie@doctors.org.uk

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monosodium urate crystals in joints and other tissues. The crystals trigger release of proinflammatory cytokines, leading to inflammation causing gouty arthritis. Gouty arthritis can progress to chronic, deforming, and physically disabling disease through the development of disfiguring tophi, joint destruction, and persistent pain[2].

Tophi are nodular masses of monosodium urate deposits. The presence of tophi is common in patients with untreated or inadequately controlled gout. Tophi can become infected, cause pain, and lead to a decrease in function. Complications may also occur when tophi develop in unusual sites such as heart valves, carpal tunnel, larynx, and spine.

Tophi develop in patients with poorly treated or uncontrolled gout. This is postulated to be due to persistently raised serum uric acid levels. The mainstay of management of tophi is reduction of serum uric acid levels through pharmacological interventions such as uricosuric agents and xanthine oxidase inhibitors. However, other interventions such as surgical excision are also used in practice.

A surgical approach may be used for direct removal of tophi, for example, when the presence of tophi results in a decrease in function or affects adjacent structures, such as in spinal cord compression.

Other interventions may work by also reducing serum uric acid (e.g., hemodialysis).

The presence of tophi can lead to significant morbidity and even mortality through potential complications. Despite this, there have been no systematic reviews to date looking at the management of tophi separately from the management of gout.

MATERIALS AND METHODS

Rephrasing the question. We redefined our original question by structuring it according to the PICOT format (Population, Intervention, Comparison, Outcome, Trial). In this context, our population was defined as adults age 18 years or older, with a diagnosis of gout as defined by the author or by the 1977 American College of Rheumatology (ACR) criteria, and the presence of 1 or more tophi. Interventions included any form of surgical removal, pharmacotherapy (urate-lowering therapy), and any other intervention (e.g., hemodialysis). We compared this to placebo, single versus combination therapy, or 1 intervention (e.g., surgical) versus another (e.g., pharmacological). Primary outcomes included tophi resolution in terms of size, number, recurrence, and study participant withdrawal due to a serious adverse event (e.g., wound infection, failure to close/surgical complications). Secondary outcomes include other adverse events, pain reduction, Health Related Quality of Life questionnaire result, serum urate normalization, and function (i.e., activity limitation).

Our preliminary searches found no randomized controlled trials (RCT) examining nonpharmacological interventions for tophi. Based on this, we extended the search to include systematic literature reviews, RCT, controlled clinical trials, observational studies, case series, and case reports.

Literature search and inclusion criteria for relevant scientific contributions. We performed a systematic literature review in order to identify relevant articles indexed in Medline (1950 to October 2011), Embase (1980 to October 2011), or the Cochrane Library. For the complete search strategy, see online supplementary data available from www.3egout.com

Additionally, conference abstracts submitted for the 2010 and 2011 annual scientific meetings of the European League Against Rheumatism (EULAR)and the ACR were hand-searched and reviewed.

Two authors (MS, OV) independently reviewed all retrieved trials to identify those that fulfilled the criteria for inclusion in this systematic review. We retrieved all relevant articles in full text for closer examination. We resolved disagreements about study inclusion or exclusion by consensus or by discussion with a third reviewer (CE) if needed. We translated studies into English where necessary.

The following relevant information was extracted from included trials using predetermined data extraction forms: study design; characteristics of the study population (age, sex, number and distribution of tophi); intervention used; control interventions; outcome measures; timing of outcome assessment; and methodologic domains relevant to risk of bias assessment.

We resolved differences in data extraction by referring back to the original articles and establishing consensus. We consulted a third reviewer (CE) to help resolve differences if necessary.

The review authors (MS and OV) independently assessed the risk of bias for all included trials and resolved any disagreements by consensus. We consulted a third reviewer (CE) to help resolve differences if necessary. We assessed the following methodological domains in conformity with the Cochrane Collaboration's recommendations[3]:

1. Random sequence generation: to determine if the method of generating the randomization sequence was adequate to prevent biased allocation to interventions.
2. Allocation concealment: to determine if adequate methods were used to conceal allocation to interventions.
3. Blinding of participants, personnel, and outcome assessors for each outcome measure.
4. Incomplete outcome data.
5. Selective outcome reporting.
6. Other potential sources of bias.

To determine risk of bias of an included study, for each criterion we evaluated the presence of sufficient information and the likelihood of potential bias. We rated each of these criteria as "Low risk," "High risk," or "Unclear risk" of bias (either lack of information or uncertainty over the potential for bias).

RESULTS

In total, 3206 articles were retrieved, of which 3115 articles were excluded by title and/or abstract. The 90 remaining articles were retrieved for detailed review. Of these, 19 articles were excluded; 72 articles were finally selected for appraisal (Figure 1).

Only 1 article with 2 RCT was retrieved. Other articles included 1 open-label extension of 2 phase III trials, 1 prospective observational cohort study, and 69 case series and reports. The article with 2 RCT was the only one included for the purpose of the Cochrane review.

Pharmacotherapy. Table 1 shows the characteristics of the pharmacotherapy studies. Sundy, *et al*[4] reported on 2 identical double-blind placebo-controlled RCT that investigated 8 mg pegloticase administered biweekly or monthly versus placebo. These have not been published separately and the data have been pooled for the tophi outcomes. Photographs of tophi before and after treatment were compared by a blinded central reader.

One hundred thirty-one patients were analyzed for tophi outcomes. The biweekly pegloticase group fared the best in tophi reduction. In this group 40% of the patients had resolution of 1 or more tophi. The relative risk of resolution

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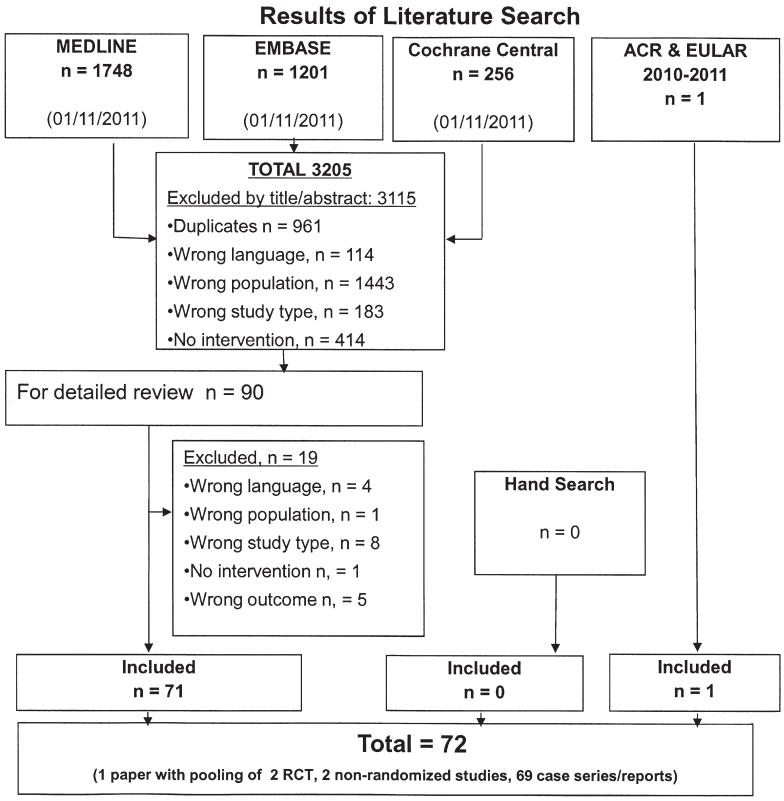

Figure 1. Procedure of the original literature search; 72 articles were retrieved for analysis.

Table 1. Study characteristics for pharmacotherapy studies.

Study	Study Type	N (dropouts)	Duration	Placebo	Comparator	Overall RoB
Sundy[4] 2011, USA, Canada, Mexico	2 × RCT	225 (19)	25 wks	Allopurinol		Unclear
Becker[5] 2009, USA, Canada	Open-label extension	1086 (168)	3 yrs	Allopurinol (max 300 mg/day) or benzbromarone (max 200 mg/day) alone		High
Perez-Ruiz[6] 2002, Spain	Cohort (prospective observational)	70 (7)	6 mo	Allopurinol (200 mg/day) + benzbromarone (50 mg/day)		High

RCT: randomized controlled trial; RoB: Risk of Bias assessment.

of 1 or more tophi was 5.45 (95% CI 1.4–21.6), compared to 2.86 in the monthly pegloticase group (95% CI 0.7–12.0).

Two hundred twelve patients were analyzed for withdrawals due to adverse events. The biweekly pegloticase group had more withdrawals due to adverse events than placebo [relative risk (RR) 7.59, confidence interval (95% CI) 1.04–55.55]. The monthly pegloticase group also had more withdrawals compared to placebo (RR 8.19, 95% CI 7.12–59.71).

Becker, *et al*[5] reported the results of EXCEL (fEbuXostat/allopurinol Comparative Extension Long-term study). This was an open-label extension of 2 phase III double-blind trials. These examined febuxostat 80 mg and 120 mg versus allopurinol (100 mg or 300 mg/day, higher dose used if serum creatinine < 1.5 mg/dl). Outcome was measured by percentage reduction in number of tophi and reduction in size or disappearance of index tophus. At baseline, 214 patients had palpable tophi. The high-dose febuxostat (120 mg) group appeared to fare better in terms of complete resolution of primary tophi. The study also noted that, overall, longterm maintenance of goal serum uric acid led to a reduction in tophi.

Perez-Ruiz, *et al*[6] reported on a prospective observational study of tophi resolution after treatment with allopurinol versus benzbromarone or combination. All patients had 1 or more tophi at baseline. There was no placebo arm to act as

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comparator. Outcome was the reduction in size of target tophus. The patients in the combination group appeared to fare best, with a mean rate of reduction until tophus resolution of 1.53 mm/month (SD 0.45). However, the mean time to resolution in this group was the longest, 27.8 months (SD 1.21). Patients with more severe tophaceous gout were given combination therapy, which may explain this finding.

Fourteen case series and reports that looked at pharmacological interventions were retrieved. Details of these are given in Table 2. There were few negative outcomes reported. Objective measures of outcome included pictoral (photographs taken before and after intervention) and size/physical measurement. Not all the studies reported objective measures of outcome.

Surgical interventions. Only case series and reports were found for surgical interventions for tophi (Table 3). In total, 40 articles were retrieved. These looked at decompression/laminectomy, excision/debridement, and soft-tissue shaving. All reported positive outcomes. However, none of the studies employed objective outcome measures.

Other interventions. The only other single intervention found in our literature search was hemodialysis. This was in a patient with chronic renal failure who was started on hemodialysis for congestive heart failure, and incidentally was noted to have a reduction of tophi. No objective measure of outcome was noted[31].

Combination therapy. The combination therapies also had few negative outcomes (Table 4). Although there are some objective measures of outcome in this group, we could not determine whether combination was superior to single surgical, pharmacological, or other therapy.

DISCUSSION

This is the first systematic literature review to examine the management of tophi in gout. We used a broad search strategy in an attempt to retrieve a wide range of studies. From our search we found that few studies to date have focused on interventions for tophi alone. In particular, there was minimal evidence for surgical or other interventions with only case series and reports deemed to have high risk of bias. In addition, there is a high probability of publication bias as poor outcomes are typically less likely to be reported. Where surgical interventions were used, these were often for complications such as neural compression in patients requiring urgent or emergency surgery. High quality evidence would be difficult to obtain in this setting.

The only RCT evidence we were able to find showed that pegloticase is effective in the reduction of tophi. However,

Table 2. Case series and reports on pharmacological interventions.

Intervention	No. Case Series/Reports	Total No. Patients	Positive Outcomes	Negative Outcomes	Objective Measure of Outcome?
IL-1 inhibitor (anakinra)[7,8]	2	4	Pain reduction, SUA reduction	None	Pictoral resolution of tophi (2)
Febuxostat[9,10]	2	2	SUA reduction; improved QOL; reduction in tophi	None	Pictoral
Allopurinol[11,12,13,14]	4	4	Improved function; reduction in tophi; SUA reduction	No resolution of tophi (1 case)	Pictoral (1); CT image (1)
Probenecid and steroid injections[15]	1	1	Improved function; pain reduction		None
Rasburicase[16,17,18]	3	12	Improved function; reduction in tophi, SUA reduction	Acute attacks of arthritis (1)	Physical measurement (12 pts)
Pegloticase[19]	1	2	SUA reduction; resolution of tophi		Size of tophi
Infliximab[20]	1	1	Pain reduction		None

SUA: serum uric acid; QOL: quality of life; CT: computed tomography scan.

Table 3. Case series and reports on surgical interventions.

Intervention	No. Case Series/Reports	Total No. Patients	Positive Outcomes	Negative Outcomes	Objective Measure of Outcome?
Decompression/ laminectomy[21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36]	16	21	Improved function; reduction in pain	Postoperative flare of gout in 2 cases	None
Excision/ amputation/ debridement[37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59]	23	27	Pain reduction; improved function; no evidence of local recurrence	Superficial wound dehiscence in 1 case	None
Soft-tissue shaving procedure[60]	1	17	Improved function; pain reduction	Skin loss (2 cases); GI bleed leading to death (1 case)	None

GI: gastrointestinal.

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Table 4. Case series and reports looking at combination therapies.

Intervention	No. Case Series/Reports	Total No. Patients	Positive Outcomes	Negative Outcomes	Objective Measure of Outcome?
Rasburicase and allopurinol[62]	1	1	Reduction in tophi; SUA reduction	Flare after each infusion	Size
Benzbromarone and allopurinol[63]	1	1	Resolution of tophi; improved function	None	Pictoral
Anakinra and hemodialysis[64]	1	1	Resolution of tophi; improved function	None	Pictoral
Benzbromarone + allopurinol, arthroscopic removal[65]	1	1	Improved function	None	None
Debridement, vacuum assisted dressing, and allopurinol[66]	1	1	No recurrence of tophi	None	None
Excision/ debridement/ joint replacement and allopurinol[67,68,69,70,71,72,73,74]	8	8	Reduction in pain; improved function	Postoperative ischemic ulceration (1); recurrence of tophi (1)	None

SUA: Serum uric acid.

there was evidence for urate-lowering therapy such as allopurinol and benzbromarone in combination, and febuxostat for treatment of tophi. In particular, achieving lower levels of serum uric acid led to faster reduction in tophi. Further studies looking at the level of serum uric acid versus speed of resolution of tophi would be useful, as target levels lower than those given in current guidelines may be beneficial for patients with severe tophaceous gout.

Our main finding from this review is the lack of good quality evidence for management of tophi and the need for further studies. However, it does agree with current practice where lowering serum uric acid levels leads to reduction in tophi.

In conclusion, there is RCT evidence that pegloticase is effective in reduction of tophi; other urate-lowering therapy (i.e., allopurinol and benzbromarone in combination, and febuxostat) has also been shown to lead to reduction of tophi; and there are many case series and reports that have described the management of tophi by surgical or other intervention in combination with pharmacotherapy, particularly where urgent removal of tophi is necessary.

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