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REVIEW ARTICLE - SAFETY AND PHARMACOVIGILLANCE

Safety of allopurinol compared with other urate-lowering drugs in patients with gout: a systematic review and meta-analysis

Isabel Castrejon · Esther Toledano · María Piedad Rosario · Estíbaliz Loza · Fernando Pérez-Ruiz · Loreto Carmona

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Abstract Allopurinol is the most widely used urate-lowering drug (ULD). Together with efficacy and cost, safety is an aspect that helps taking clinical decisions. This systematic review analyzes allopurinol safety. The literature search was performed in MEDLINE, EMBASE, and the Cochrane Library (January 2014). Selection criteria: (a) patients >18, (b) gout by the ACR criteria or evidence of urate crystal in synovial fluid, (c) comparator (placebo or other ULD), and (d) RCTs, cohorts, or meta-analysis. Primary outcomes: rate of adverse events and death. The quality was assessed with the Jadad's scale. A meta-analysis with fixed effects was performed. From 544 studies, seven met the eligibility criteria and were included. All RCT presented a low power for safety. All RCTs included a mixed population of patients with gout and hyperuricemia. Allopurinol (300 mg) was compared to febuxostat (40–240 mg) in five RCTs, to benzbromarone and probenecid in two RCTs, and to placebo in one. In the RCTs comparing allopurinol with benzbromarone and probenecid, the highest discontinuation rate was with probenecid (26 %), followed by allopurinol (11 %) and benzbromarone (4 %). The incidence of adverse events was similar between allopurinol (range 38.6–85) and febuxostat (range 41.8–80). Six patients on febuxostat and three on allopurinol died during the studies; no deaths were judged related to drug. The combined risk of adverse events was RR = 1.04 (95 % CI 0.98, 1.11). Allopurinol is a safe option, slightly better than other ULDs. The grade of evidence is high, but further research is needed to evaluate higher doses and long-term safety.

Keywords Gout · Systematic review · Allopurinol · Urate-lowering drugs

I. Castrejon (✉)
Division of Rheumatology, Rush University Medical Center, 1611 West Harrison Street, Suite 510, Chicago, IL 60612, USA
e-mail: isabelcastrejonf@gmail.com

E. Toledano
Department of Rheumatology, Hospital Clínico San Carlos, Madrid, Spain

M. P. Rosario
Research Unit, Spanish Society of Rheumatology, Madrid, Spain

E. Loza · L. Carmona
Institute for Musculoskeletal Health, Madrid, Spain

F. Pérez-Ruiz
Department of Rheumatology, Hospital Universitario Cruces, Baracaldo, Spain

Introduction

Gout is the most common inflammatory arthropathy in males over 40 [1], and its prevalence continues to increase [2]. It usually presents with acute attacks including joint swelling and pain, which can lead to chronic arthritis. While there is no cure for the disease, treatment can prevent recurrent gout attacks and improve its chronic form. Currently, new urate-lowering drugs (ULD) have become available, and a renaissance of interest in gout has occurred.

Managing gout is intrinsically straightforward; however, there is evidence that the quality of gout care continues to be inadequate not only because of a potential failure of clinical practice also drug development can play a role [3].

The majority of guidelines recommend reducing and maintaining SU levels below 6 mg/dl [4]. This strategy allows the mobilization of monosodium urate crystals out of joints and soft tissue eliminating the formation of tophi. The lower the SU levels are reduced the faster the tophi will be resolved [5]. With appropriate therapy and compliance,

most patients with gout should be able to achieve full remission.

Depending on the mechanism of action, there are two classes of ULD to decrease the level of serum urate (SU): The xanthine oxidase inhibitors (allopurinol and febuxostat) and the uricosuric that increase uric acid excretion (probenecid, benzbromarone and sulfinpyrazone). Allopurinol has been the main drug available for decades and currently is the most prescribed urate-lowering drugs. This purine analog was initially developed as an antineoplastic agent, and it is easy to administer (generally requiring only a once daily dose), inexpensive, and generally well tolerated. The recommended initial dose is 100 mg daily, but this has to be adjusted to reach a therapeutic dose according to plasma or urinary uric acid concentration to a maximum of 800 mg approved by the US Food and Drug Administration for patients with a normal renal function.

Allopurinol is generally well-tolerated and a very effective drug, but it is underused possibly because concerns about the hypersensitivity syndrome, a rare but potentially fatal adverse event [6]. The allopurinol hypersensitivity syndrome has been associated with renal impairment. Although there are broadly used guidelines to adjust allopurinol dose based on creatinine clearance [7], it has been shown that higher allopurinol doses than recommended in this guidelines are effective with few adverse events [8].

The selection of the safer treatment in patients with gout and other comorbidities can be a challenge for the clinicians. The appearance of new therapies could provide additional options for patients with gout that may allow for safer management of their disease. For example, febuxostat is a novel non-purine analog xanthine oxidase inhibitor with a similar efficacy compared to allopurinol, which may require fewer dose adjustments in patients with mild to moderate renal dysfunction [9]. Approved doses in the USA are 40 and 80 mg daily and in Europe 80 and 120 mg [10].

This study aims to assess the safety of allopurinol compared to placebo or other ULD for the treatment of gout. The methodological approach to answer this question was a systematic literature review and meta-analysis as part of the gout guidelines by the Spanish Society of Rheumatology Consensus of gout. These guidelines are developed as a national effort aimed at promoting evidence-based medicine by formulating detailed treatment and management recommendations.

Materials and methods

A systematic review was undertaken with the objective of identifying all studies published up until January 2014 providing information about allopurinol safety. This review has been performed following the Cochrane recommendations [11]. We first transformed the research question using the patient, intervention, comparator, and outcome (PICO) approach. A librarian developed the search strategy. The following electronic databases were searched: *The Cochrane Library* (2014); MEDLINE (1950–January 2014); and EMBASE (1980–January 2014). The search was limited by language (English, French, and Spanish), but not by year of publication or type of publication. The full search strategy in Appendix 1 was developed for MEDLINE and was adapted for the other electronic databases.

Selection of studies and data collection

EndNote X5 software was used to manage the records retrieved from searches of electronic databases. Two reviewers (IC and ET) applied the screening criteria to review all identified citations independently. Clinical trials, cohorts, or previous systematic reviews that evaluated the safety of allopurinol for the treatment of gout were eligible for inclusion. The selection criteria were predefined by protocol. In order to incorporate a study: (1) The studied population had to include adults (+18) with gout; (2) at least one of the study groups had to have received treatment with allopurinol; and (3) the outcome had to be a measure of safety (such as death or any side effect). All citation identified by either reviewer was retrieved and analyzed to see whether they meet these pre-specified inclusion criteria. Disagreements were resolved by consensus with a third reviewer (EL). Subsequently, the selected articles were reviewed in detail, and articles that did not fulfill all the inclusion criteria were excluded from the systematic review. The references of published review articles were screened for additional manuscripts that met the inclusion and exclusion criteria.

The selected manuscripts were reviewed in further detail, and data were extracted using ad hoc standard forms. One reviewer collected the data of the selected studies, including the number of patients and their characteristics, the comparator group, the doses of allopurinol and ULD, the duration of follow-up, the study quality, and relevant outcomes. Only outcomes related to safety were incorporated into the analysis. When raw data were not provided, data were extracted from figures and tables to calculate the necessary information.

Assessment of methodological quality

Methodological quality was assessed by the reviewers using the validated Jadad scale for clinical trials [12]. The Jadad scale includes three questions scored with one point each of them: Was the study described as randomized?

Was the study described as double blind? And was there a description of withdrawals and dropouts? Additional points are given whether randomization and blinding methods were appropriate. A paper reporting a clinical trial could therefore receive a Jadad score from 0 to 5.

Data analysis

Data extracted from the included trials were presented in evidence tables to improve the readability of the review. Dichotomous variables were presented as number and percentage of patients with adverse events.

Data were summarized in a meta-analysis with fixed effects when they were sufficiently homogeneous, both clinically and statistically. In the studies with different arms of febuxostat depending on the dose, we combined them assuming the same risk of adverse events. Besides, for the meta-analyses, we also assumed that the risk of adverse events was the same irrespective of the duration of the treatments. All analyses, confidence intervals, and graphics were performed with Stata 12 (Stata Corporation, College Station, TX 77845, USA).

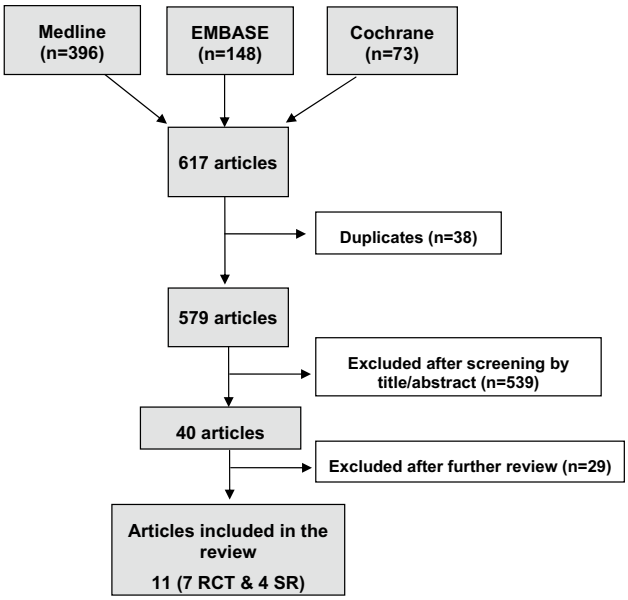

Fig. 1 Search methods and reasons for exclusion of studies from the review. A total of 617 references were identified in PubMed, MEDLINE, and the Cochrane Library. After screening by title and abstract, 539 references were excluded with 40 remaining references for a further review. Finally, 11 articles were included in this review: seven RCT and four reviews

Results

In the electronic search, a total of 617 citations were retrieved: 396 from MEDLINE, 148 from EMBASE, and 73 from the Cochrane Library. A flowchart summarizing the search results is presented in Fig. 1. In a first review based on abstracts and titles, we excluded 539 citations. Of the 40 full texts retrieved for the final review, 29 were excluded, see Appendix 2 for details, and a total of 11 met the inclusion criteria (See Table 1).

There were a total of seven randomized, double-blind, placebo-controlled trials and four systematic reviews in this review including data on allopurinol safety. We did not identify any cohort in our literature search. Appendix 3 summarizes information about 4 reviews which include articles already considered in the present review. Two are part of the NICE recommendations [13, 14] and the other two are reviews about febuxostat, one of them about cardiovascular and serious adverse events [15, 16]. The trials included are listed in Table 1, along with a description of the study design, population studied, comparator groups, and quality of the studies.

All the included clinical trials evaluated primarily efficacy instead of safety. Sample sizes ranged from 45 to 2.268 with a total of 4.506 adults patients with gout or hyperuricemia, mean age ranging from 51.8 to 59 years and a majority of males (>82 %). A total of 696 participants were randomized to allopurinol (up to 300 mg), 134 to placebo, 3,585 to febuxostat (40–120 mg), 56 to benzbromarone, and 35 to probenecid. Participants met the preliminary criteria of the ACR for acute gout arthritis and had serum uric acid levels of >8.0 mg/dl.

Allopurinol reported dosages were 100, 200, and 300 mg/day, and febuxostat dosages were 40, 80, 120, and 240 mg/day. Only Schumacher et al. [17] included a placebo group.

The majority of trials reported the proportion of participants with serum uric acid levels of <6.0 mg/dl as the primary outcome measure and other measures of efficacy. In this review, only safety outcomes were included. Only one clinical trial evaluated the safety of allopurinol versus placebo [17]. Two clinical trials compared allopurinol with benzbromarone [18] and probenecid [19], and the remaining four clinical trials included different doses of febuxostat ranging from 40 to 120 mg as comparator [20–23]. Reported adverse events were similar across trials. Trials reported any adverse event, serious adverse events, and those occurring in at least 2–5 % of participants in any group.

All studies included both patients with gout (defined by the ACR criteria [24] or by confirmation of urate crystals in the synovial fluid) and patients with hyperuricemia (defined as a serum urate higher than 8 mg/dl). In all studies, the safety was reported as incidence of side effects for each treatment group. Most adverse events were mild to moderate in severity, and the most commonly reported adverse events were abnormal liver function, diarrhea, and rash.

Table 1 Characteristics of the included studies

Study	Population	Intervention	Outcomes: adverse events	Quality
Becker et al. [21] *USA and Canada* 52-weeks follow-up Phase 3 R double-blind multicenter trial	*N* = 760; patients fulfilling the ACR criteria for gout or SUC >8 mg/dl Mean age 51.8 years 96 % males	Allopurinol 300 mg (253) Febuxostat 80 mg (256) Febuxostat 120 mg (251)	% any adverse event or death % any serious adverse event (considered by the investigator) % most frequent adverse events (>2 % subjects): liver function abnormalities, diarrhea, headache, joint-related signs, gastrointestinal symptoms, neurological symptoms, nausea, asthenia, rash	Randomization was described and appropriate Blinding was not described Withdrawals were described *Jadad = 3*
Schumacher et al. [17] *USA* 28-weeks follow-up Phase 3 R double-blind trial	*N* = 1070; patients fulfilling the ACR criteria for gout or SUC >8 mg/dl with serum creatinine <2 Mean age 52 years 94 % males	Allopurinol 300 mg (268) Placebo (134) Febuxostat 80 mg (267) Febuxostat 120 mg (267) Febuxostat 240 mg (134)	% any adverse event % any serious adverse event (cardiovascular) % most frequent adverse events (>5 % subjects): upper respiratory infection, musculoskeletal symptoms, liver function abnormalities, diarrhea, headache, joint-related signs, gastrointestinal symptoms, neurological symptoms, nausea	Randomization was described and appropriate Blinding was described and appropriate Withdrawals were described *Jadad = 5*
Becker et al. [20] USA 24-weeks follow-up Phase 3 double-blind RCT	*N* = 2,269; diagnosis of gout by the ARA preliminary criteria Mean age 53 years 95 % males	Allopurinol 300 mg (756) Febuxostat 40 mg (757) Febuxostat 80 mg (756)	% any adverse event or death % any serious adverse event (considered by the investigator) % most frequent adverse events (>5 % subjects): upper respiratory infection, liver function abnormalities, rash, diarrhea, musculoskeletal symptoms, cardiovascular events	Randomization was described and appropriate Blinding was not described Withdrawals were described *Jadad = 3*
Kamatani et al. [23] Japan 8-weeks follow-up Phase 3 double blind	*N* = 242; patients with SUC >8 mg/dl and gout Mean age 52 years 98 % males	Allopurinol 200 mg (120) Febuxostat 40 mg (122)	% most frequent adverse events (≥5 % subjects): pharyngitis, upper respiratory infection, diarrhea, liver function abnormalities	Randomization was not described Blinding was not described Withdrawals were described *Jadad = 1*
Kamatani [22] Japan 16-weeks follow-up Phase 3 double blind	*N* = 38; patients with SUC >8 mg/dl and gout Mean age 53.5 years 100 % males	Allopurinol 200 mg (19) Febuxostat 40 mg (10) /60 mg (9)	% frequent adverse events (no table)	Randomization was not described Blinding was not described Withdrawals were described *Jadad = 1*
Reinders et al. [18] Netherlands 8-weeks follow-up Multicentre R controlled trial	*N* = 65; gout by microscopic evidence of crystal or ACR criteria Mean age 59 years 82 % males	Allopurinol 300 mg (36) Benzbromarone 200 mg (29)	% any adverse event % frequent adverse events: gastrointestinal symptoms, neurological symptoms, hepatitis y rash	Randomization was described and appropriate Blinding was described and appropriate Withdrawals were described *Jadad = 5*
Reinders et al. [19] Netherlands Multicentre R controlled trial	*N* = 96; gout by microscopic evidence of crystal or ARA criteria Mean age 57 years 95 % males	Stage 1: Allopurinol (82) Stage 2: Benzbromarone 200 mg (27) Probenecid 1,000 mg (35)	% any adverse event % frequent adverse events: gastrointestinal symptoms, neurological symptoms, fatigue, cramps, hepatitis, rash y visual problems	Randomization only in second part Blinding was described but inappropriate Withdrawals were described *Jadad = 2*

ACR American College of Rheumatology, *SUR* serum urate concentration, *R* randomized

The quality of the studies was variable with a high quality in the studies by Schumacher et al. [17] and Reinders et al. [18] and moderate in the others.

Safety of allopurinol compared to placebo and febuxostat

Four RCTs were included. The incidence of any adverse events and severe adverse events are summarized in Table 2. The most common adverse events were abnormal liver function, diarrhea, and rash (Table 3).

Becker et al. [21] in a double-blind, multicenter RCT analyzed the effect of two single doses of febuxostat (80 and 120 mg) with allopurinol. The incidence of adverse events was similar in the three arms of treatment. The majority of adverse events were mild. Four patients in the febuxostat groups died (0.8 %) and none in the allopurinol group, although the investigators did not find any relation with the study drugs. There was, however, a higher number of withdraws with higher doses of febuxostat (120 mg) compared to allopurinol, and this difference was statistically significant (98/251 66/253; $p = 0.003$). The most frequent causes for discontinuation were lost to follow-up, adverse events, and gout flares.

A 28-weeks double-blind, placebo-controlled RCT compared in 1.072 patients with gout and/or hyperuricemia, the efficacy, and safety of febuxostat (80, 120, and 240 mg) versus allopurinol (300 mg) and placebo. The incidence of adverse events was similar between groups [17]. However, the incidence of diarrhea and dizziness was higher with febuxostat 240 mg compared to the other groups. All rash events were combined to assess whether there was any difference between groups, and the incidence was similar. The most common severe adverse events were cardiovascular events, but all of them in patients with a previous history of heart disease. There was one cardiovascular event in the placebo group, allopurinol, and febuxostat 240 mg (<1 %) and five in febuxostat 80 mg and 120 mg (2 %). No deaths were reported during this study.

Adverse events also occurred with similar frequency in all treatment groups in the study by Becker et al. [20]. In addition, this study included patients with renal failure, moderate to severe, in which adverse events were of similar incidence to the total patient group. Five patients died, two in the febuxostat group, and three in the allopurinol group, but these deaths were not related to the treatments according to the researchers. Regarding rates of discontinuation, there were no differences between treatments arms. The most frequent cause of withdraw was abnormal liver function (2 % in the febuxostat 40 mg group and 1 % in the febuxostat 80 mg and allopurinol group). The incidence of rash was similar in the three groups. The incidence of cardiovascular events was 5 % in each febuxostat group and 6 % for allopurinol without statistical significant differences.

In the study of Kamatani et al. [23], no differences were found in the incidence of adverse events between febuxostat (40 mg) and allopurinol. Adverse events appeared mainly between weeks 2 and 6 in the febuxostat group and at week 2 in the allopurinol group. In another study of Kamatani [22], there were no differences in safety between the treatment groups.

Allopurinol was in general safe and well tolerated. As exposed in the methods section, febuxostat doses were combined to perform meta-analyses (Fig. 2). There was a high heterogeneity between the included studies (heterogeneity Chi squared = 0.65, $p = 0.96$). We did not find differences in the risk of any type of adverse events between allopurinol (300 mg) and febuxostat (40–240 mg). The combined risk of adverse events was RR = 1.04 (95 % CI 0.98, 1.11).

Safety of allopurinol compared to benzbromarone and probenecid

There are two studies, which compare the safety of allopurinol versus probenecid and benzbromarone. In the first one [19], allopurinol 300 mg was administrated to 86 patients over 2 months. If allopurinol treatment was not tolerated or the therapeutic goal of serum uric acid below 5 mg/dl was not achieved, patients were randomized to benzbromarone or probenecid for another 2 months. Adverse events were expressed as the proportion of patients in which the drug was discontinued due to an adverse event divided by the total of adverse events. A higher rate of patients discontinued treatment due to adverse effects in the probenecid group (26 %, 95 % CI 12–45 %), followed by allopurinol (11 %, 95 % CI 5–20 %) and benzbromarone (4 %, 95 % CI 0–19 %).

Gastrointestinal symptoms were more frequent with probenecid (23 %), compared to benzbromarone (12 %) and allopurinol (7 %), but rarely required discontinuation of therapy. Only five patients (16 %) in the probenecid group and 1 (1 %) in the allopurinol group had to stop the medication. The cases of rash were more frequent in the allopurinol group making to withdraw the drug in six patients (7 %) versus one patient (3 %) in the probenecid group and none in the benzbromarone group.

In a second study [18], patients were randomized to allopurinol or benzbromarone. A greater number of patients discontinued the treatment in the benzbromarone group (12 %) compared to allopurinol group (7 %). The most common adverse events in the benzbromarone group were gastrointestinal symptoms (8 %) and dizziness (4 %); these were not reported in the allopurinol group. Only two patients had rash (7 %) in the allopurinol group.

Summarizing the results of this review, we can conclude that the safety of allopurinol is that of febuxostat at doses below 120 mg and that of probenecid and benzbromarone (level of evidence 1B, evidence from at least one high quality RCT).

Table 2 Adverse events with allopurinol versus placebo and other ULD

Study	*D* (m)	Allopurinol (300 mg)	Febuxostat				Benzbromarone (200 mg)	Probenecid (1,000 mg)	Placebo
			40 mg	80 mg	120 mg	240 mg			
Any adverse event									
Becker et al. [21]	13	215/253 (85)	–	205/256 (80)	189/251 (75)	–	–	–	–
Schumacher et al. [17]	7	200/268 (75)	–	161/267 (68)	183/269 (68)	98/134 (73)	–	–	97/134 (72)
Becker et al. [20]	6	433/756 (57.3)	410/756 (54.2)	429/757 (56.7)	–	–	–	–	–
Kamatani et al. [23]	2	49/121 (38.6)	51/122 (41.8)	–	–	–	–	–	–
Kamatani [22]	3	16/19 (84.2)	13/19 (68.4)	–	–	–	–	–	–
Reinders et al. [18]	4	2/30 (7)	–	–	–	–	5/25 (20)	–	–
Reinders et al. [19]	2	18/82 (22)	–	–	–	–	5/24 (20)	12/31 (39)	–
Severe adverse events									
Becker et al. [21][a]	13	19/253 (8)	–	11/256 (4)	21/251 (8)	–	–	–	–
Schumacher et al. [17]	7	1/268 (<1)	–	5/267 (2)	5/269 (2)	1/134 (<1)	–	–	1/134 (<1)
Becker et al. [20][b]	6	31/756 (4.1)	19/757 (2.5)	28/756 (3.7)	–	–	–	–	–
Cardiovascular events									
Schumacher et al. [17]	7	1/268 (0.4)	–	5/267 (2)	5/269 (2)	1/134 (0.7)	–	–	1/134 (0.7)
Becker et al. [20]	6	3/756 (0.4)	0/757 (0)	3/756 (0.4)	–	–	–	–	–

Total adverse event/total patients (%)

[a] Four patients in the febuxostat group died (0.8 %) and none in the allopurinol group, although researchers did not find any relationship with the therapy

[b] Five patients died during the follow-up: two with febuxostat and three with allopurinol, although researchers did not find any relationship with the therapy

Discussion

This manuscript is a systematic review that examines the literature on the safety of allopurinol compared to other ULD. Allopurinol has been the benchmark for chronic gout therapy since its approval by the FDA in 1966 [25]. Even though gout is the most common inflammatory arthropathy and is easily treatable, many patients with gout are inadequately treated. One reason for this may be a lack of understanding and fear of potential adverse effects of therapies used to lower SU levels.

This review is limited by the quantity and quality of published manuscripts. No studies have addressed safety as the principal outcome, and included studies were heterogeneous in terms of follow-up, doses, and sample sizes. Although the dose of allopurinol used in most studies is similar, it must be taken into account that this dose might not correspond to the standard dose that should be used in clinical practice.

The majority of trials supporting the registration of febuxostat compared therapeutic doses of febuxostat to subtherapeutic doses of allopurinol, and therefore the relative efficacy of febuxostat could have been overestimated. Moreover, the dose used in the febuxostat groups is highly variable from one study to another, ranging from 40 mg—below than is recommended in clinical practice—to 240 mg, which is higher than commonly used in clinical practice. A further major flaw in this review is that all the studies included only short-term safety analysis and to evaluate the safest therapeutic option, it is necessary to know long-term safety.

We have tried to synthesize what the studies actually provided in terms of side effects, but none of this study was designed to show safety, and therefore have no enough detail on serious adverse events. Even with an incidence of adverse events highly variable across studies, no statistically significant differences between the treatment groups were found. Possibly the variability in these percentages is due to a different methodology when collecting adverse events. Some studies consider only events directly related to the drug, and other studies consider all adverse events that appear. Another aspect that can influence this variability on incidence is the different follow-up periods between studies.

Even though most studies found no significant differences in safety between different treatments, it is necessary to highly some aspects. Treatment withdrawals and abnormal liver function were reported more frequently with

Table 3 More frequent adverse events with allopurinol compared to placebo and other ULD

Study	*D* (m)	Allopurinol	Febuxostat				Benzbromarone	Probenecid	Placebo
			40 mg	80 mg	120 mg	240 mg			
Abnormal liver function									
Becker et al. [21]	13	11/253 (4)	–	9/256 (4)	13/251 (5)	–	–	–	–
Schumacher et al. [17]	7	15/268 (6)	–	17/267 (6)	10/269 (4)	6/134 (4)	–	–	3/134 (2)
Becker et al. [20]	6	50/756 (6.6)	63/756 (8.3)	52/757 (6.9)	–	–	–	–	–
Kamatani et al. [23]	2	7/121 (5.8)	3/122 (2.5)	–	–	–	–	–	–
Kamatani [22]	3	0/19 (0)	2/19 (10.5)	–	–	–	–	–	–
Diarrhea									
Becker et al. [21]	13	8/253 (3)	–	8/256 (3)	7/251 (3)	–	–	–	–
Schumacher et al. [17]	7	17/268 (6)*	–	16/267 (6)*	19/269 (7)*	18/134 (13)*	–	–	11/134 (8)
Becker et al. [20]	6	57/756 (7.5)	45/756 (5.9)	47/757 (6.2)	–	–	–	–	–
Kamatani et al. [23]	2	9/121(7.4)	4/122 (3.3)	–	–	–	–	–	–
Rash									
Becker et al. [21]	13	4/253 (1.6)	–	1/256 (0.4)	1/251 (0.4)	–	–	–	–
Becker et al. [20]	6	55/756 (7.3)	44/756 (5.8)	42/757 (5.6)	–	–	–	–	–
Kamatani et al. [23]	2	3/121 (2.5)	0/122 (0)	–	–	–	–	–	–
Reinders et al. [19]	2	6/82 (7)	–	–	–	–	0/24 (0)	1/31 (3)	–
Reinders et al. [18]	4	2/30 (7)	–	–	–	–	0/25 (0)	–	–

Total adverse event/total patients (%)

D duration of the follow-up

* Statistically significant differences

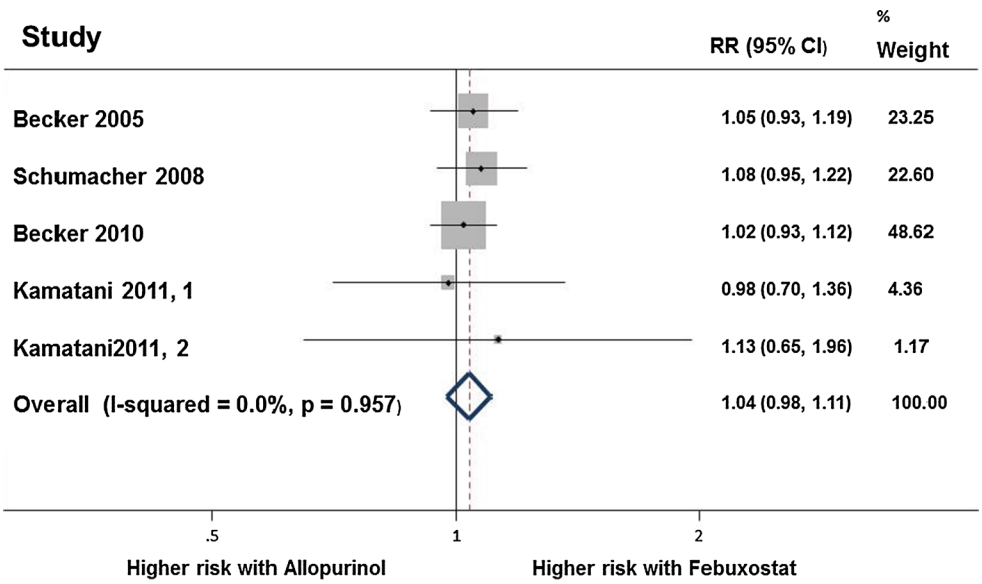

Fig. 2 Comparison allopurinol versus febuxostat, any outcome adverse events

high doses of febuxostat (120 mg) compared to allopurinol being this differences statistically significant [21]. In addition, there were more cases of diarrhea and dizziness with higher doses of febuxostat (240 mg) compared to lower doses of the same drug and allopurinol [17]. From these data, we can conclude that a dose of 300 mg allopurinol is safer than doses of febuxostat higher than 120 mg.

Concerning the studies comparing allopurinol with benzbromarone and probenecid, there were more cases of withdrawal with probenecid versus allopurinol. The gastrointestinal symptoms were also more frequent in the group of probenecid. According to these data, allopurinol can be considered more secure than probenecid, but no safer than benzbromarone. As for other effects, such as the

appearance of rash, all studies showed a greater tendency in the allopurinol group, although the differences were not statistically significant.

Regarding cardiovascular events, although the data of Becker et al. [21] produced some initial alarm, with four deaths in the febuxostat group and none in the allopurinol group in an additional study by Becker et al. [20], there was no increased risk of cardiovascular events in the group of febuxostat. Although there is a trend in cardiovascular effects with febuxostat, these differences were not statistically significant when compared with allopurinol.

This review presents some limitations worth noting. The studies heterogeneity made difficult to compare results. Also the comparators were very heterogeneous, but allopurinol was constant in each evaluated study because allopurinol safety was the main objective in our analysis. Because allopurinol is not always regarded as a safe drug, it was used in these trials in a very low and suboptimal dose. With this subtherapeutic dose (albeit commonly prescribed in real care), safety of allopurinol cannot appropriately be assessed and the relative efficacy of other drugs may have been overestimated.

Adverse events were also evaluated in very different follow-up times due to the large variability in the duration of the clinical trials included. The most important limitation is that safety was not the primary outcome measure in any of the studies. As none of these studies were designed to evaluate safety data concerning safety were limited. Moreover, the included RCTs designed specifically for efficacy failed to have denominators large enough to observe one single case of allopurinol hypersensitivity syndrome. This limitation may be solved using cohorts to evaluate long-term safety in larger populations. The development of new drugs may provide benefit for some patients, but might not contribute much to the overall disease burden of chronic gout. It would be a more reasonable approach to develop sufficient knowledge of long-term safety and appropriate doses in a real care setting collecting data through clinical cohort studies over the world.

In summary, allopurinol is a safe treatment option compared to other ULDs, but higher doses and longer follow-ups need to be evaluated. This review could provide a step toward reeducating clinicians, and their perceptions of how safe are ULDs to treat patients with gout. Additional safety concerns can arise beyond signals seen during clinical trials as a new medication is used in clinical practice, but reviewing the evidence from the literature allopurinol is a safe option compared not only to placebo but also to other ULD.

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Conflict of interest The authors declare no conflict of interest.

Appendix 1: MEDLINE search

P (patients)	Search (("Gout"[Mesh]) OR Gouts OR "Arthritis, Gouty"[Mesh] OR Gouty Arthritis OR Arthritides, Gouty OR Gouty Arthritides) OR ("Juvenile gout"[Supplementary Concept] OR Gouty nephropathy, familial juvenile OR Nephropathy, familial, with gout OR Familial juvenile hyperuricaemic nephropathy) OR (acute gout) OR (gouty) OR (gouty arthritis) OR (acute gouty arthritis) OR (tophaceous gout) OR (chronic tophaceous gout) OR (chronic tophaceous gout) OR (gout hyperuricemia) OR (gout renal) OR (hyperuricemia gout) OR (gout arthritis) OR (chronic gout) OR ("Hyperuricemia"[Mesh]) OR ("Uric Acid"[Mesh] OR Acid, Uric OR Trioxopurine OR 2,6,8-Trihydroxypurine OR Potassium Urate OR Urate, Potassium OR Urate OR Ammonium Acid Urate OR Acid Urate, Ammonium OR Urate, Ammonium Acid OR Sodium Urate Monohydrate OR Monohydrate, Sodium Urate OR Urate Monohydrate, Sodium OR Monosodium Urate Monohydrate OR Monohydrate, Monosodium Urate OR Urate Monohydrate, Monosodium OR Sodium Acid Urate Monohydrate OR Sodium Urate OR Urate, Sodium OR Monosodium Urate OR Urate, Monosodium OR Sodium Acid Urate OR Acid Urate, Sodium OR Urate, Sodium Acid) OR (intercritical gout) OR (monohydrate crystals) OR (primary gout) OR (secondary gout)
I (intervention)	Search "Allopurinol"[Mesh] OR Zyloprim OR Wellcome Brand of Allopurinol OR Allopurinol Wellcome Brand OR Zyloric OR Glaxo Wellcome Brand of Allopurinol OR Allopurinol OR Bicther Brand of Allopurinol OR Allopurinol Bicther Brand OR Allorin OR Douglas Brand of Allopurinol OR Allopurinol Douglas Brand OR Allpargin OR Merz Brand of Allopurinol OR Allopurinol Merz Brand OR Allural OR Pan Quimica OR Quimica, Pan OR Apulonga OR Dorsch Brand of Allopurinol OR Allopurinol Dorsch Brand OR Apurin OR Multipharma Brand of Allopurinol OR Allopurinol Multipharma Brand OR Atisuril OR Byk Gulden Brand of Allopurinol OR Bleminol OR gepepharm Brand of Allopurinol OR Allopurinol gepepharm Brand OR Caplenal OR Rhône-Poulenc Rorer Brand of Allopurinol OR Rhône-Poulenc Rorer Brand of Allopurinol OR APS Brand of Allopurinol OR Allopurinol APS Brand OR Capurate OR Fawns

continued

0 (outcome)	Search ((((((((((((((((((((((((“adverse effects “[Subheading] OR side effects OR undesirable effects OR injurious effects)) OR (“Safety”[Mesh] OR Safeties)) OR (“Drug Toxicity”[Mesh] OR Drug Toxicities OR Toxicities, Drug OR Toxicity, Drug OR Drug Safety OR Safety, Drug OR Adverse Drug Reaction OR Adverse Drug Reactions OR Drug Reaction, Adverse OR Drug Reactions, Adverse OR Reaction, Adverse Drug OR Reactions, Adverse Drug OR Adverse Drug Event OR Adverse Drug Events OR Drug Event, Adverse OR Drug Events, Adverse OR Event, Adverse Drug OR Events, Adverse Drug)) OR (“toxicity “[Subheading] OR toxic potential OR margin of safety)) OR (drug fatality)) OR (‘drug mortality’ OR ‘fatal adverse drug reaction’ OR ‘fatal adverse reaction’ OR ‘fatal side effect’)) OR (drug mortality OR fatal adverse drug reaction OR fatal adverse reaction OR fatal side effect)) OR (“poisoning “[Subheading] OR poisonous effects)) OR (“Drug Hypersensitivity”[Mesh] OR Drug Hypersensitivities OR Hypersensitivities, Drug OR Drug Allergy OR Allergies, Drug OR Drug Allergies OR Hypersensitivity, Drug OR Allergy, Drug)) OR (‘drug sensitivity’ OR ‘drug sensitivity test’ OR ‘drug subsensitivity’ OR ‘drug susceptibility’ OR ‘parasitic sensitivity tests’ OR ‘susceptibility, drug’)) OR (drug sensitivity OR drug sensitivity test OR drug subsensitivity OR drug susceptibility OR parasitic sensitivity tests OR susceptibility, drug)) OR (sensitivity drug)) OR (“Drug Interactions”[Mesh] OR Drug Interaction OR Interaction, Drug OR Interactions, Drug)) OR (“drug effects “[Subheading] OR pharmacologic effects OR effect of drugs)) OR (“Adverse Drug Reaction Reporting Systems”[Mesh] OR Drug Reaction Reporting Systems, Adverse)) OR (‘adverse drug reaction’ OR ‘adverse drug effect’ OR ‘adverse drug eventor adverse effect’ OR ‘adverse reaction’ OR ‘adverse reaction, drug’ OR ‘drug adverse effect’ OR ‘drug adverse reaction’ OR ‘drug reaction, adverse’ OR ‘drug side effect’)) OR (‘adverse drug reaction’ OR ‘adverse drug effect’ OR “adverse drug eventor” OR “adverse effect” OR ‘adverse reaction’ OR ‘adverse reaction, drug’ OR ‘drug adverse effect’ OR ‘drug adverse reaction’ OR ‘drug reaction, adverse’ OR ‘drug side effect’)) OR (adverse drug reaction OR adverse drug effect OR “adverse drug eventor” OR “adverse effect” OR adverse reaction OR adverse reaction, drug OR drug adverse effect OR drug adverse reaction OR drug reaction, adverse OR drug side effect)) OR (“drug carcinogenicity” OR ‘carcinogenicity, drug induced’)) OR (“drug carcinogenicity” OR carcinogenicity, drug induced)) OR (“drug cytotoxicity” OR “cytotoxicity, drug”)) OR (“Treatment Outcome”[Mesh] OR Outcome, Treatment OR Rehabilitation Outcome OR Outcome, Rehabilitation OR Treatment Effectiveness OR Effectiveness, Treatment OR Treatment Efficacy OR Efficacy, Treatment) OR “Hypersensitivity”[Mesh] OR Hypersensitivities OR Allergy OR Allergies OR Allergic Reaction OR Allergic Reactions OR Reaction, Allergic OR Reactions, Allergic OR Search “Stevens-Johnson Syndrome”[Mesh] OR Stevens Johnson Syndrome OR Search ((((“Allopurinol/adverse effects”[Mesh]) OR (“Gout Suppressants/adverse effects”[Mesh] OR “Gout Suppressants/toxicity”[Mesh])) OR (“Drug Eruptions/chemically induced”[Mesh] OR “Drug Eruptions/complications”[Mesh]))OR(“Eosinophilia/chemically induced”[Mesh]OR”Eosinophilia/complications”[Mesh]) OR DRESS OR “drug related eosinophilia with systemic symptoms”
Study	Search ((((((((((((“Review”[Publication Type] OR Review, Systematic OR Review, Multicase OR Review Literature OR Review, Academic OR Review of Reported Cases OR Review)) OR (((“Clinical Trial”[Publication Type]) OR “Validation Studies”[Publication Type]) OR “Evaluation Studies”[Publication Type])) OR (“Clinical Trial, Phase I”[Publication Type] OR Clinical Trial, Phase 1)) OR (“Clinical Trial, Phase II”[Publication Type] OR Clinical Trial, Phase 2 OR Clinical Trial, Phase II)) OR (“Clinical Trial, Phase III”[Publication Type] OR Clinical Trial, Phase 3 OR Clinical Trial, Phase III)) OR (“Clinical Trial, Phase IV”[Publication Type] OR Clinical Trial, Phase 4 OR Clinical Trial, Phase IV)) OR (“Controlled Clinical Trial”[Publication Type])) OR (“Multicenter Study”[Publication Type] OR Multicenter Studies OR Multicenter Study)) OR (“Randomized Controlled Trial”[Publication Type] OR Randomized Controlled Trial)) OR (“Cohort Studies”[Mesh] OR Cohort Study OR Studies, Cohort OR Study, Cohort OR Concurrent Studies OR Studies, Concurrent OR Concurrent Study OR Study, Concurrent OR Historical Cohort Studies OR Studies, Historical Cohort OR Cohort Studies, Historical OR Cohort Study, Historical OR Historical Cohort Study OR Study, Historical Cohort OR Analysis, Cohort OR Analyses, Cohort OR Cohort Analyses OR Cohort Analysis OR Closed Cohort Studies OR Cohort Studies, Closed OR Closed Cohort Study OR Cohort Study, Closed OR Study, Closed Cohort OR Studies, Closed Cohort OR Incidence Studies OR Incidence Study OR Studies, Incidence OR Study, Incidence OR Cohort Studies)) OR (“Cohort Studies”[Mesh] OR cohort study OR studies, cohort OR study, cohort OR concurrent studies OR studies, concurrent OR concurrent study OR study, concurrent OR historical cohort studies OR studies, historical cohort OR cohort studies, historical OR cohort study, historical OR historical cohort study OR study, historical cohort OR analysis, cohort OR analysis, cohort OR cohort analyses OR cohort analysis OR closed cohort studies OR cohort studies, closed OR closed cohort study OR cohort study, closed OR study, closed cohort OR studies, closed cohort OR incidence studies OR incidence study OR studies, incidence OR study, incidence OR cohort studies)) OR (“Longitudinal Studies”[Mesh] OR Longitudinal Study OR Studies, Longitudinal OR Study, Longitudinal OR Longitudinal Survey OR Longitudinal Surveys OR Survey, Longitudinal OR Surveys, Longitudinal OR Longitudinal Studies)) OR (“Follow-Up Studies”[Mesh] OR Follow-Up Studies OR Follow-Up Study OR Studies, Follow-Up OR Study, Follow-Up OR Follow-up Studies OR Follow-up Study OR Studies, Follow-up OR Study, Follow-up OR Follow-Up Studies))
Limits	Humans, English, French, Spanish

Appendix 2: Excluded studies and reason for exclusion

Article	Reason for exclusion
Kim (2013)	Incidence of cutaneous adverse reactions in allopurinol users
White (2012)	Gout patients at high risk of CV events
Wells (2012)	Secondary analysis of the CONFIRMS trial comparing Afro-Americans with Caucasian
Tayar (2012)	Febuxostat review and meta-analysis
Chohan (2012)	Comparison of female versus male gout patients
Schumacher (2012)	Rilonacept and allopurinol versus placebo
Becker (2011)	Side effects depending on patient age not treatment
Suarez-Almazor (2010)	Protocol to review febuxostat use in gout
Saito (2010), Hanvivadhanakul (2002), Stolbach (1982)	No gout patients
Poon (2009), Luk (2009), Sundy (2007), Perez-Ruiz (1998), Gibson (1982)	No data about allopurinol safety
Reinders (2007)	Allopurinol versus allopurinol and probenecid
Keenan (2012), Kim (2006), Wortmann (2005), Pascual (2000), Pascual (2007)	Narrative reviews
Catton (2006)	Protocol to review allopurinol use in gout
Pohar (2006)	Canadian recommendation to use febuxostat
Takahashi (2003)	Allopurinol was not included as treatment arm
Vazquez-Mellado (2001)	Prevalence study of side effect of allopurinol in patients with gout
Perez-Ruiz (1999)	Patients with gout and renal function impairment
Delbarre (1966), Kuzell (1966)	Case reports

Appendix 3: Characteristics of the included reviews and meta-analysis

Review and meta-analysis	
Stevenson (2011) Evidence Review Group(ERG) NICE recommendations	Includes: Becker (2005) Schumacher ACR-1837 (2005)
Singh (2010) Meta-analysis of allopurinol and febuxostat safety	Includes: Becker (2010) Schumacher (2008) Becker (2005)
Stevenson (2009) Evidence Review Group(ERG) NICE recommendations	Includes: Becker (2005) Schumacher ACR-1837 (2005)
Yu (2007) Review about Febuxostat efficacy	Includes: Becker (2005) Schumacher ACR-1837 (2005)

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