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Pegloticase for chronic gout (Review)

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[Intervention Review]

Pegloticase for chronic gout

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ABSTRACT

Background

Pegloticase is a potential new treatment option for patients with chronic gout intolerant to other urate-lowering therapies.

Objectives

To assess safety (adverse events, death) and efficacy (pain, function, frequency of flares, quality of life, uric acid level, radiographic damage) of pegloticase in various doses or as compared to placebo or other interventions for treatment of hyperuricemia in patients with chronic gout.

Search methods

We searched six databases: The Cochrane Central Register of Controlled Trials (CENTRAL), via *The Cochrane Library*, OVID MEDLINE, CINAHL (via EBSCOHost), OVID SPORTdiscus, EMBASE and the Science Citation Index (Web of Science).

Selection criteria

All published randomized controlled trials (RCTs) or controlled clinical trials that compared various doses of pegloticase alone or pegloticase alone or in combination with other urate-lowering or anti-inflammatory medications to placebo alone or placebo in combination with these medications, in patients with gout.

Data collection and analysis

Two review authors (AA, JS) independently extracted data from the included trials, including trial and population characteristics, primary and secondary outcomes. For dichotomous and continuous outcomes, we calculated the risk ratio and mean difference, respectively with 95% confidence interval. Major outcomes were: (a) Efficacy: frequency of gout flares and change in serum uric acid; and (b) safety: adverse events, serious adverse events, withdrawals and death. Minor/secondary outcomes were pain, patient/physician global assessment, tophus burden, health related quality of life, function and radiographic progression.

Main results

Only one open-label, phase-II RCT (n=41) met the selection criteria that compared various doses of pegloticase without comparison to placebo or another treatment. Patients were randomized to one of the four doses of pegloticase for 12 to 14 weeks - 4mg every 2 weeks, 8mg every 2 weeks, 8mg every 4 weeks and 12mg every 4 weeks. Percent responders (uric acid below 6 mg/dl 80% or more time) in the four dose groups were 56%, 88%, 52% and 62%. Percent time without hyperuricemia (uric acid below 6 mg/dl) was 78%, 92%, 76% and 76% respectively. No between dose differences were noted. Most common adverse events (10% or more patients) included nephrolithiasis, arthralgia, anemia, dyspnea, headache, muscle spasms, nausea and pyrexia. 89% reported one or more gout flares during the study. Pain, patient/physician global, function, quality of life, tophus size/regression and radiographic progression were not reported in this study.

Pegloticase for chronic gout (Review)

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Authors' conclusions

There are no published double-blind, placebo-controlled RCTs of pegloticase. More evidence is needed to assess risks/benefits of pegloticase in patients with chronic gout.

PLAIN LANGUAGE SUMMARY

Pegloticase for chronic gout

This summary of a Cochrane review presents what we know from research about the effect of pegloticase on chronic gout. There was one study included in this review which looked at different doses. The review shows that:

- it is unknown whether pegloticase can improve the pain and function of people with chronic gout.

Even though there were no differences in improvement, no matter which dose of pegloticase was taken, the uric acid was better controlled in the 8 mg every 2 week dose. In patients who had not responded to other medications, 90% of patients had below normal levels of uric acid at this dose.

We often do not have precise information about side effects and adverse events. This is particularly true for rare but serious side effects. Possible side effects of pegloticase are kidney stones, joint pain and anemia.

What is gout, and what is pegloticase?

Gout is a sudden, very painful joint inflammation (arthritis) that usually affects the big toe. Due to increase in the uric acid level in blood and then in the joints, urate crystals form on the joint and make it painful to move your toe or even to touch it. A sudden attack of gout can sometimes be followed years later by chronic gout that affects both small and large joints of hands and feet.

Pegloticase is meant to work by converting the urate crystals to something that will not form on the joints. It might also enable the body to handle the urate crystals that have already built up on the joint. Pegloticase is a new gout drug that is still under development. This means that it is currently not available because it is still being tested.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Proportion of treatment responders in ITT and completer populations

Treatment Group	% Treatment Responders
4 mg q 2 wk ITT	58%
4 mg q 2 wk completer	50%
8 mg q 2 wk ITT	85%
8 mg q 2 wk completer	85%
8 mg q 4 wk ITT	57%
8 mg q 4 wk completer	75%
12 mg q 4 wk ITT	60%
12 mg q 4 wk completer	80%

Summary of findings 2. Percentage of time without hyperuricemia in ITT and completer populations

Treatment Group	Mean Total % Nonhyperuricemic Time
4 mg q 2 wk ITT	78%
4 mg q 2 wk completer	81%
8 mg q 2 wk ITT	90%
8 mg q 2 wk completer	90%
8 mg q 4 wk ITT	78%
8 mg q 4 wk completer	88%
12 mg q 4 wk ITT	78%
12 mg q 4 wk completer	81%

BACKGROUND

Description of the condition

Gout is a common medical problem that affects at least one percent of men in Western countries (Terkeltaub 2003). Men aged 40 and over, and postmenopausal women are most commonly diagnosed with gout, with a male-to-female ratio of 4:1 (Saag 2006). The epidemiologic data indicates that incidence of gout is rising steadily in the U.S. for both men and women (Arromdee 2002; Choi 2005).

The risk for gout increases when the concentration of uric acid is above 7 mg/dl with increased plasma urate concentration (serum urate), which leads to monosodium urate crystals forming in the body. These urate crystals precipitate and deposit into the joints of a patient, and these crystals can also form in tendons or tissue (Terkeltaub 2003; So 2008). The disease is diagnosed definitively through identification of intracellular crystals in the synovial fluid of joints. During metabolism, uric acid [urate] is produced as a byproduct of purine digestion; this product is poorly soluble in serum when concentrations are at/above 7 mg/dl. Typically, uric acid production in humans is balanced by the appropriate excretion and production. Overproduction of urate can result from increased production of purine from increased ATP degradation or more rarely, an error in purine metabolism. Decrease in urate excretion may be caused by problems with the kidneys, various drugs and diseases.

Gout can present in several forms. It can present with recurrent acute arthritis attacks, intense inflammation in one or several joints which is usually associated with the presence of monosodium urate monohydrate crystals in synovial fluid. This can be followed years later by chronic gout that affects both small and large joints of hands and feet, associated with chronic inflammation of these joints, many times resembling rheumatoid arthritis. Acute and chronic gout are associated with elevated serum urate concentrations (hyperuricemia) and with aggregates of sodium urate monohydrate crystals, referred to as *tophi* deposited in and around joints (Eggebeen 2007).

Description of the intervention

The pharmacological therapeutic strategies for gout include treatments targeted at treating acute inflammation during recurrent gouty attacks and treatment of hyperuricemia and tophaceous gout with urate-lowering therapy, which targets the underlying metabolic disorder. Treatment options for acute gouty arthritis includes non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin, oral and intra-articular corticosteroids and colchicine (Biggers 2008). However, long-term use of colchicine may have serious adverse effects even at low doses (Terkeltaub 2003). Other treatments include decreasing the serum urate, most commonly through an xanthine oxidase inhibitor such as allopurinol and oxypurinol, uricosurics drugs [probenecid; sulfapyrazone and benzbromarone (not available in the U.S.)]. Behavioral interventions targeting lifestyle modifications, including weight reduction and reduction in alcohol intake, are recommended for patients for gout.

Pegloticase is a biological agent currently in development for treatment of patients with severe gout that is refractory to treatment with currently approved urate-lowering agents (specifically allopurinol), either because of intolerance/

hypersensitivity to these medications or because of co-morbidities that limit use of these medications. Pegloticase is a modified porcine recombinant uricase that converts uric acid to a more soluble compound, allantoin (Biggers 2008; So 2008; Chohan 2009).

It is also described as a modified mammalian uricase (Sundy 2008). Biologics are in general much more expensive than the usual medications. Since pegloticase is not currently marketed, its price is unknown, but is likely to be higher than current treatments such as allopurinol. The US FDA has designated pegloticase for development as an orphan agent on the grounds that it may fulfil a currently unmet medical need in the small percentage of gout patients (estimated at between 25,000 and 75,000 persons or ~1 to 1.5% of the estimated 3 to 5 million gout patients in the U.S) with refractory gout as defined above. Clinical trials are currently in process and the drug has been submitted to the FDA for consideration.

How the intervention might work

Humans are unable to complete the conversion of uric acid to allantoin due to evolutionary modification of the urate oxidase gene (Sundy 2007). Allantoin is a more soluble and easily excreted end product of metabolizing purine in the body (Sundy 2008).

Pegloticase use results in a decrease of serum urate concentration, which controls the clinical consequences of hyperuricemia in patients who have treatment-failure gout. Decreasing the serum urate concentration may also aid in degradation and excretion of existing crystal tophi, and thus prevent other long-term clinical consequences that include joint, bone, cartilage and tissue destruction (Yue 2008).

Pegloticase therapy for gout represents a novel approach to treating the hyperuricemia that is a constant accompaniment of gout: conversion of urate to the more soluble purine end product, allantoin, by a uricase engineered (by PEGylation) to extend the biological half life of the enzyme. Prior use of uricase preparations for prophylaxis/treatment of tumor lysis syndrome (rasburicase) or for chronic gout (uricozyme) has been reported, but the potential/demonstrated immunologic consequences of chronic treatment with these agents has limited this pursuit.

Why it is important to do this review

Many patients with chronic gout fail current treatment options. Availability of a new treatment option that is safe and effective will be a significant advance in the treatment of refractory gout. By performing this review for pegloticase, we will assess whether the evidence supports the safety and efficacy of pegloticase as a urate-lowering agent. Cochrane systematic reviews of colchicine (Schlesinger 2006) and systemic corticosteroids for acute gout (Janssens 2008) have been published.

OBJECTIVES

To assess safety (adverse events, serious adverse events, death) and efficacy (pain, function, frequency of flares, quality of life, uric acid level, radiographic damage) of various doses of pegloticase used intravenously or as compared to placebo or other interventions for treatment of hyperuricemia in patients with chronic gout.

METHODS

Criteria for considering studies for this review

Types of studies

All published randomized controlled trials (RCTs) or controlled clinical trials (methods of allocating participants to a treatment which are not strictly random, e.g., date of birth, hospital record number or alternation) were considered for inclusion.

Types of participants

Adults 18 years or older, with gout as diagnosed based on the presence of monosodium urate crystals in synovial fluid from the affected joint or tophus, or if the patient exhibited a minimum of six of the thirteen clinical, laboratory, and x-ray ARA preliminary criteria to establish a diagnosis of primary gout (Wallace 1977).

Types of interventions

Pegloticase alone in various doses or in combination with other urate-lowering agents or anti-inflammatory medications compared to placebo alone or placebo in combination with other urate-lowering agents or anti-inflammatory medications. There were no restrictions with regard to dosage or duration of intervention.

Types of outcome measures

The choice of outcomes was based on proposed domains by Grainger et al. (Grainger 2009) and Schumacher et al. (Schumacher 2009) in accordance with OMERACT filter. Data regarding these outcomes have been presented at the last two OMERACT meetings.

Primary outcomes

1. Major outcomes: Efficacy as assessed by frequency of gout flares and change in serum uric acid and safety as assessed by the number and type of adverse effects (AEs) and serious adverse events (SAEs), withdrawals (total, due to lack of efficacy, due to adverse events) and death.

Secondary outcomes

1. Pain - on Likert scales including visual analog scale (VAS), numeric rating scale (NRS) or qualitative scales
2. Patient global and physician global assessment
3. Tophus burden as measured by regression of tophi, including disappearance of tophi and velocity of tophus regression
4. Health related quality of life as assessed by generic measures such as short form-36 (SF-36) and Gout Assessment Questionnaire (GAQ) (Hirsch 2008)
5. Function as assessed by activities of daily living including composite outcomes such as Health Assessment Questionnaire (HAQ) (Fries 1980) or other activities of daily living scales (ADLs) and work productivity
6. Joint damage as assessed by validated radiographic scores, such as Larsen (Larsen 1977) or Sharp (Sharp 1971), or by radiographic changes

Of the outcomes listed above, three were voted with >70% consensus at the last OMERACT meeting, including, pain (96%), SF-36 (77%) and patient global (83%) (Grainger 2009). Other outcomes here are not validated, but are in the process of validation. We used the clinically most relevant outcomes.

The GAQ is designed for gout patients, in order to assess how gout impacts their quality of life. Questions include clinical descriptors, treatment, gout history, demographic information; how gout affects their daily life overall and also their physical function, social interactions, occupational functioning, and psychological state (Hirsch 2008).

We realized that randomized controlled trials included in this review were limited in their ability to assess safety. We searched the U.S. Food and Drug Administration (FDA) web site for labels and warnings and other similar regulatory agency's web sites to summarize warnings related to use of pegloticase in gout.

Search methods for identification of studies

Electronic searches

We searched the following databases for randomized or quasi-randomized trials:

1. The Cochrane Central Register of Controlled Trials (CENTRAL), via *The Cochrane Library*, Wiley InterScience (www.thecochranelibrary.com), current issue; (Appendix 1)
2. OVID MEDLINE, 1966 - July 2009; (Appendix 2)
3. CINAHL (via EBSCOHost), 1982 - July 2009; (Appendix 3)
4. OVID SPORTdiscus, 1949 - July 2009; (Appendix 4)
5. EMBASE 1980 - July 2009; (Appendix 5)
6. Science Citation Index (Web of Science) 1945 - July 2009 (Appendix 6).

Searching other resources

The FDA web site was searched for warnings related to pegloticase.

The search was not limited by language, year of publication or type of publication.

We included only studies published in English. We did not include any abstracts in this review.

Data collection and analysis

Selection of studies

We utilized our criteria to identify potential trials for inclusion.

Two review authors (JS, AA) independently assessed the methods sections of all identified trials according to predetermined criteria (see 'Selection criteria'). Any disagreements were resolved by consensus.

Data extraction and management

Two review authors (JS, AA) independently extracted data from the included trials. The extracted data included information such as the population of study, interventions, number of centers, funding sources, and outcomes and analyses using standardized data extraction forms. When we needed more information, the authors of the studies were contacted.

We extracted raw data for outcomes of interest such as the standard deviation and mean for continuous data and number of events for dichotomous data from the published reports to evaluate efficacy. We extracted data based on the intention-to-treat (ITT) analysis.

Assessment of risk of bias in included studies

Two review authors (JS, AA) independently assessed the risk of bias of each included trial. Disagreements were resolved by discussion between the two review authors. Since there were unresolved disagreements, we did not need an arbiter/third review author.

To assess the risk of bias in each of the included studies, review authors used the Cochrane Collaboration recommendations for assessment. The main criteria applied to measure the risk of bias included: presence of blinding in the studies (patients, assessors and physicians), allocation concealment, random sequence generation, incomplete outcome data, and sensitive outcome reporting (Higgins 2008). The risk of bias in each study was explicitly judged on each criterion using the following standard: Yes (low risk of bias), No (high risk of bias), or unclear (either lack of information or uncertainty over the potential for bias).

Measures of treatment effect

The results of each RCT were plotted as point estimates, such as risk ratios (RRs) with corresponding 95% confidence interval for dichotomous outcomes, and mean and standard deviation for continuous outcomes. We extracted all possibly extractable results from the included trials. When this was impossible, for example if data are reported as median scores only, we presented and described them in a separate table. For continuous measures, we calculated mean differences when possible because results presented in this form are easier interpreted by clinicians. Standardized mean differences were used for measure of treatment effect when outcomes assess the same construct but use different outcome measures, such as data which use different and inconvertible scales to measure the same construct of interest.

Unit of analysis issues

The Patient was the unit of analysis.

Dealing with missing data

We summarized this in the study characteristics and summarization of the risk of bias tables. No imputation was done.

Assessment of heterogeneity

The elements evaluated to assess for clinical homogeneity were the duration of gout, outcomes, and control groups. If studies were shown to be clinically heterogeneous, we excluded them from the meta-analysis and performed analysis on them separately. We performed the I^2 statistic to quantify heterogeneity. In interpreting the I^2 statistic, we complied with the guidelines put forth in the Cochrane Handbook recommendations, which determine that 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% considerable heterogeneity (Deeks 2008).

Assessment of reporting biases

In order to assess reporting biases, we had planned on making a funnel plot when doing a meta-analysis for 10 or more studies. The funnel plot is a scatter plot that takes the sample size on the y-axis and the treatment effect along the x-axis. A good indication of reporting bias is observation of asymmetry in the funnel plot. However, due to the fact that only one study qualified for inclusion, this could not be performed.

Data synthesis

Most data synthesis that was planned per protocol could not be performed in absence of a placebo group.

The random-effects model was to be used as a default for pooling outcomes in a meta-analysis of studies that were determined as clinically homogeneous. We used the fixed effect model to evaluate any bias in smaller studies.

The mean difference was to be calculated (absolute change expressed in percentage and in its original units) for continuous outcomes such as pain measured on a Visual Analog scale, numeric rating scale, or qualitative scale. The absolute benefit divided by the baseline mean of the control group was the planned method for calculation of the relative difference in the change from baseline.

In studies where trials employed comparable scales, the mean difference (MD) was to be calculated by weighing the absolute change based on group size.

We planned on measuring health related quality of life using the Gout Assessment questionnaire (GAQ) and short form-36 (SF-36), if available.

The quality of evidence in the included review was assessed by two independent review authors (JS, AA) applying the GRADE standard of quality assessment, which outlines four levels: high, moderate, low, and very low (Atkins 2004, Atkins 2004a). Evidence was considered:

1. High quality if randomized trials were employed; or were obtained through double-upgraded observational studies.
2. Moderate quality if downgraded randomized trials were employed; or were obtained through upgraded observational studies.
3. Low quality if double-downgraded randomized trials were employed; or were obtained through observational studies.
4. Very low quality if triple-downgraded randomized trials were employed; or downgraded observational studies; or data was obtained using case series/case reports.

Review authors also had the authority to downgrade trial evidence by one or two levels, if one or more of the following factors were judged to be present:

1. Serious (-1) or very serious (-2) limitation to study quality
2. Important inconsistency (-1)
3. Some (-1) or major (-2) uncertainty about directness
4. Imprecise or sparse data (-1)
5. High probability of reporting bias (-1).

The main results of the review were to be presented in the summary of finding table. Following the recommendations of the Cochrane Collaboration, the summary of finding table includes important data including the quality of evidence, the magnitude of the interventions examined, and the sum of available data on the main outcomes (Schunemann 2008a). In addition to the absolute and relative magnitude of effect provided in the summary of findings table, the number needed to treat (NNT) would be calculated from the control group event rate (unless the population event rate is known) and the relative risk using the Visual Rx NNT calculator (Cates 2009). For continuous outcomes, the NNT would be calculated using the Wells calculator software available at the CMSG editorial office. The minimal clinically important difference (MCID) for each outcome would be determined for input into the calculator. The summary of findings table includes an overall grading of the evidence related to each of the main outcomes, using the GRADE approach (Schunemann 2008).

Subgroup analysis and investigation of heterogeneity

The following sub-group analyses were planned to explore possible effect size differences, if sufficient data are available:

1. Allopurinol-failure vs. Allopurinol-naïve
2. Use with uricosurics vs. without uricosurics

Sensitivity analysis

In order to assess for any bias attributed to allocation concealment, a sensitivity analysis was planned in the presence of sufficient data following the criteria mentioned in the 'assessment of risk of bias' section above.

RESULTS

Description of studies

Sundy 2008 was a randomized, open-label, multicenter, parallel-group study of multiple doses and dose regimens of pegloticase, in the duration of 12 to 14 weeks. The purpose of the study was to assess the efficacy of pegloticase in achieving and maintaining blood plasma urate levels of <6 mg/dl in gout patients whose gout had failed to respond to other treatments, and to assess the pharmacokinetics and safety of pegloticase. Pharmacokinetics, efficiency, immunogenicity, and safety of pegloticase were evaluated during this study.

Forty one patients were included in the study to one of four treatment groups: 4 mg every 2 weeks (n = 7), 8 mg every 2 weeks (n = 8), 8 mg every 4 weeks (n = 13), and 12 mg every 4 weeks (n = 13). Prior to study enrolment, patients underwent a 1-week urate-lowering treatment washout period; this treatment could not be used during the study. Patients were randomized to one of four treatment groups in a 1:1:1:1 randomization ratio; the randomization was performed using a sealed envelope technique based on a series of random numbers blocked in groups of four, by investigative site. The pegloticase (4 mg/ml) was diluted in 100 ml phosphate buffered saline (PBS) and administered by IV infusion over a 30 minute period. The protocol was modified after approximately 90% of patients were enrolled due to some infusion reactions; the pegloticase was diluted in 200 mL PBS and administered over 60 minutes. Blood samples were obtained at each visit for analyses.

Patients were enrolled at nine rheumatology sites in the US during 2004, both academic and private-practice sites. Adult men and women with serum urate levels at or above 8 mg/dl were screened for possible enrolment. Patients had to be over age 18, have had established and symptomatic gout, defined as having at least one of the following criteria: >1 tophus, one gout flare within the previous six months, or chronic gouty arthropathy. Patients should also have been treated unsuccessfully due to intolerance or inadequate response, with a urate-lowering treatment, or have had a contraindication to these treatments. Treatment with urate-lowering therapy as deemed appropriate by a physician for at least three months, with serum urate not being reduced to 6 mg/dl was defined to be an inadequate response.

Efficacy end points were evaluated by plasma urate measurement, determined in blood specimens obtained at each study visit. As pegloticase in blood remains active in vitro, the plasma samples were cooled and acidified immediately after collection in order to inactivate the pegloticase enzyme. Urate levels were then determined using a coupled enzymatic reaction, with the final product fluorometrically measured. Pegloticase was also measured in a flurometric manner, meaning that standard pharmacokinetic parameters were evaluated. The primary end point was the percentage of responders in each treatment group with plasma urate levels at/below 6 mg/dl for at least 80% of the study period of 12 to 14 weeks. The secondary end points included percentage of time without hyperuricemia (at or below 6 mg/dl); mean plasma urate; and relative reduction of plasma urate level from baseline. Adverse events were also documented and monitored to evaluate the safety and tolerability of multiple-dose pegloticase treatments. Gout flares were not regarded as AE.

The study was supported and sponsored by Savient Pharmaceuticals, Inc. Savient Pharmaceuticals, Inc. had a primary role in protocol design, data collection and analysis either directly or through a contracted research organization. Various authors on the study have received consulting/speaking fees from Savient Pharmaceuticals Inc.; some authors are employees of Savient pharmaceuticals, Inc. and are listed on the pending patent applications for Pegloticase usage. Authors affiliated with Savient Pharmaceuticals, Inc. wrote and participated in final approval of the manuscript, and Savient Pharmaceuticals, Inc., supported publication of study results.

Results of the search

The initial search in July 2009 retrieved 376 search results (Figure 1). Of these 376, we identified 29 studies for further research (Baraf 2005; Baraf 2006; Baraf 2008; Baraf 2008a; Becker 2005; Becker 2008; Bieber 2004; Biggers 2008; Bomalaski 2002; Edwards 2008; Ganson 2006; Joseph-Ridge 2006; Louyot 1970; Louyot 1971; Mizon 1971; Mizon 1971a; Schumacher 2008; Sherman 2008; Sundy 2004; Sundy 2005; Sundy 2006; Sundy 2007; Sundy 2007a; Sundy 2008; Sundy 2008a; Sundy 2009; Terkeltaub 2009; Yue 2006; Yue 2008). Of these 29 studies, one qualified for inclusion in the review (Sundy 2008). An updated search in December 2009 identified 16 additional studies (Arora 2009; Baker 2009; Campara 2009; Cao 2009; Cleveland 2009; Ea 2009; Fridolin 2009; George 2009; Gruber 2009; Liu 2009; Ribeiro 2009; Riches 2009; Saketkoo 2009; Smith 2009; Terkeltaub 2009; Wipfler-Freibmuth 2009), but no additional studies qualified for inclusion.

Figure 1. Study Selection Flow Chart

Included studies

Of the 292 results, one study was included in this systematic review (Sundy 2008). Overall, there were 41 patients included in the study. The study included allocation of patients to varying dosage levels and frequencies of pegloticase. Of the four treatment interventions: 7 patients received 4 mg every 2 weeks, 8 patients were in the 8 mg every 2 weeks group, 13 patients received 8 mg every 4 weeks, and 13 patients received 12 mg every 4 weeks. Please refer to the characteristics of included studies table for detailed information on the included study.

Excluded studies

45 articles were excluded from the meta analysis. Twelve were conference proceedings (Baraf 2005; Baraf 2006; Baraf 2008; Becker 2008; Cleveland 2009; Edwards 2008; Sundy 2004; Sundy 2005; Sundy 2006; Sundy 2008; Sundy 2009; Yue 2006). Seven articles were not RCT but review articles (Bieber 2004, Biggers 2008, Joseph-Ridge 2006, Riches 2009, Sherman 2008, Terkeltaub 2009,

Yue 2008). Nine articles were not randomized studies (Baker 2009, Baraf 2008, Bomalaski 2002, Ganson 2006, Smith 2009, Sundy 2007, Sundy 2007a, Sundy 2008, Traynor 2009). Nine articles were excluded because they did not include pegloticase (Arora 2009; Becker 2005; Campara 2009; Ea 2009; Mizon 1971; Mizon 1971a; Saketkoo 2009; Schumacher 2008; Wipfler-Freibmuth 2009). Four articles were patents (Cao 2009; Fridolin 2009; George 2009; Liu 2009). Finally, four articles were not in English (Gruber 2009; Louyot 1971; Louyot 1970; Ribeiro 2009).

Please refer to the table of excluded studies for detailed information on each study.

Risk of bias in included studies

Sundy 2008 reports an adequate method of randomization and allocation concealment. The possibility of bias appears low in this study. The study was open-label. Refer to Figure 2 and Figure 3 and Risk of Bias tables for more information on all sections of risk of bias.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Allocation

[Sundy 2008](#) reported an adequate method of allocation concealment and randomization.

Blinding

The [Sundy 2008](#) study was an open-label study.

Incomplete outcome data

The study had adequate methods of handling missing outcome data.

Selective reporting

Because the protocol available for this trial did not provide sufficient information, we did not have an adequate amount of

information to make a definitive judgment on the presence of selective reporting in the trial.

Other potential sources of bias

Developers and manufacturers of pegloticase played a role in: sponsoring the study: the manufacturer was the employer of study authors and some study authors were shareholders. The manufacturer funded or sponsored the study, had a primary role in designing the protocol, data collection and analysis directly or through contract research organizations, and/or participating in components of the study.

Effects of interventions

See: [Summary of findings for the main comparison Proportion of treatment responders in ITT and completer populations](#); [Summary of findings 2 Percentage of time without hyperuricemia in ITT and completer populations](#)

The only included study is an open-label study with no placebo arm, that compared various doses of pegloticase.

The study notes that one patient was withdrawn by the study authors, but do not distinguish which group this individual was taken from and so this number was not included in the numbers listed below.

[Table 1](#) shows the results for the entire group and the ITT population.

Pegloticase dosage of 4 mg every 2 weeks

Primary Outcomes:

1. Efficacy as assessed by frequency of gout flares and change in serum uric acid:
 - a. Treatment responder as defined as patients with plasma urate ≤ 6 mg/dl for at least 80% of the study period, was achieved by 56%
 - b. Patients had the 78% of time without hyperuricemia.
 - c. Mean plasma urate concentrations were maintained at well below 6 mg/dl during the time periods between doses.
 - d. 86% of patients reported one or more gout flares during the study
2. Safety as assessed by
 - a. The number and type of adverse effects (AEs) and serious adverse events (SAEs):

All patients included in this group experienced the following adverse events (values are the % of patients reporting the following events):

- i. Nephrolithiasis - 14%
- ii. Arthralgia - 14%
- iii. Dyspnea - 14%
- iv. Muscle spasms - 14%
- v. Nausea - 43%
- vi. Pyrexia - 14%
- vii. Back pain - 14%
- viii. Diarrhea - 14%
- ix. Erythema - 14%
- x. Hypersensitivity - 14%

- xi. Rash - 29%

A total of two patients experienced serious adverse events in this group. The study does not differentiate what types of adverse events occurred for this group versus the whole.

- b. Withdrawals: (i) Total, (ii) due to lack of efficacy, (iii) due to adverse events:

- i. Total: 3
- ii. Due to lack of efficacy: 0
- iii. Due to adverse events: 3

- c. Death: No deaths occurred during the course of the study.

Secondary outcomes: none of the secondary outcomes (pain, patient/physician global assessment, tophus burden, health related quality of life, function and radiographic changes) were assessed in the study.

Study authors terminated assignment of participants to this group due to lack of efficacy once seven patients had been assigned.

Pegloticase dosage of 8 mg every 2 weeks

Primary Outcomes:

1. Efficacy as assessed by frequency of gout flares and change in serum uric acid:
 - a. Treatment responder as defined as patients with plasma urate ≤ 6 mg/dl for at least 80% of the study period, was achieved by 88%
 - b. Patients had the highest percentage of time, i.e., 92% without hyperuricemia of the four treatment groups.
 - c. Mean plasma urate concentrations were maintained at well below 6 mg/dl during the time periods between doses.
 - d. 63% of patients reported one or more flares of gout during the study.
2. Safety as assessed by
 - a. The number and type of adverse effects (AEs) and serious adverse events (SAEs):

75% of patients included in this group experienced adverse events including the following (values are the % of patients reporting the following events):

- i. Nephrolithiasis - 13%
- ii. Anemia - 38%
- iii. Headache - 13%
- iv. Muscle spasms - 13%
- v. Nausea - 13%
- vi. Diarrhea - 13%

A total of three patients experienced serious adverse events in this group. The study does not differentiate what types of adverse events occurred for this group versus the whole.

- b. Withdrawals: (i) Total, (ii) due to lack of efficacy, (iii) due to adverse events:

- i. Total: 0
- ii. Due to lack of efficacy: 0

iii. Due to adverse events: 0

c. Death: No deaths occurred during the course of the study.

Secondary Outcomes:

None of the secondary outcomes (pain, patient/physician global assessment, tophus burden, health related quality of life, function and radiographic changes) were assessed in the study.

Pegloticase dosage of 8 mg every 4 weeks

Primary outcomes:

1. Efficacy as assessed by frequency of gout flares and change in serum uric acid:
 - a. Treatment responder as defined as patients with plasma urate ≤ 6 mg/dl for at least 80% of the study period, was achieved by 52%.
 - b. Patients had the 76% of time without hyperuricemia.
 - c. Mean plasma urate concentrations were maintained at well below 6 mg/dl during the time periods between doses.
 - d. 92% of patients reported one or more gout flares during the study.

2. Safety as assessed by

a. The number and type of adverse effects (AEs) and serious adverse events (SAEs):

- a. 100% of patients included in this group experienced the following adverse events (values are the % of patients reporting the following events):
 - i. Nephrolithiasis - 8%
 - ii. Arthralgia - 23%
 - iii. Dyspnea - 23%
 - iv. Headache - 8%
 - v. Muscle spasms - 8%
 - vi. Pyrexia - 15%
 - vii. Back pain - 15%
 - viii. Diarrhea - 8%
 - ix. Erythema - 15%
 - x. Fatigue - 8%
 - xi. Hypersensitivity - 8%
 - xii. Pruritus - 23%

Serious adverse events: A total of two patients experienced serious adverse events in this group. The study does not differentiate what types of adverse events occurred for this group versus the whole.

b. Withdrawals: (i) Total, (ii) due to lack of efficacy, (iii) due to adverse events:

- i. Total: 5
- ii. Due to lack of efficacy: 0
- iii. Due to adverse events: 5

c. Death: No deaths occurred during the course of the study.

Secondary Outcomes: None of the secondary outcomes (pain, patient/physician global assessment, tophus burden, health related quality of life, function and radiographic changes) were assessed in the study.

Pegloticase dosage of 12 mg every 4 weeks

Primary outcomes:

1. Efficacy as assessed by frequency of gout flares and change in serum uric acid:
 - a. Treatment responder as defined as patients with plasma urate ≤ 6 mg/dl for at least 80% of the study period, was achieved by 62%.
 - b. Patients had 76% percentage of time without hyperuricemia (mean $\pm$ SD being 91.9% $\pm$ 22.6%) of the four treatment groups.
 - c. Mean plasma urate concentrations were maintained at well below 6 mg/dl during the time periods between doses.
 - d. 100% of patients reported one or more gout flares during the course of the study.

2. Safety as assessed by

a. The number and type of adverse effects (AEs) and serious adverse events (SAEs):

92% of patients included in this group experienced the following adverse events (values are the % of patients reporting the following events):

- i. Nephrolithiasis - 23%
- ii. Arthralgia - 8%
- iii. Anemia - 8%
- iv. Headache - 15%
- v. Muscle spasms - 8%
- vi. Pyrexia - 7%
- vii. Fatigue - 15%
- viii. Upper respiratory tract infection - 2

Serious adverse events: A total of two patients experienced serious adverse events in this group. The study does not differentiate what types of adverse events occurred for this group versus the whole.

b. Withdrawals: (i) Total, (ii) due to lack of efficacy, (iii) due to adverse events:

- i. Total: 7
- ii. Due to lack of efficacy: 0
- iii. Due to adverse events: 7

c. Death: No deaths occurred during the course of the study.

Secondary Outcomes: None of the secondary outcomes (pain, patient/physician global assessment, tophus burden, health related quality of life, function and radiographic changes) were assessed in the study.

Subgroup Analyses

We had planned the following sub-group analyses to explore possible effect size differences, if sufficient data were available. Due to lack of more than one study per subgroup for the subgroup comparisons, we were able to perform only the first comparison. For subgroup comparisons, as only one study was available, that did not have separate groups of patients with/without prior allopurinol failure or uricosurics, no formal comparisons could be performed.

1. Allopurinol-failure vs. allopurinol-naïve - the study did not distinguish which subjects had previously been treated with allopurinol, so the results did not differentiate between these two groups.
2. Use with uricosurics vs. without uricosurics - study protocol dictated that eligible patients undergo a 1-week urate-lowering treatment washout period, and that these treatments could not be used during the study period; we were therefore unable to complete this analysis.

FDA website search for Warnings and adverse events

We searched the FDA website for warnings and adverse events related to pegloticase on 10/20/2009. Because pegloticase is not yet an FDA-approved drug, there is still ongoing debate on the safety and merits of the drug.

During an Arthritis Advisory Committee meeting focusing on pegloticase IV infusion, it was recommended that the label call out special warnings for patients with uncompensated cardiovascular disease, including: uncompensated congestive heart failure, unstable angina, uncontrolled hypertension, and uncontrolled arrhythmia.

Treatment guidance also recommended watching for: gout flare prophylaxis; infusion reaction prophylaxis and management; monitoring of SUA for first 3 months; discontinuation of use when serum uric acid < 6 mg/dL; and to discontinue use after a moderate/severe infusion reaction.

Overall, it was noted that the risk associated with pegloticase administered every 2 weeks for patients with treatment-failure gout is predictable and manageable. There are transient increased incidence of gout flare, and infusion reactions are avoided by ending treatment for patients with a loss of serum urate response. Monitoring serum urate response is important to minimize exposure to pegloticase in transient responders. Also, possible cardiovascular risk as noted above can be addressed by using a comprehensive risk minimization plan. (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM167777.pdf>)

Further notes from the committee meeting reference that the warning label should include contraindication for patients with G6PD deficiency, and warning to patients who have uncompensated cardiovascular disease that they should not receive treatment, as patients with this condition were not included in the clinical trials for this medication and therefore there is an absence of data for this patient population. (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM174953.pdf>)

DISCUSSION

Summary of main results

In this review of RCTs of pegloticase for treatment of chronic gout, only one RCT met the inclusion criteria and was included. This was phase II open-label study with a small sample size that compared the various doses of pegloticase without any comparisons to placebo or other treatment options. The most important finding of this systematic review is that at present,

there are no double-blinded, placebo-controlled RCTs of efficacy and safety of pegloticase in patients with gout. In this study, only 4 doses/schedules of pegloticase were compared to each other, without adequate power to detect between-group differences. No differences were noted between various doses. Clearly, double-blind, placebo-controlled RCTs are needed to draw any firm conclusions regarding benefits and hazards of pegloticase in patients with gout. Except gout flare and uric acid lowering, none of the other patient-reported outcomes such as pain, function, quality of life or global assessment or clinical outcomes such as tophus size and radiographic changes were presented.

The study authors note that the differences between study groups were not significant. According to this single study (Sundy 2008), the most effective dosage of pegloticase appeared to be 8 mg every 2 weeks. Pegloticase administered in multiple dosages rapidly reduced and maintained plasma urate levels at or below 6 mg/dL in most patients. All dosage levels achieved urate levels below the target of 6 mg/dL over the 12 to 14 week study period in most patients with treatment-failure gout enrolled in the study. This suggested that pegloticase may be an effective treatment for gout in patients with chronic gout. The highest proportion of patients who met the primary end point and had the highest percentage of time without hyperuricemia was the 8 mg every 2 weeks group.

There are risks associated with treatment especially for patients with heart problems. Interpretations regarding safety are very limited based on a single study of 41 patients followed for 12 to 14 weeks. Most adverse effects included infusion reactions, other adverse events and gout flares. Withdrawals due to adverse events did not differ significantly between groups. Similar efficacy and safety were noted for the other dosing regimens of pegloticase. It must be noted that the sample size for this study was small and the study was not powered for safety as primary outcome. Therefore, both the common and uncommon adverse events of pegloticase are unknown at this time. Long-term surveillance studies and RCTs with placebo-controlled studies are needed to provide these important data. The study authors note that ongoing pegloticase trials include several strategies for reducing infusion reactions, which will presumably limit this phenomenon.

Overall completeness and applicability of evidence

We have included the only published RCT of pegloticase in patients with gout. Thus, this evidence report is current and up to-date. While more trials are ongoing, there are no published results as of yet. We plan to update this review once more data become available.

Quality of the evidence

The quality of evidence found in the trials included in this review appear to be high because the studies reported adequate methods of allocation concealment, and sequence generation using opaque envelopes. The only source of concern for quality of evidence may be that we did not have access to enough information such as complete study protocols to make definitive judgments regarding the risk of selective reporting. Also, because the trial was funded by manufacturer of pegloticase, a risk of manufacturer influence is present as well. See Figure 2 and Figure 3 for more information.

Potential biases in the review process

All titles, abstracts were extracted independently by two reviewers. All data were also extracted independently by two reviewers to avoid typing errors. We are limited in our ability to comment on outcomes not reported in the published reports, such as radiographic data or summary scores from quality of life instruments such as Short-Form 36. Typically, these studies are published after the main trial results have been published. We were also limited in analysis of safety data, since one small study of 41 patients is available for analysis. Furthermore, there seems to be unpublished studies that we had no access to that may have included other safety concerns with pegloticase, which the FDA did have access to as they consider the merits of Pegloticase.

Agreements and disagreements with other studies or reviews

To our knowledge, there are no other published systematic reviews of meta-analyses of pegloticase for chronic gout. Thus there are no other studies to compare.

AUTHORS' CONCLUSIONS

Implications for practice

More research is needed before we can determine the efficacy and safety of pegloticase. Currently pegloticase has not been approved by any regulatory agencies to our knowledge. Therefore, there are

no clinical implications for practice at this time. The U.S. Food and Drug Administration (FDA) is reviewing the investigational new drug application for pegloticase for gout.

Based on limited evidence ([Sundy 2008](#)), it appears that pegloticase has the potential to effectively reduce uric acid levels in patients. The evidence from this study does not suggest any differences based on dosing regimens. Further research is required to determine whether pegloticase use would result in important clinical end points being reached such as resolution of tophi and gout flare reduction long-term due to effective reduction of urate levels. It is not known whether it is better than placebo. It is not clear at this time whether it is safe. This is important, especially with the recently recognized cardiovascular risk in gout and possible association of some treatments with increased cardiovascular outcomes. This treatment may be an effective option for patients who are intolerant to current treatment or whose disease does not respond to current treatment options.

Implications for research

Insufficient evidence exists at this time regarding safety and efficacy of pegloticase. Although pegloticase appears to be effective in reducing urate levels, more studies are needed to answer the remaining questions related to safety and efficacy of pegloticase.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Sundy 2008

Methods	41 patients were randomized to undergo 12 to 14 weeks of pegloticase treatment at 1 of 4 dosage levels.
Participants	41 patients - majority of patients were male (85%) and obese (mean $\pm$ SD BMI 31.3 ± 4.4 kg/m ²); mean age 58.1 ± 13.8 years, mean duration of gout 14.4 years ± 9.8 years. 83% patients were white, 12% African American, 5% other ethnicities
Interventions	4 mg every 2 weeks, 8 mg every 2 weeks, 8 mg every 4 weeks, 12 mg every 4 weeks.
Outcomes	Plasma uricase activity, plasma urate, antipegloticase antibodies measured. Pharmacokinetic parameters assessed, adverse events recorded.
Notes	15 study withdrawals. Prior to randomization, patients underwent 1-week urate lowering treatment washout period.
Risk of bias	

Sundy 2008 (Continued)

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomization done in 1:1:1:1 ratio.
Allocation concealment?	Low risk	Randomization done in 1:1:1:1 ratio. Performed by sealed envelope technique based on series of random numbers, blocked in groups of 4, by investigative site.
Blinding? All outcomes	High risk	Study was open-label.
Incomplete outcome data addressed? All outcomes	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	Savient Pharmaceuticals, Inc. had a primary role in designing the protocol, data collection and data analysis either directly or through a contract research organization. This may have affected the risk of bias.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Arora 2009	Not pegloticase.
Baker 2009	Not randomized study.
Baraf 2005	Conference proceedings.
Baraf 2006	Conference proceedings.
Baraf 2008	Conference proceedings.
Baraf 2008a	Not randomized study.
Becker 2005	Not pegloticase.
Becker 2008	Conference proceedings.
Bieber 2004	Review article.
Biggers 2008	Review article.
Bomalaski 2002	Not randomized study.
Campara 2009	Not pegloticase.
Cao 2009	Patent.
Cleveland 2009	Conference proceedings.

Pegloticase for chronic gout (Review)

Study	Reason for exclusion
Ea 2009	Not pegloticase.
Edwards 2008	Conference proceedings.
Fridolin 2009	Patent.
Ganson 2006	Not randomized.
George 2009	Patent.
Gruber 2009	Not in English.
Joseph-Ridge 2006	Review article.
Liu 2009	Patent.
Louyot 1970	Not in English.
Louyot 1971	Not in English.
Mizon 1971	Not pegloticase.
MIzon 1971a	Not pegloticase, same as Mizon 1971.
Ribeiro 2009	Not in English.
Riches 2009	Review article.
Saketkoo 2009	Not pegloticase.
Schumacher 2008	Not pegloticase.
Sherman 2008	Review article.
Smith 2009	Not randomized study.
Sundy 2004	Conference proceedings.
Sundy 2005	Conference proceedings.
Sundy 2006	Conference proceedings.
Sundy 2007	Not randomized study.
Sundy 2007a	Not randomized study.
Sundy 2008a	Not randomized study.
Sundy 2009	Conference proceedings.
Terkeltaub 2009	Review article.
Traynor 2009	Not randomized study.
Wipfler-Freibmuth 2009	Not pegloticase.

Study	Reason for exclusion
Yue 2006	Conference proceedings.
Yue 2008	Review article.

ADDITIONAL TABLES

Table 1. Demographic and clinical characteristics at baseline

	4 mg every 2 weeks (n=7)	8 mg every 2 weeks (n=8)	8 mg every 4 weeks (n=13)	12 mg every 4 weeks (n=13)	Total (n=41)
Age, years	49.7 ± 15.0	59.4 ± 16.0	60.3 ± 10.6	59.5 ± 14.4	58.1 ± 13.8
Male, %	100	63	85	92	85
BMI, kg/m ²	35.5 ± 2.9	27.3 ± 4.0*	30.9 ± 3.8	32.3 ± 4.6	31.3 ± 4.4
Gout disease duration, years	15.4 ± 7.3	19.6 ± 14.2	12.9 ± 8.8	12.2 ± 8.5	14.4 ± 9.38
No of gout attacks in last 12 months**	10 ± 12	13 ± 8	7 ± 6	6 ± 4	8 ± 7
Tophi present, %	71	75	69	69	71
Urate-lowering treatment use %	71	25	23	31	34
Treatment-failure status, %: Inadequate response	71	38	23	23	34
Treatment-failure status, %: Intolerability	29	63	69	69	61
Treatment-failure status, %: Not reported	0	0	8	8	5
Serum urate at screening mg/dl	9.4 ± 0.8	10.6 ± 2.8	10.7 ± 1.8	10.2 ± 1.5	10.3 ± 1.8
Plasma urate, mg/dl	7.3 ± 1.8	9.1 ± 1.7	9.0 ± 3.4	8.9 ± 2.3	8.7 ± 2.5

Except where indicated otherwise, values are the mean ± DS. ITT = intent-to-treat; BMI = body mass index.

* $P < 0.05$ versus 4 mg every 2 weeks group

**Self-reported

APPENDICES

Appendix 1. CENTRAL search strategy

The Cochrane Library Issue 3, 2009 (WileyInterScience)

Central: 2 --> 0

Issue 4, 2009

0

- #1 MeSH descriptor Gout explode all trees
- #2 gout*:ti,ab
- #3 (#1 OR #2)
- #4 MeSH descriptor Polyethylene Glycols explode all trees
- #5 MeSH descriptor Urate Oxidase, this term only
- #6 pegloticase:ti,ab
- #7 uricas*:ti,ab
- #8 peg-uricase:ti,ab
- #9 Krystexxa:ti,ab
- #10 urat* next oxidas*:ti,ab
- #11 CB-8129:ti,ab
- #12 Uricozyme:ti,ab
- #13 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
- #14 (#3 AND #13)

Appendix 2. MEDLINE search strategy

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to July Week 1, 2009

135 -->132 after de-duplication

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 10, 2009

10 -->3 after de-duplication

- 1. exp Gout/
- 2. gout\$.tw.
- 3. 1 or 2
- 4. exp Polyethylene Glycols/
- 5. Urate Oxidase/
- 6. pegloticase.tw.
- 7. uricas\$.tw.
- 8. peg-uricase.tw.
- 9. Krystexxa.tw.
- 10. urat\$ oxidas\$.tw.
- 11. CB-8129.tw.
- 12. Uricozyme.tw.

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13. or/4-12

14. 3 and 13

Appendix 3. CINAHL search strategy

CINAHL (EBSCOhost) 1982 to 2009

42 --> 27 after de-duplication

2009 to 2009

3 --> 1 after de-duplication

S15 S3 and S14

S14 S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13

S13 ti Uricozyme or ab Uricozyme

S12 ti CB-8129 or ab CB-8129

S11 ti urat* oxidas* or ab urat* oxidas*

S10 ti Krystexxa or ab Krystexxa

S9 ti peg-uricase or ab peg-uricase

S8 ti uricas* or ab uricas*

S7 ti pegloticase or ab pegloticase

S6 (MH "Enzymes+")

S5 (MH "Glycols+")

S4 (MH "Polyethylenes")

S3 S1 or S2

S2 ti gout* or ab gout*

S1 (MH "Gout")

Appendix 4. SPORT discus search strategy

Dissertation Abstracts

1 --> 1 after de-duplication

2009 to 2009

0

Gout* in citation and abstract AND pegloticase or uricas* or peg-uricase or Krystexxa or CB-8129 or "urat* oxidas*" or Uricozyme in citation and abstract

Current Controlled Trials

281 (from which 1 identified as relevant)

Gout*

Result from CCT

[Safety and Efficacy Study of PEG-Uricase in the Treatment of Hyperuricemic Patients With Symptomatic Gout](#) Status: Completed Source of record: National Institutes of Health (NIH) - randomized trial records held on NIH *ClinicalTrials.gov* website.

Appendix 5. EMBASE search strategy**EMBASE 1980 to 2009 Week 27**

239 --> 181 after de-duplication

2009 to 2009 Week 50

14 -->5 after de-duplication

1. exp gout/
2. gout\$.tw.
3. 1 or 2
4. pegloticase/
5. exp macrogol derivative/
6. exp urate oxidase/
7. pegloticase.tw.
8. uricas\$.tw.
9. peg-uricase.tw.
10. Krystexxa.tw.
11. urat\$ oxidas\$.tw.
12. CB-8129.tw.
13. Uricozyme.tw.
14. or/4-13
15. 3 and 14

Appendix 6. Science citation index search strategy**Web of Knowledge 1945 - 2009**

88 -->35 after de-duplication

2009 to 2009

18 -->7 after de-duplication

#1 Topic = gout*

#2 Topic = pegloticase or uricas* or peg-uricase or Krystexxa or CB-8129 or "urat* oxidas*" or Uricozyme

#3 #1 AND #2

WHAT'S NEW

Date	Event	Description
11 February 2010	Amended	CMSG ID: C199-R

CONTRIBUTIONS OF AUTHORS

JS- title registration, Concept

JS, AA- Protocol development

JS, AA- Protocol review and editing

AA, JS- review titles and abstracts

AA, JS- Data Extraction and Analysis

AA, JS- Results and draft of the review

AA, JS- Editing the review

DECLARATIONS OF INTEREST

JS - Research grants from Takeda, Savient and AMGEN pharmaceuticals; Consultant/honraria- Savient, Abbott and URL pharmaceuticals; Research grants from National Institutes of Health, Department of Veterans Affairs, Arthritis Foundation, University of Minnesota, Minnesota Medical Foundation and Cochrane Collaboration.

AA - None

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Internal sources

- Minneapolis VA Medical Center, Minneapolis, MN 55417, USA.

External sources

- NIH CTSA Award 1 KL2 RR024151-01 (Mayo Clinic Center for Clinical and Translational Research), USA.

75% time-protection for research

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, we had not included the comparison of various doses of pegloticase. In the review, we included this comparison, since we felt it was informative and the only included study provided these data.

NOTES

None

INDEX TERMS

Medical Subject Headings (MeSH)

Chronic Disease; Clinical Trials, Phase II as Topic; Drug Administration Schedule; Gout [*drug therapy]; Polyethylene Glycols [*therapeutic use]; Randomized Controlled Trials as Topic; Urate Oxidase [*therapeutic use]; Uricosuric Agents [*therapeutic use]

MeSH check words

Humans