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Evaluation of the efficacy and safety of pegloticase for the treatment of chronic refractory gout through meta-analysis

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SUMMARY Gout is the most common arthritis that affects more than 2% of adults in developed countries. 3% to 4% of gout is chronic refractory gout. Conventional treatments are considered invalid. A new drug, pegloticase is used to treat chronic refractory gout, and there are still many questions about efficacy and safety. We searched PubMed, web of science, and the Cochrane Library. Preprints and references of related literature were also considered. Related efficacy and safety indicators were statistically analyzed by Review Manager 5.4 to conduct meta-analysis. A total of one article and one clinical trial were included. Pegloticase is able to reduce serum uric acid and reduce tender joints, thereby improving joint function. But pegloticase has more adverse events. Pegloticase can be used to treat chronic refractory gout. However, Pegloticase has a higher risk of adverse events. Considering the efficacy and safety, the scope of clinical applications of pegloticase can be further widened in patients in good medical condition.

Keywords chronic refractory gout, pegloticase, meta-analysis

1. Introduction

Gout is the most common inflammatory arthritis, with prevalence now exceeding 2% in adults in developed countries (*1*). The worldwide incidence of gout has increased gradually due to poor dietary habits such as fast foods, lack of exercise, increased incidence of obesity, and metabolic syndrome. Gout is caused by the deposition of monosodium urate crystals in the joints following chronic hyperuricemia (*2*). In gout, the therapeutic goal is to lower serum uric acid below 6 mg/dL, but the British Society for Rheumatology gives a lower target that serum uric acid should be reduced to less than 5 mg/dL (*3*). However, gout is a chronic disease. Even after serum uric acid is reduced to the target, gout can still flare up in the next 12 to 18 months (*4*).

During gout exacerbations, patients experience severe pain. After about 5 to 10 days, gout will go to a chronic-phase. Uric acid crystals can accumulate in joints and other positions causing disability, especially in metatarsophalangeal 1 joints. Due to joint pain, inflammation, and flares, gout poses a major burden on the patient's daily life, and even causes disability (*5*). Patients with gout have a higher risk of death from all causes, especially cardiovascular disease (*6*). There is a case report decreasing the accumulation of urate crystals in the retina causing macular degeneration (*7*). The prevention and treatment of gout flares become especially important.

Available treatment strategies for gout include two major types of treatment: xanthine oxidase inhibitors, and uricosuric agents. But all these drugs have side effects (*8*). Even worse, these drugs are less effective for chronic refractory gout (CRG).

2. Pegloticase dilemma

Pegloticase (Krystexxa®), a pegylated recombinant mammalian uricase, is a US Food and Drug Administration–approved medication for treatment of uncontrolled gout in 2010. Pegloticase provides a new approach to the treatment of CRG. Pegloticase, a recombinant uricase, catalyzes the conversion of uric acid to allantoin (*9*). Allantoin is more soluble and easily excreted. Uric acid-lowering therapy improved when 8 mg was injected every two or four weeks, enabling serum uric acid below 6 mg/dL in some patients with CRG (*9*).

There are still some unclear issues regarding the safety of pegloticase to date. On 30 June 2016, the European Commission withdrew marketing authorization for pegloticase in the European Union. Consequently,

comprehensive efficacy and safety assessments are still required for pegloticase before more approval for clinical use by the regulatory agents.

3. Meta-analysis

Our study was registered in PROSPERO (CRD42022322978). The PRISMA guideline was followed throughout. Literature search, data extraction and data analysis were performed independently by two researchers. Divergence was examined by a third researcher. If something appeared different, a third investigator intervened in data extraction. Specific details are given in PROSPERO (*https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=322978*).

4. Main finding

Figure 1 shows the detailed literature search and screening process. A total of 7 articles fulfill the inclusion criteria. Among six included studies completed according to NCT00325195 and/or NCT01356498. NCT01356498, an open label extension study was excluded because the control group did not meet the criteria. Albert 2020(10) and NCT00325195 were included in the meta-analysis finally.

Albert *et al*. believe that pegloticase can be used to treat CRG, and that methotrexate/pegloticase co-therapy have a higher response rate than pegloticase alone (*10*). NCT00325195 found that pegloticase produces good clinical curative effects in CRG. Although advance events were experienced, most patients tolerated pegloticase.

According to the meta-analysis, pegloticase has a noticeable effect in the reduction of uric acid. Pegloticase has poor safety profiles. Pegloticase potently decreases the number of tender joints without significant reduction in swollen joints. Eight mg pegloticase every 2 weeks significantly reduces pain in patients, while 8 mg pegloticase every 4 weeks is ineffective, according to the Health Assessment Questionnaire. Regardless of the dose used, pegloticase improves the quality of life of patients, according to the SF-36 Physical Component Summary Score. The specifics are detailed in Table 1.

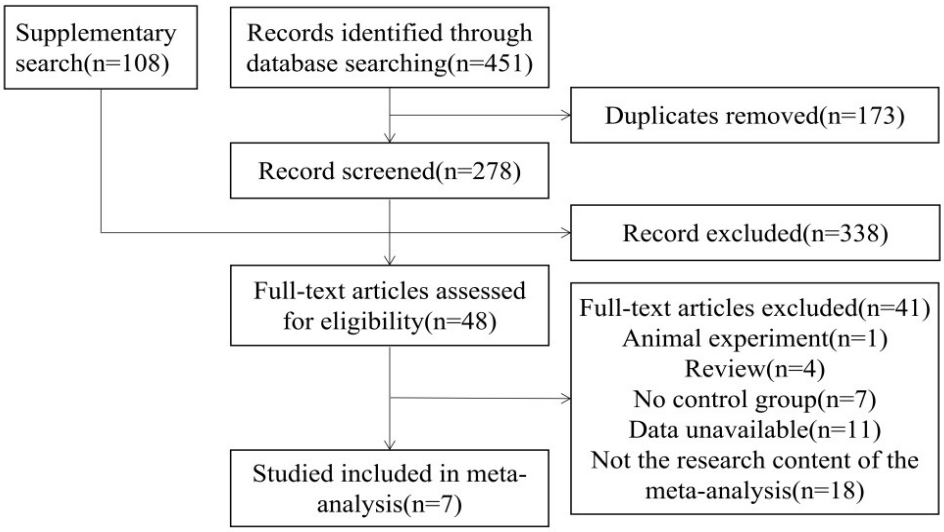

Figure 1. Flowchart of the systematic literature search.

Table 1. Pooled results for meta-analysis about the efficacy and safety of pegloticase

Outcome Measures	Subgroup	Number of Trials	Statistical Method	Effect Estimate	*p* for Heterogeneity
Plasma Uric Acid Responder	q2 Wks	2	OR (M-H, Random, 95% Cl)	67.26 [8.18, 552.87]	< 0.0001
	q4 Wks	1	OR (M-H, Random, 95% Cl)	46.24 [2.75, 778.33]	0.008
Advance Events	q2 Wks	2	RR (M-H, Random, 95% Cl)	8.04 [1.59, 40.70]	0.01
	q4 Wks	1	RR (M-H, Random, 95% Cl)	8.70 [1.20, 63.22]	0.03
Change in Number of Swollen Joints	q2 Wks	1	MD (IV, Random, 95% Cl)	-2.90 [-7.08, 1.28]	0.17
	q4 Wks	1	MD (IV, Random, 95% Cl)	-2.50 [-6.39, 1.39]	0.21
Change in Number of Tender Joints	q2 Wks	1	MD (IV, Random, 95% Cl)	-6.20 [-10.73, -1.67]	0.007
	q4 Wks	1	MD (IV, Random, 95% Cl)	-4.90 [-9.28, -0.52]	0.03
Health Assessment Questionnaire	q2 Wks	1	MD (IV, Random, 95% Cl)	-12.80 [-24.52, -1.08]	0.03
	q4 Wks	1	MD (IV, Random, 95% Cl)	-8.30 [-19.11, 2.51]	0.13
SF-36 Physical Component Summary Score	q2 Wks	1	MD (IV, Random, 95% Cl)	4.70 [1.29, 8.11]	0.007
	q4 Wks	1	MD (IV, Random, 95% Cl)	5.20 [1.91, 8.49]	0.002

q2 Wks: 8 mg pegloticase every 2 weeks; q4 Wks: 8 mg pegloticase every 2 weeks; Cl: confidence intervals.

5. Discussion and evaluation

In the meta-analysis, only two studies met the criteria and were included. At present, the clinical research of pegloticase has the problem of a small sample size and insufficient research centers. These studies have predominantly focused on North America cohorts. Considering the differences in enzymes due to genetic differences in races, the relationship between safety and race remains to be studied. The most important finding of this study is that we have not been able to apply pegloticase to a wide range of clinical applications.

Pegloticase has a significant effect compared with placebo in the treatment of CRG. The Health Assessment Questionnaire and SF-36 Physical Component Summary Score reflect the quality of life and physical function, respectively. Except for 8 mg pegloticase every 4 weeks in the Health Assessment Questionnaire, the remaining subgroups showed that pegloticase was beneficial to patients. Although the reduction in swollen joints was not statistically significant, tender joints were significantly reduced. Considering that the swelling does not go away in the short term, swollen joints may decrease as tophi dissolves. However, the effective rate of pegloticase is very low. In NCT00325195, the treatment efficacy of CRG is less than 50%.

Given that more than 40% of patients develop antibodies against pegloticase, strategies for delivering pegloticase are being reassessed (*11*). Methotrexate has been the most investigated agent as a drug that reduces the tolerability of pegloticase. Immunosuppression with methotrexate may prevent loss of pegloticase tolerability and also be used to recover sensitivity after the development of intolerance (*12,13*). There is a potential impact on liver/kidney toxicity with methotrexate (*14*). Mycophenolate mofetil has enticing clinical potential to prolong the efficacy of pegloticase. No drug, however, is truly perfect. The use of mycophenolate mofetil was associated with an increase in gastrointestinal adverse events, hematological adverse events, and minute virus of canine infection (*15*). But it is not clear whether this association is specific. Large-scale clinical experiments are currently lacking.

According to the meta-analysis, the adverse events of pegloticase were significantly higher than placebo. The most common adverse events reported with pegloticase in the published trials include gout flares and infusion reactions associated with antibody response. 91% of infusion reactions occurred in patients with serum uric acid concentrations > 6 mg/dL (*16*). Infusion reactions decrease with decreasing serum uric acid concentration. Khanna *et al*. carried out a phase II, randomized, double-blind, placebo-controlled trial that concluded mycophenolate mofetil prolongs the efficacy of pegloticase (*14*). And mycophenolate mofetil can be used in patients with chronic kidney disease (*17,18*). However, pegloticase does not improve renal function, either with or without tophi (*19*). The infusion reaction of pegloticase can be effectively prevented with immunotherapy. The infusion reaction of pegloticase can be effectively controlled. It cannot be ignored that patients using pegloticase in NCT00325195 died. Specific causes of death are unclear, but it is cautionary. With the further use of pegloticase, new adverse events were discovered. A study reported hemolytic anemia using pegloticase in patients with G6PD deficiency (20). The use of pegloticase in CRG patients with G6PD deficiency has only received extensive attention in recent years.

In conclusion, the efficacy and safety of pegloticase are unsatisfactory. However, for CRG, pegloticase is currently the best treatment. The adverse events of pegloticase can be prevented. Based on current research, there are no serious safety concerns with pegloticase. Pegloticase can be used clinically for the treatment of CRG if the patients are in good medical condition.

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References

1. Richette P, Bardin T. Gout. Lancet. 2010; 375:318-328.
2. Anderson A, Singh JA. Pegloticase for chronic gout. Cochrane Database Syst Rev. 2010; CD008335.
3. Perez-Ruiz F, Dalbeth N. Gout. Rheum Dis Clin North Am. 2019; 45:583-591.
4. Robinson PC, Stamp LK. The management of gout: Much has changed. Aust Fam Physician. 2016; 45:299-302.
5. Ashiq K, Bajwa MA, Tanveer S, Qayyum M, Ashiq S, Khokhar R, Abid F. A comprehensive review on gout: The epidemiological trends, pathophysiology, clinical presentation, diagnosis and treatment. J Pak Med Assoc. 2021; 71:1234-1238.
6. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation. 2007; 116:894-900.
7. Jiang Y, Brenner JE, Foster WJ. Retinal complications of gout: a case report and review of the literature. BMC Ophthalmol. 2018; 18:11.
8. Dalbeth N, Gosling AL, Gaffo A, Abhishek A. Gout. Lancet. 2021; 397:1843-1855.
9. Lyseng-Williamson KA. Pegloticase: in treatment-refractory chronic gout. Drugs. 2011; 71:2179-2192.
10. Albert JA, Hosey T, LaMoreaux B. Increased efficacy and tolerability of pegloticase in patients with uncontrolled gout co-treated with methotrexate: A retrospective study. Rheumatol Ther. 2020; 7:639-648.
11. Sivera F, Andres M, Dalbeth N. A glance into the future of gout. Ther Adv Musculoskelet Dis. 2022; 14:1759720X221114098.
12. Bessen SY, Bessen MY, Yung CM. Recapture and improved outcome of pegloticase response with methotrexate-A report of two cases and review of the literature. Semin Arthritis Rheum. 2019; 49:56-61.
13. Botson JK, Tesser JRP, Bennett R, Kenney HM, Peloso

PM, Obermeyer K, LaMoreaux B, Weinblatt ME, Peterson J. Pegloticase in combination with methotrexate in patients with uncontrolled gout: A multicenter, open-label study (MIRROR). J Rheumatol. 2021; 48:767-774.
14. Khanna PP, Khanna D, Cutter G, Foster J, Melnick J, Jaafar S, Biggers S, Rahman A, Kuo HC, Feese M, Kivitz A, King C, Shergy W, Kent J, Peloso PM, Danila MI, Saag KG. Reducing immunogenicity of pegloticase with concomitant use of mycophenolate mofetil in patients with refractory gout: A phase II, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol. 2021; 73:1523-1532.
15. Wang K, Zhang H, Li Y, Wei Q, Li H, Yang Y, Lu Y. Safety of mycophenolate mofetil versus azathioprine in renal transplantation: a systematic review. Transplant Proc. 2004; 36:2068-2070.
16. Cunha RN, Aguiar R, Farinha F. Impact of pegloticase on patient outcomes in refractory gout: Current perspectives. Open Access Rheumatol. 2018; 10:141-149.
17. Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, Petri M, Gilkeson GS, Wallace DJ, Weisman MH, Appel GB. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med. 2005; 353:2219-2228.
18. Meriggioli MN, Ciafaloni E, Al-Hayk KA, Rowin J, Tucker-Lipscomb B, Massey JM, Sanders DB. Mycophenolate mofetil for myasthenia gravis: an analysis of efficacy, safety, and tolerability. Neurology. 2003; 61:1438-1440.
19. Lawrence Edwards N, Singh JA, Troum O, Yeo AE, Lipsky PE. Characterization of patients with chronic refractory gout who do and do not have clinically apparent tophi and their response to pegloticase. Rheumatology (Oxford). 2019; kez017.
20. Adashek ML, Bourji KI. Pegloticase induced hemolytic anemia in a patient with G6PD deficiency. J Hematol. 2018; 7:83-85.

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