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Real-world patterns of pegloticase use for treatment of gout: descriptive multidatabase cohort study

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ABSTRACT

Objective Pegloticase is used in severe refractory gout or in cases of intolerance to other urate-lowering therapies. We sought to evaluate the patterns of pegloticase use in the USA and the incidence of safety outcomes.

Methods We conducted a retrospective descriptive study using data from two US commercial insurance claims databases (2010–2018). We identified new initiators of pegloticase with ≥1 gout diagnosis code in the 365-day baseline period prior to pegloticase initiation. We measured the number and duration of pegloticase infusions. We assessed the risk of anaphylaxis or anaphylactoid reactions, cardiovascular events, including myocardial infarction or stroke, and hospitalisation for heart failure (new onset or exacerbations) while undergoing pegloticase therapy.

Results Among 2.9 million patients with ≥1 diagnosis of gout, we identified only 483 (179 in Optum and 304 in MarketScan) pegloticase initiators. The mean age and % female was 55.6 years, 10.9% for MarketScan and 60.6 years and 17.3% for Optum. Hypertension was present in up to 85%, diabetes mellitus in 38%, chronic kidney disease in 46% and heart failure in 21% of the patients. The median number of infusions was four and the duration of therapy was 3 months. During the mean 0.5-year follow-up time on pegloticase, there were 3 (0.6%) anaphylaxis, 7 (1.4%) composite cardiovascular, 31 (6.4%) heart failure hospitalisations and 3 (0.6%) deaths.

Conclusion Pegloticase is rarely used in gout, and the median duration of pegloticase therapy was 3 months. There were few anaphylaxis events captured in this claims-based study, while heart failure hospitalisations were common.

Strengths and limitations of this study

- This study is the first study that provides information on the patterns of pegloticase use and its safety in a real-world setting.
- The strength of this study includes generalisability as it is based on two large nationwide commercial insurance claims databases in the USA.
- This study was not able to ascertain the actual cause for drug discontinuation.
- It is challenging to identify infusion reactions, particularly mild cases, in claims data.
- The study databases did not contain information on laboratory test results, including serum urate levels.

INTRODUCTION

Gout is the most common inflammatory arthritis worldwide caused by hyperuricaemia and tissue deposition of monosodium urate crystals and is characterised by recurrent flares.[1] Urate-lowering therapies (ULTs) are effective drugs to prevent gout flares and to help avoid or reduce joint destruction and gout-related disability.[2] While xanthine–oxidase inhibitors such as allopurinol and febuxostat are effective ULTs, some patients may not reach the goal serum urate level of less than 6 mg/dL due to limited efficacy or side effect and safety concerns that limit their use in some individuals.[3–5] Approximately 2% of patients with gout are thought to have chronic refractory disease (ie, persistent hyperuricaemia with frequent gout flares, tophi and/or chronic gouty arthritis in which other ULTs failed to lower the serum urate level below the goal or were contraindicated).[3 6]

Pegloticase is a pegylated porcine recombinant uricase which breaks down uric acid into soluble metabolite.[3] It is a highly effective alternative for gout treatment, but some concerns regarding infusion reactions, medication resistance, cost and burden of infusion and potential risk of cardiovascular events limit its use.[5 7 8] Pegloticase use is generally reserved for severe refractory gout with resistance or intolerance to other ULTs,[9] and the 2020 American College of Rheumatology (ACR) guideline strongly recommends against using pegloticase as the first-line therapy.[4] To date, the real-world use of pegloticase since its US Food and Drug Administration (FDA) approval in 2010 is not known. The current US FDA drug label for pegloticase includes warnings for anaphylaxis, infusion reactions, congestive heart failure and gout flares.[10]

The objective of this study was to describe the patterns of pegloticase treatment in a

real-world cohort of patients with gout and the incidence of safety outcomes with its use.

METHODS

Data sources

We conducted a descriptive study using healthcare claims data from IBM MarketScan database (MarketScan) from 2010 to 2017 and Optum Clinformatics DataMart (Optum) from 2010 to 2018. MarketScan and Optum are commercial insurance administrative claims databases in the USA that contain information on patients' demographics and longitudinal claims, including outpatient visits, hospitalisations, procedures and outpatient drug dispensing.

Study cohort

We identified patients who received an infusion for pegloticase. Of those, we selected initiators of pegloticase who had their first dose of pegloticase after at least 365 days of continuous enrolment (ie, baseline period) free of pegloticase use. The date of first pegloticase infusion was defined as the index date. Patients were required to have at least one International Classification of Diseases, 9th Revision (ICD-9) or International Classification of Diseases, 10th Revision (ICD-10) diagnosis code for gout in the baseline 365-day period prior to the index date. We excluded patients who were younger than age 18 at the index date and individuals with rasburicase use at any time prior to the index date. To determine how commonly or uncommonly pegloticase was used in the study cohort compared with other urate-lowering agents, we identified the number of allopurinol and febuxostat initiators by applying the same rules previously mentioned.

In the primary as-treated analysis for safety outcomes, follow-up time started on the index date and ended on the first occurrence of the following events: end of database period, plan disenrolment, death and discontinuing pegloticase treatment (ie, last infusion date+30 days for a grace period). In the sensitivity analysis, we used intention-to-treat analysis with censoring at 180 and 365 days from the index date regardless of pegloticase treatment duration.

Outcomes

We assessed the number of pegloticase infusions, intervals between the infusions and duration of therapy. We also assessed switching to allopurinol, febuxostat or probenecid from pegloticase after the index date.

We measured occurrence of anaphylaxis or anaphylactoid reactions defined by a combination of codes for anaphylaxis or adverse effect of drug with related procedure codes.[11] Since not all reactions that lead to treatment cessation are anaphylaxis, we also measured ordering of tryptase, which is a measure of mast cell activation and sometimes tested when there is a concern for drug reaction.[12] Other safety outcomes of interest were a composite cardiovascular endpoint, including myocardial infarction (MI) or stroke based on inpatient diagnosis codes; hospitalisation for heart failure, including new-onset heart failure and heart failure exacerbations; and all-cause death.[10] In addition, we assessed the risk of a composite cardiovascular endpoint among allopurinol and febuxostat initiators; however, we did not conduct a comparative analysis with pegloticase initiators, given substantial confounding by indication between pegloticase and allopurinol/febuxostat users.

Covariates

We measured patient characteristics during the baseline 365 days preceding the index date, including demographics, comorbidities, markers of healthcare use intensity and ordering of laboratory tests. We assessed baseline medication use, including gout-related drugs and oral corticosteroids.

Statistical analysis

We used descriptive statistics for patients' baseline characteristics. For each outcome, we used generalised linear model with Poisson distribution to assess the incidence rates (IRs) with 95% confidence intervals (CI). All statistical analyses were performed using SAS, version 9.4.

The study was approved by the Institutional Review Board of the Brigham and Women's Hospital which waived the requirement for informed consent (Protocol 2015P001748).

Patient and public involvement statement

Not applicable as this study was a retrospective cohort study using two large de-identified insurance claims databases.

RESULTS

Study cohort

The two study databases included over 2.9 million patients with at least 1 ICD-9 or ICD-10 code for gout; however, we identified only 717 patients (435 in MarketScan and 282 in Optum) who received any number of infusions for pegloticase. No rasburicase users were identified in either dataset. After applying all the inclusion and exclusion criteria, the final study cohort included only a total of 483 pegloticase initiators (304 in MarketScan and 179 in Optum) (figure 1). In contrast, there were 300 088 allopurinol (182 177 in MarketScan and 117 911 in Optum) and 66 725 febuxostat (36 225 in MarketScan and 17 896 in Optum) initiators in the study dataset using the same inclusion and exclusion criteria.

Baseline characteristics of Pegloticase initiators

The mean (SD) age of the MarketScan cohort was 55.6 (12.8) years and 10.9% was female. The Optum cohort was older than the MarketScan cohort with the mean (SD) age of 60.6 (12.9) years and 17.3% female (table 1). Cardiovascular comorbidities were prevalent in both cohorts. Hypertension was present in 73.0% of MarketScan and 84.9% of Optum cohorts, and diabetes was

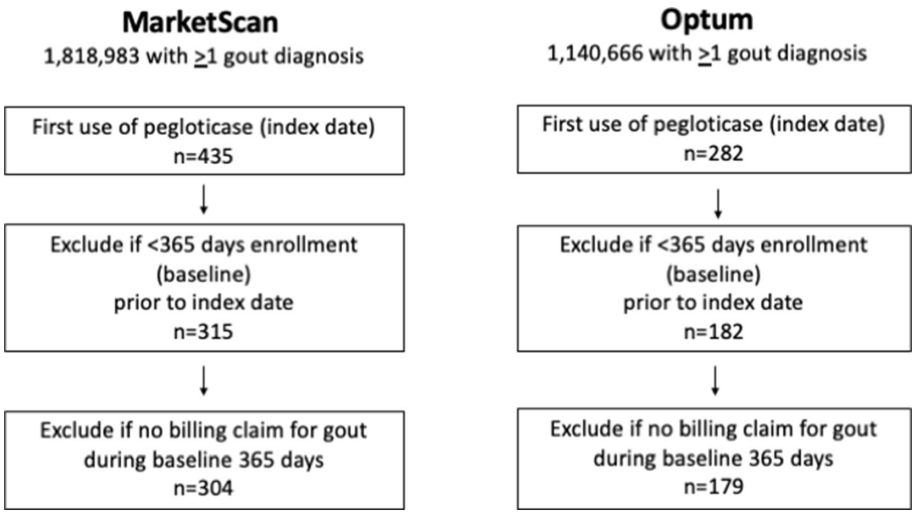

Figure 1 Flowchart of cohort selection for patients with gout initiating pegloticase. No rasburicase use or aged <18 was identified. The final study cohort included a total of 483 pegloticase initiators from both datasets.

prevalent in 34.9% and 38.0% of the cohorts. Heart failure was present in 12.5% of MarketScan and 20.7% of Optum cohorts. We found a high prevalence of chronic kidney disease (34.2% in MarketScan and 45.8% in Optum).

As expected, use of gout-related medications at baseline was common. Over 65% of patients used colchicine and over 67% used steroids during baseline. In 365 days prior to initiating pegloticase, 33.6% of MarketScan and 47.5% of Optum cohorts had at least one dispensing for allopurinol, 38.8% of MarketScan and 36.9% of Optum cohorts received at least one dispensing for febuxostat. Prior use of anakinra was noted in 6%–7% in both databases.

Overall, allopurinol initiators were younger and had a less burden of comorbidities than febuxostat or pegloticase initiators in either dataset. Furthermore, febuxostat initiators had less comorbidities and less use of medications than pegloticase initiators as expected (online supplemental table 1).

Patterns of Pegloticase use

The median duration of pegloticase therapy was 93 days (IQR (IQR) 56–186) in MarketScan and 105 (IQR 56–127) in Optum. The median number of pegloticase infusions was 4 (IQR 2–10) for MarketScan and 5 (IQR 2–12) in Optum (online supplemental figure 1), with a median interval between infusions of 14 days in both databases. 26 (8.6%) patients in MarketScan and 18 (10.1%) in Optum received over 20 infusions during the study period.

During the mean (SD) 1.86 (1.61) years of study period in MarketScan, 52 (17.1%) patients had continuous use of pegloticase, 89 (29.3%) patients switched to allopurinol, 99 (32.6%) to febuxostat, and 4 (1.3%) to probenecid. 60 (19.7%) patients discontinued pegloticase without switching to other urate-lowering drugs. Similarly, in Optum, over the mean (SD) 1.58 (1.66) years of study period, 41 (22.9%) patients continued pegloticase until the end of study period, 56 (31.3%) patients switched to allopurinol, 43 (24.0%) to febuxostat, and 3 (1.7%) to probenecid; however, 36 (20.1%) discontinued pegloticase without further use of other urate-lowering drugs.

Safety outcomes

During the mean 0.5 years of pegloticase treatment in both datasets, 3 (0.6%) developed an anaphylaxis or anaphylactoid reaction event: IR was 21.2 per 1000 person-years (95% CI 6.8 to 65.6) in MarketScan and no events in Optum (table 2). There was no incidence of tryptase ordering in MarketScan but two ordered in Optum (IR 21.4 per 1000 person-years, 95% CI 5.3 to 85.4).

Among pegloticase initiators (table 2), seven (1.4%) composite cardiovascular events occurred: IR was 14.1 per 1000 person-years (95% CI 3.5 to 56.5) in MarketScan and 53.6 per 1000 person-years (95% CI 22.3 to 128.7) in Optum. Thirty-one (6.4%) patients had hospitalisations for heart failure. Among 408 patients with no baseline heart failure (142 in Optum and 266 in MarketScan), 9 (2.2%) were hospitalised for new-onset heart failure with the IR per 1000 person-years of 33.3 (95% CI 12.5 to 88.7) in MarketScan and 63.1 (95% CI 26.2 to 151.5) in Optum. In 75 patients with baseline heart failure (37 in Optum and 38 in MarketScan), 22 (29.3%) had hospitalisations for heart failure exacerbation with the IR per 1000 person-years of 1019.7 (95% CI 603.9 to 1721.7) in MarketScan and 637.6 (95% CI 318.8 to 1274.9) in Optum. There were no deaths during follow-up in MarketScan, while all-cause death occurred in three patients in Optum (IR 31.9 per 1000 person-years, 95% CI 10.3 to 98.9). These IRs for cardiovascular events and all-cause mortality are generally higher than the IRs calculated for allopurinol and febuxostat initiators in both datasets, although the follow-up time in the as-treated analysis (ie, treatment duration) was two to three times longer for the allopurinol and febuxostat groups than the pegloticase group (see online supplemental table 2).

In the sensitivity analysis using intention-to-treat analysis at 180 and 365 days, there was no change in the number of anaphylaxis or anaphylactoid reaction events but few

Table 1 Patient characteristics in 365 days before initiating pegloticase for gout

	MarketScan	Optum
N	304	179
Mean age (SD) (years)	55.62 (12.83)	60.58 (12.85)
Female sex (%)	10.9	17.3
Comorbidities		
Hypertension (%)	73.0	84.9
Diabetes mellitus (%)	34.9	38.0
Hyperlipidaemia (%)	51.6	70.0
Obesity (%)	24.0	40.2
Smoking (%)	10.2	20.7
Atrial fibrillation (%)	14.5	17.3
Heart failure (%)	12.5	20.7
Coronary artery disease (%)	12.8	26.3
Stroke (%)	3.0	6.2
Chronic kidney disease (%)	34.2	45.8
End-stage renal disease/dialysis (%)	2.0	6.2
Chronic obstructive pulmonary disease (%)	11.8	15.1
Liver disease (%)	9.5	13.4
Malignancy (%)	10.2	8.4
Mean combined comorbidity score (SD)	1.84 (2.65)	2.71 (3.32)
Medication use		
NSAID/COX-2 inhibitor use (%)	51.3	40.0
Colchicine use (%)	72.0	65.4
Allopurinol use (%)	33.6	47.5
Febuxostat use (%)	38.8	36.9
Probenecid use (%)	8.2	4.5
Oral steroid use (%)	67.1	72.1
Mean cumulative prednisone equivalent dose (SD) (mg)	1171.5 (2003.4)	1182.0 (1756.3)
Anakinra use (%)	5.9	6.7
Opioid use (%)	59.9	53.1
Healthcare use patterns		
Any ED visit (%)	43.8	41.3
Any hospitalisation (%)	28.0	22.9
Mean number of outpatient visits (SD)	13.6 (9.2)	14.0 (9.6)
Mean number of unique prescription drugs (SD)	11.5 (7.6)	12.8 (8.0)
Serum uric acid ordered (%)	82.2	94.4
Serum creatinine ordered (%)	84.2	94.4

ED, emergency department; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation.

more events for cardiovascular composite outcome, heart failure and death (data not shown).

DISCUSSION

Although pegloticase is highly effective in reducing serum urate levels in patients with gout refractory to conventional ULT,[3] the use of pegloticase was only observed in 0.02% of patients with gout using data from two large commercial insurance claims databases in the USA. Multiple factors including its high cost, inconvenience (ie, at least 2-hour infusion every 2 week), safety concerns and insurance coverage have likely limited the use of pegloticase in a real-world setting. Our finding of low uptake of pegloticase in the USA is also in line with the 2020 ACR gout management guideline, which recommends against using pegloticase as the first-line therapy and in patients with infrequent gout flares (<2 flares/year).[4] Among the initiators of pegloticase from both datasets, the median duration of therapy was only 3 months, and less than 10% of 483 patients who initiated pegloticase received over 20 infusions (ie, approximately 10 months of pegloticase treatment) during the study period. While it is difficult to ascertain the reason for stopping pegloticase in this administrative claims-based study, over 50% of pegloticase starters were switched to allopurinol, febuxostat or probenecid during the study period, which suggests pegloticase was stopped due to intolerance or ineffectiveness.

Notably, pegloticase initiators had a high burden of comorbidities, and we noted a number of different safety events of interest during the follow-up period, including three anaphylaxis or anaphylactoid reaction events, seven composite cardiovascular (MI or stroke) events and three all-cause deaths. Hospitalisations for heart failure, which is listed as one of the warnings on the US FDA label for pegloticase,[10] were common occurring in 31 patients (6.4%): new-onset heart failure occurred in 9 patients (2.2% of patients with no baseline heart failure) and hospitalisations for heart failure exacerbations were in 22 patients (29.3% of patients with baseline heart failure).

The incidence rates of cardiovascular events or all-cause mortality were much higher in pegloticase initiators than allopurinol or febuxostat initiators; however, in an observational setting (ie, without randomisation), it is challenging to determine whether the higher rates of these safety events are due to the underlying clinical characteristics of pegloticase users or, at least in part, related to the drug.

Since the initial randomised clinical trials that demonstrated efficacy of pegloticase for patients with gout who were refractory to other ULT, there were known concerns regarding infusion reactions with pegloticase use.[3] In the clinical trials, infusion reactions occurred in 113 (6.7%) of 1695 patients, among which 6 (0.4%) met criteria for anaphylaxis.[13] The majority of patients who experienced infusion reactions were non-responders (serum urate level >6 mg/dL),[13] which was considered a marker for resistance to pegloticase and indicates formation of antipegloticase antibodies.

Anaphylaxis or anaphylactoid reaction measured in our study would not capture infusion reactions that are less severe but more common and may be clinically significant enough to lead to treatment cessation. Tryptase ordering, which is done in some but not all infusion reactions, also likely undercaptures infusion reactions and was ordered in only two cases. Additionally, pegloticase may be stopped due to rising serum urate levels that signify resistance and presence of

Table 2 Incidence of safety outcome events for patients with gout after initiation of pegloticase

	MarketScan			Optum		
Outcome	N event	Mean (SD) years of follow-up	IR* (95% CI)	N event	Mean (SD) years of follow-up	IR* (95% CI)
Anaphylaxis or anaphylactoid reactions	3	0.47 (0.50)	21.2 (6.8 to 65.6)	0	0.53 (0.62)	–
Composite cardiovascular events (MI or stroke)	2	0.47 (0.49)	14.1 (3.5 to 56.5)	5	0.52 (0.62)	53.6 (22.3 to 128.7)
Hospitalisation for new-onset heart failure	4	0.45 (0.49)	33.3 (12.5 to 88.7)	5	0.56 (0.67)	63.1 (26.2 to 151.5)
Hospitalisation for heart failure exacerbations	14	0.36 (0.41)	1020 (603.9 to 1721.7)	8	0.34 (0.36)	637.6 (318.8 to 1274.9)
All-cause death	0	0.47 (0.50)	–	3	0.53 (0.62)	31.9 (10.3 to 98.9)

*IR is per 1000 person-years.
CI, confidence interval; IR, incidence rate; MI, myocardial infarction; SD, standard deviation.

antipegloticase antibodies,[14] but serum urate values were not available in our study.

While potential infusion reactions can be mitigated by careful monitoring of urate levels to detect antibody formation, pegloticase use is generally reserved for refractory gout or in cases of contraindications to other oral ULTs (eg, allopurinol, febuxostat and probenecid).[9] For instance, severe chronic kidney disease may limit the use of other ULT. Accordingly, in our study of pegloticase initiators, there was a high prevalence of chronic kidney disease, although many of the patients in the study switched back to other ULTs after stopping pegloticase.

There was also a high prevalence of cardiovascular disease in the study cohort, which raises an important safety concern because gout itself is also associated with increased risk of MI, stroke and heart failure.[15 16] The rates of new-onset heart failure in pegloticase users in our study were comparable to the rates seen in a study of older patients with gout in the Medicare database who were initiating allopurinol or febuxostat.[17] However, heart failure exacerbations occurred at higher rates in our study of pegloticase initiators (IR 1019.7 per 1000 person-years in MarketScan and 637.6 in Optum) compared with the rates reported in older Medicare patients who were initiating allopurinol (IR 440.6 per 1000 person-years, 95% CI 431.8 to 449.6) or febuxostat (IR 427.0 per 1000 person-years, 95% CI 411.6 to 442.9).[17] In light of a recent FDA black box warning regarding the risk of cardiovascular death with febuxostat use after the publication of the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial,[18 19] heart failure risk with pegloticase use, a listed warning on the US FDA drug label may be an important area that requires more research because more patients with history of cardiovascular disease with contraindications to allopurinol could use pegloticase rather than febuxostat. Furthermore, future research may be needed to determine the effect of different gout flare prophylaxis drugs (ie, colchicine, interleukin-1 blocker, steroids or non-steroidal anti-inflammatory drugs) on cardiovascular risk of pegloticase.

This is the first study looking at the real-world use of an effective but underused medication in the treatment of gout. While we suspected the rates of pegloticase use would be low, we identified only 483 pegloticase initiators from years 2011 through 2018 in two large US nationwide commercial insurance claims databases. The limitations of our study include the inability to ascertain the actual cause for pegloticase discontinuation and/or switching back to other ULTs and lack of methods for identifying infusion reactions or laboratory values of serum urate levels that could indicate pegloticase failure in this claims-based study.

Further, while we observed high rates of heart failure exacerbations, it is unclear whether the use of pegloticase may be associated with higher risk of heart failure exacerbations or if this rate difference is due to higher baseline risk in pegloticase users with gout. The rarity of pegloticase use and inherent substantial confounding by indication present methodological challenges in conducting real-world comparative safety studies to assess cardiovascular outcomes with use of pegloticase versus other ULT agents.

In conclusion, this real-world data study using two large US insurance claims databases showed that the use of pegloticase is very rare (0.02%) in patients with gout since its FDA approval in 2010. Even among the initiators of pegloticase, the median duration of therapy was 3 months. Overall, pegloticase initiators had a high burden of comorbid conditions and healthcare resource uses, suggesting that pegloticase was used as a last resort in patients with refractory gout and a high comorbidity burden. Anaphylaxis or anaphylactoid reactions were uncommon (<1%) as measured in our study; however, as heart failure hospitalisations were common during the therapy with pegloticase, future study, preferably a trial, should further investigate the risk of heart failure in pegloticase users, given the high risk of cardiovascular morbidity and mortality in patients with gout.

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developing the analytical protocol and conducting statistical programming/analysis and reviewing the paper draft. SCK has contributed to obtaining the funding and data, designing the study, developing the analytic protocol, conducting statistical analysis, data interpretation, and reviewing the paper draft and finalising the paper.

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Data availability statement Data may be obtained from a third party and are not publicly available. Both MarketScan and Optum datasets are not publicly available.

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REFERENCES

1 Neogi T. Clinical practice. gout. *N Engl J Med* 2011;364:443–52.
2 Becker MA, Schumacher HR, Benjamin KL, *et al*. Quality of life and disability in patients with treatment-failure gout. *J Rheumatol* 2009;36:1041–8.
3 Sundy JS, Baraf HSB, Yood RA, *et al*. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. *JAMA* 2011;306:711-20.
4 FitzGerald JD, Dalbeth N, Mikuls T, *et al*. American College of rheumatology guideline for the management of gout. *Arthritis Care Res* 2020;2020:744–60.
5 Strilchuk L, Fogacci F, Cicero AF. Safety and tolerability of available urate-lowering drugs: a critical review. *Expert Opin Drug Saf* 2019;18:261–71.
6 Schlesinger N, Lipsky PE. Pegloticase treatment of chronic refractory gout: update on efficacy and safety. *Semin Arthritis Rheum* 2020;50:S31–8.
7 Guttmann A, Krasnokutsky S, Pillinger MH, *et al*. Pegloticase in gout treatment - safety issues, latest evidence and clinical considerations. *Ther Adv Drug Saf* 2017;8:379–88.
8 Gentry WM, Dotson MP, Williams BS, *et al*. Investigation of pegloticase-associated adverse events from a nationwide reporting system database. *Am J Health Syst Pharm* 2014;71:722–7.
9 Khanna D, Fitzgerald JD, Khanna PP, *et al*. *American College of rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia*, 2012.
10 Fda. Krystexxa (Pegloticase) injection label, 2012. Available: www.fda.gov/medwatch [Accessed 05 Aug 2020].
11 Walsh KE, Cutrona SL, Foy S, *et al*. Validation of anaphylaxis in the food and drug administration's Mini-Sentinel. *Pharmacoepidemiol Drug Saf* 2013;22:1205–13.
12 Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. *Immunol Allergy Clin North Am* 2006;26:451–63.
13 Calabrese LH, Kavanaugh A, Yeo AE, *et al*. Frequency, distribution and immunologic nature of infusion reactions in subjects receiving pegloticase for chronic refractory gout. *Arthritis Res Ther* 2017;19:191.
14 Lipsky PE, Calabrese LH, Kavanaugh A, *et al*. Pegloticase immunogenicity: the relationship between efficacy and antibody development in patients treated for refractory chronic gout. *Arthritis Res Ther* 2014;16:R60.
15 Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. *Am J Med* 2012;125:679–87.
16 Seminog OO, Goldacre MJ. Gout as a risk factor for myocardial infarction and stroke in England: evidence from record linkage studies. *Rheumatology* 2013;52:2251–9.
17 Zhang M, Solomon DH, Desai RJ, *et al*. Assessment of cardiovascular risk in older patients with gout initiating febuxostat versus allopurinol: population-based cohort study. *Circulation* 2018;138:1116–26.
18 White WB, Saag KG, Becker MA, *et al*. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med* 2018;378:1200–10.
19 FDA. Fda adds Boxed warning for increased risk of death with gout medicine Uloric (febuxostat) | FDA. Available: https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-increased-risk-death-gout-medicine-uloric-febuxostat [Accessed 28 Nov 2019].