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The Efficacy and Safety of Different Doses of Febuxostat Versus Allopurinol in the Treatment of Gout: A Meta-Analysis

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ABSTRACT

This study aimed to compare the therapeutic effect and drug safety of different doses of febuxostat and allopurinol in the treatment of patients with gout. A computer search was made for related literature from the period of 2008 to August 2022 in PubMed, Embase, the Cochrane Library, the Web of Science, the Cumulative Index to Nursing and Allied Health, China National Knowledge Infrastructure (HowNet), and the Wanfang and WeiPu databases using the following keywords: gout, febuxostat and allopurinol. The effects of febuxostat and allopurinol on serum uric acid, serum uric acid compliance rate, endothelin-1 (ET-1) and adverse events were systematically evaluated. The mean difference (MD) and odds ratio (OR) of the combined effects were calculated, and the range of effects was estimated using a 95 % confidence interval (CI). After systematic search and screening, 11 high-quality randomised controlled trials were included in this study. There was no significant difference in the effect of febuxostat and allopurinol on serum uric acid (MD: 12.97; 95% CI: −37.90, 63.84; $P = 0.62$). The control rate of serum uric acid when taking febuxostat 120 mg (OR: 4.15; 95% CI: 2.52, 6.82; $P < 0.00001$) was significantly higher than when taking febuxostat 80 mg (OR: 2.09; 95% CI: 1.09, 4.01; $P = 0.03$). Compared with 300 mg allopurinol, when the dose of febuxostat was 80 mg, the level of ET-1 in patients with gout was significantly improved (MD: −3.18; 95% CI: −5.38, −0.97; $P = 0.005$). There was no significant difference in the incidence of adverse events between patients taking febuxostat and allopurinol (OR: 0.92; 95% CI: 0.83, 1.02; $P = 0.13$), and abnormal liver function (OR: 0.96; 95% CI: 0.79, 1.17; $P = 0.69$) and gastrointestinal adverse reactions (OR: 1.00; 95% CI: 0.80, 1.23; $P = 0.97$) were not statistically significant. To conclude, Febuxostat has certain advantages over allopurinol in improving serum uric acid and ET-1 levels in patients with gout, and it appears to be as safe a treatment as allopurinol. Febuxostat 80 mg may be the lowest dose that can achieve therapeutic efficacy, and there is no significant difference in the incidence of adverse reactions between the two drugs.

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WWY and ZF presented the concept, designed the study, analysed and interpreted the data, wrote the manuscript, performed acquisition of data and statistical analysis. WYY conducted critical revision of the manuscript for intellectual contents.

Key words
Febuxostat, Allopurinol, Gout, Validity, Safety

INTRODUCTION

Gout is a crystal-associated arthropathy caused by the deposition of monosodium urate, and it is closely related to hyperuricemia, which results from purine metabolic disorders or reduced uric acid excretion (Ragab *et al*., 2017). In recent years, as more people follow a modern lifestyle, epidemiological studies have found that the incidence of gout is on the rise (Soriano *et al*., 2011; Trifirò *et al*., 2013; Zhu *et al*., 2011), its prevalence increases with age (Kuo *et al*., 2015) and it has become an independent risk factor for cardiovascular disease (Choi *et al*., 2007; Annemans *et al*., 2008). Therefore, gout is a public health concern, and early control measures are necessary.

The main goal when managing patients with hyperuricemia and gout is to reduce and maintain serum uric acid levels below 6.8 mg/dl (Pascual and Sivera, 2007; Zhang *et al*., 2006) and, over time, to reduce the frequency of acute gout attacks (Sarawate *et al*., 2006). At present, the pharmacological approach to achieving this goal is to use drugs that increase uric acid excretion, such as probenecid, or xanthine oxidase inhibitors, including allopurinol and febuxostat, to inhibit uric acid production. At present, allopurinol is widely used to maintain normal serum uric acid levels in patients with gout. In the United States, although the maximum dose of allopurinol is 800 mg/d, more than 90% of prescriptions only use a dose of 300 mg/d (Allopurinol, 2006; Sarawate *et al*., 2006). Febuxostat is a relatively new oral non-purine xanthine oxidase inhibitor

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that was launched in the United States in 2009. Previous studies have shown that febuxostat is effective in reducing uric acid, and there is a certain dose-response relationship. It was found that a dose in the range of 10 to 120 mg caused serum uric acid levels to decrease proportionally. When the dose was 80 mg, the compliance rate of serum uric acid exceeded 50%, but when it was 120 mg, the compliance rate increased by about 10% (Becker *et al*., 2004, 2005). However, there is a lack of research on the effect of different doses of febuxostat on uric acid levels in patients with gout. Therefore, the purpose of this study was to compare the therapeutic effect and safety of different doses of febuxostat and allopurinol in patients with gout and to clarify the relationship between drug dose and efficacy to provide a reference for the clinical medication of such patients.

MATERIALS AND METHODS

Search strategy

A systematic literature search of PubMed, Embase, the Cochrane Library, the Web of Science, the Cumulative Index to Nursing and Allied Health, China National Knowledge Infrastructure (HowNet), and the Wanfang and WeiPu databases was performed, following the guidelines set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Page *et al*., 2021). The English database retrieval period was from 2008 to 31 August 2022, and the Chinese database retrieval period was from 2013 to 31 August 2022. The English database search strategy used the following keywords: gout, febuxostat and allopurinol. The Chinese database used the same search keywords, and the keywords were connected using AND. In addition, the target literature was obtained by reviewing the references included in the studies. The detailed literature search strategies were as follows: (‘gout’ [MeSH Terms] OR ‘gout’ [All Fields]) AND (‘febuxostat’ [MeSH Terms] OR ‘febuxostat’ [All Fields]) AND (‘allopurinol’ [MeSH Terms] OR ‘allopurinol’ [All Fields] OR ‘allopurinols’ [All Fields]).

Inclusion and exclusion criteria

The criteria for including studies were as follows: (1) Chinese and English studies published in peer-reviewed journals exploring the efficacy and safety of different doses of febuxostat and allopurinol in the treatment of gout; (2) the subjects had been diagnosed as having gout, based on American College of Rheumatology diagnostic criteria or them having serum uric acid levels ≥480 μmol/L (8.0 mg/dl) (Khanna *et al*., 2012), and there were no limits to the patient’s age, gender or duration of illness; (3) the intervention measures were febuxostat and allopurinol; (4) the literature reported serum uric acid levels, serum uric acid compliance rates (subjects with serum uric acid level ≤6.0 mg/dl), endothelin-1 (ET-1) and the incidence of adverse events after treatment; and (5) the study type was a randomised controlled trial.

The following kinds of studies were excluded: (1) non-population studies; (2) conference articles, case reports or systematic reviews; (3) articles in which the research outcome information was insufficient and could not be analysed; (4) repeated reports of research; and (5) articles which could not be obtained in their entirety.

Study selection and data extraction

Two reviewers independently applied the selection criteria to each articles abstract and full text. A third reviewer joined the discussion when they disagreed until a consensus was achieved. After the literature screening, the two reviewers independently extracted the following data concerning febuxostat and allopurinol: Literature information, demographic characteristics of the subjects, dose amount, time of administration and outcome index information.

Quality evaluation

The Cochrane Collaboration risk assessment tool was used to evaluate the quality of the literature (Higgins and Altman, 2008). The research methodology was evaluated in terms of random distribution method, allocation concealment, blind method, the integrity of the results data, the selective reporting of research results and other potential sources of bias.

Statistical analysis

Revman 5.3 software was used for statistical analysis. The effects of the numeration data and the measurement data were expressed by the odds ratio (OR) and the mean difference (MD), and the 95 % confidence interval (CI) was used to estimate the interval range of the effect. A heterogeneity test was used to determine the degree of heterogeneity; if $I^2 < 50\%$ or $p > 0.1$, it was considered that the research was homogeneous, and the fixed effect model (Mantel–Haenszel) was used for analysis; if $I^2 > 50\%$ or $p \leq 0.1$, it was considered that the included studies were heterogeneous, and the random effect model (Der Simonian–Laird) was used for analysis. If the heterogeneity was substantial, sensitivity analysis was used to explore the source of the heterogeneity. With respect to the dose of febuxostat, subgroup analysis was divided into febuxostat 40 mg, febuxostat 80 mg and febuxostat ≥120 mg groups. To explore the therapeutic effect and safety of different doses of febuxostat and allopurinol on patients with gout, a 300 mg dose of allopurinol was taken as the control, and $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

Study characteristics

After a systematic search of the Chinese and English databases, 768 studies were included in the literature screening process. Of these, 352 duplicate research articles; 162 systematic reviews, animal studies and case reports; and a further 243 articles were excluded because they did not meet the inclusion criteria. Finally, 11 studies published between 2005 and 2020 and mainly from China and the United States, with one from South Korea, were included in the current study (Becker *et al*., 2005; Wu *et al*., 2016; Tao *et al*., 2014; Che and Yan, 2020; Li and Qiu, 2017; Zhang *et al*., 2017; Jiang *et al*., 2014; Wang *et al*., 2013; Schumacher Jr *et al*., 2008; Kim *et al*., 2014; Becker *et al*., 2010). Among 5,069 subjects with gout, 1,648 patients took 300 mg of allopurinol daily, 327 patients took 40 mg of febuxostat daily, 1,649 patients took 80 mg of febuxostat daily, 1,311 patients took 120 mg of febuxostat daily, and 134 patients took 240 mg of febuxostat daily. The study population was predominantly male, with a relatively high body mass index. More basic characteristics of the studies that were included are shown in Figure 1 and Table I.

Table I. Basic characteristics of included studies.

Study	Location	Age (y)	Male (%)	BMI (kg/m2)	Disease duration (y)	Baseline serum uric acid (μmol/L)	Sample size	Intervention	Duration (week)
Becker *et al*., 2005	USA	51.8±12.1	96	32.5±6.0	11.9±9.6	588.0±74.4	255	Febuxostat 80 mg	52
						530.4±75.6	250	Febuxostat 120 mg	
						594.0±73.8	251	Allopurinol 300 mg	
Schumacher *et al*., 2008	USA	52±12	94	33±7	11±9	>=480	267	Febuxostat 80 mg	28
							269	Febuxostat 120 mg	
							134	Febuxostat 240 mg	
							268	Allopurinol 300 mg	
Becker *et al*., 2010	USA	52.8±11.7	94.4	32.8±6.3	11.6±9.3	576±69	757	Febuxostat 80 mg	24
						576±72	756	Febuxostat 120 mg	
						570±71	756	Allopurinol 300 mg	
Wang *et al*., 2013	China	49.36±11.46	94.9	26.33±3.26	NR	570.22±71.48	159	Febuxostat 40 mg	24
						573.26±80.47	156	Febuxostat 80 mg	
						572.80±74.17	158	Allopurinol 300 mg	
Kim *et al*., 2014	Korea	49.6±11.5	100	25.9±2.9	NR	582±66	35	Febuxostat 40 mg	4
						570±78	35	Febuxostat 80 mg	
						570±60	36	Febuxostat 120 mg	
						570±60	36	Allopurinol 300 mg	
Tao *et al*., 2014	China	54.7±10.1	98.3	25.2±2.6		639±92	20	Febuxostat 40 mg	24
						595±81	20	Febuxostat 80 mg	
						665±102	20	Allopurinol 300 mg	
Jiang *et al*., 2014	China	54.68±10.09	98.3	25.17±2.58	NR	639.00±92.32	20	Febuxostat 40 mg	24
						595.40±81.05	20	Febuxostat 80 mg	
						665.40±102.73	20	Allopurinol 300 mg	
Wu *et al*., 2016	China	42.6±11.2	97.9	NR	NR	638±96	16	Febuxostat 40 mg	24
						589±87	16	Febuxostat 80 mg	
						650±94	16	Allopurinol 300 mg	
Li and Qiu, 2017	China	53.1±2.7	98.7	NR	NR	638.12±92.43	26	Febuxostat 40 mg	20
						631.23±82.11	26	Febuxostat 80 mg	
						633.21±101.32	26	Allopurinol 300 mg	
Zhang *et al*., 2017	China	46.0±9.5	84.8	NR	3.8±1.78	615.25±62.94	46	Febuxostat 80 mg	24
						608.34±65.03	46	Allopurinol 300 mg	
Che and Yan, 2020	China	56.9±11.7	77.8	NR	6.3±2.5	634.2±95.4	51	Febuxostat 40 mg	12
						588.3±87.5	51	Febuxostat 80 mg	
						659.2±89.6	51	Allopurinol 300 mg	

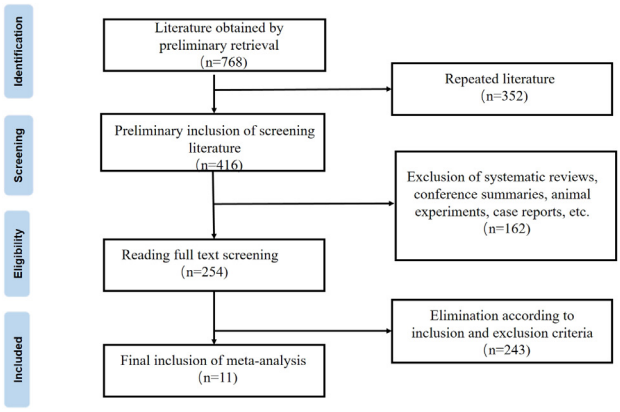

Fig. 1. Literature screening flow chart.

Literature quality evaluation

After evaluating the quality of the research using the Cochrane Collaboration's risk assessment tool, 11 studies met the inclusion criteria. The high quality of the research, the random allocation method and data integrity were the three aspects with the lowest risk of bias, but there was still a certain risk of bias due to the process of blinding (Figs. 2 and 3).

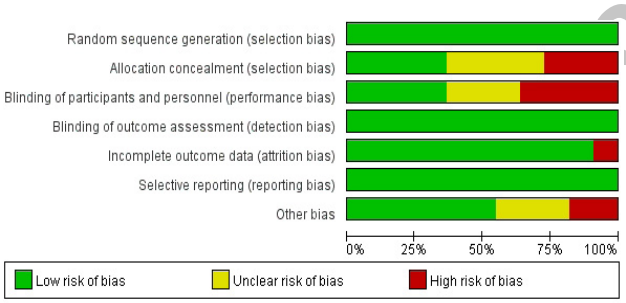

Fig. 2. Literature quality evaluation chart.

Serum uric acid levels

Five studies reported the effects of febuxostat and allopurinol on serum uric acid in patients with gout. Heterogeneity evaluation results (I^2 = 84%) suggested the use of a random effects model for statistical analysis. There was no significant difference between the effect of febuxostat at 40 mg and 80 mg and the effect of allopurinol on serum uric acid (MD: 12.97; 95% CI: −37.90, 63.84; P = 0.62), but the results of the individual action of each dose are different. The effect of allopurinol 300 mg on uric acid was better than that of febuxostat 40 mg (MD: 54.92; 95% CI: 18.23–91.61; P = 0.003). However, the effect of allopurinol 300 mg and febuxostat 80 mg on serum uric acid levels in patients with gout showed no statistically significant difference (MD: −23.34; 95% CI: −37.90, 63.84; P = 0.37). After excluding one study (Zhang *et al.*, 2017), the heterogeneity was reduced to I^2 = 0%, but there was no significant effect on the overall evaluation results (Fig. 4).

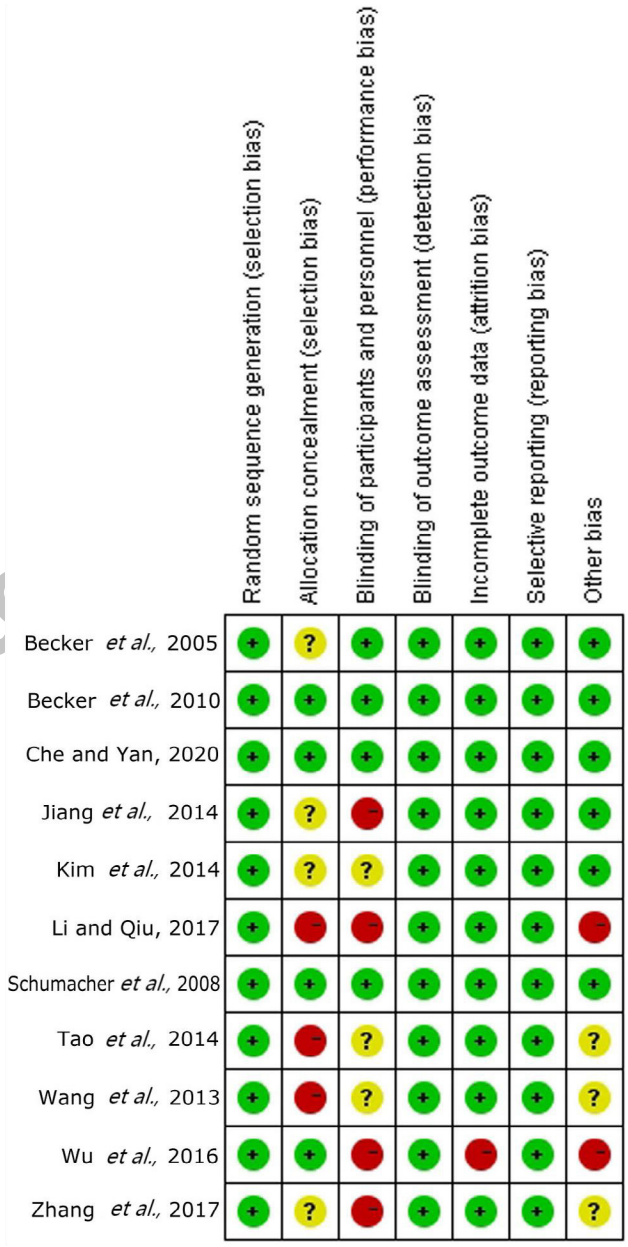

Fig. 3. Summary of risk bias of included studies.

Serum uric acid compliance rate

Five studies reported the proportion of patients with serum uric acid ≤6.0 mg/dl after treatment (i.e., the serum uric acid compliance rate). The results of heterogeneity analysis (I^2 = 92%) suggested that there was a certain

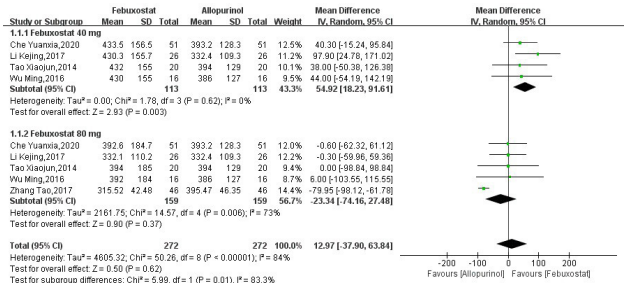

Fig. 4. Forest plot of the effect of febuxostat and allopurinol on serum uric acid level in patients.

heterogeneity between the studies, and the random effect model was used to calculate the combined effect size. Compared with the intervention of allopurinol 300 mg, the proportion of serum uric acid ≤6.0 mg/dl was higher in subjects taking febuxostat (OR: 2.35; 95% CI: 1.52, 3.62; P = 0.0001). From the perspective of different doses of febuxostat, the effect of febuxostat 40 mg on improving the compliance rate of serum uric acid was not statistically significant (OR: 1.17; 95% CI: 0.76, 1.78; P = 0.48). When taking febuxostat 80 mg, the standard rate of serum uric acid (OR: 4.15; 95% CI: 2.52, 6.82; P < 0.00001) was significantly higher than that in the allopurinol treatment group (OR: 2.09; 95% CI: 1.09, 4.01; P = 0.03). In addition, no obvious source of heterogeneity was found in the sensitivity analysis, suggesting that the heterogeneity between the studies was stable (Fig. 5).

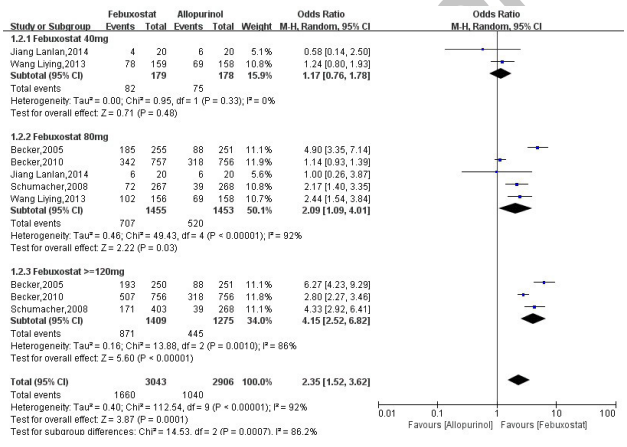

Fig. 5. Forest plot of the effect of febuxostat and allopurinol on the compliance rate of serum uric acid level in patients.

Endothelin-1

Three studies reported the effects of febuxostat and allopurinol on ET-1. The result of the heterogeneity analysis was I^2 = 42%, and there was good homogeneity among the studies. The fixed effect model was used for systematic evaluation. The effects of febuxostat and allopurinol on ET-1 were not statistically significant (MD: −1.19; 95% CI: −2.92, 0.54; P = 0.18). Compared with the effect of 300 mg allopurinol, the effect of 40 mg febuxostat on ET-1 was not statistically significant (MD: 2.00; 95% CI: −0.97, 4.79; P = 0.16). However, ET-1 levels were significantly improved in patients with gout with 80 mg febuxostat doses (MD: −3.18; 95% CI: −5.38, −0.97; P = 0.005) (Fig. 6).

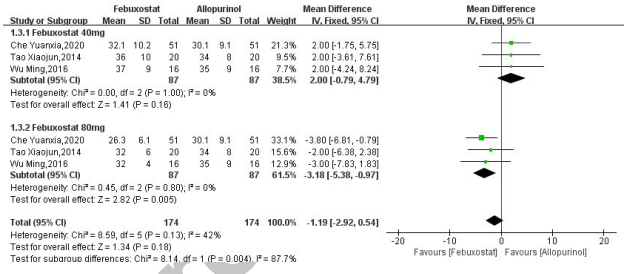

Fig. 6. Forest plot of the effect of febuxostat and allopurinol on ET-1 (ng/L) in patients.

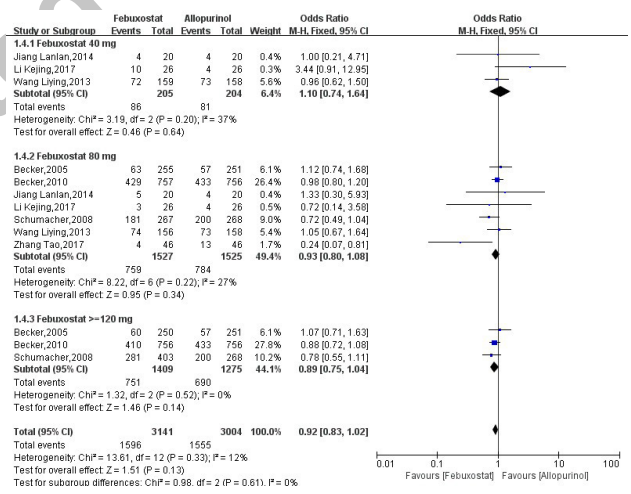

Fig. 7. Results of adverse events between febuxostat and allopurinol.

Incidence of adverse events

A total of seven studies reported the incidence of adverse events during febuxostat and allopurinol intervention. The heterogeneity evaluation results (I^2 = 12%) showed that the heterogeneity between the studies was small and the homogeneity was good, so the fixed effect model was used for systematic evaluation. There was no significant difference in the incidence of adverse events overall between patients taking febuxostat and those taking allopurinol (OR: 0.92, 95% CI: 0.83, 1.02; P = 0.13), and, compared to 300 mg allopurinol, doses of 40

mg febuxostat (OR: 1.10; 95% CI: 0.74, 1.64; $P = 0.64$), febuxostat 80 mg (OR: 0.93; 95% CI: 0.80, 1.08; $P = 0.34$) and febuxostat ≥120mg (OR: 0.89; 95% CI: 0.89, 1.04; $P = 0.14$) showed no statistically significant difference with regard to adverse events in patients (Fig. 7). There were no statistically significant differences between febuxostat and allopurinol in abnormal liver function (OR: 0.96; 95% CI: 0.79, 1.17; $P = 0.69$) or gastrointestinal adverse reactions (OR: 1.00; 95% CI: 0.80, 1.23; $P = 0.97$) (Figs. 8 and 9).

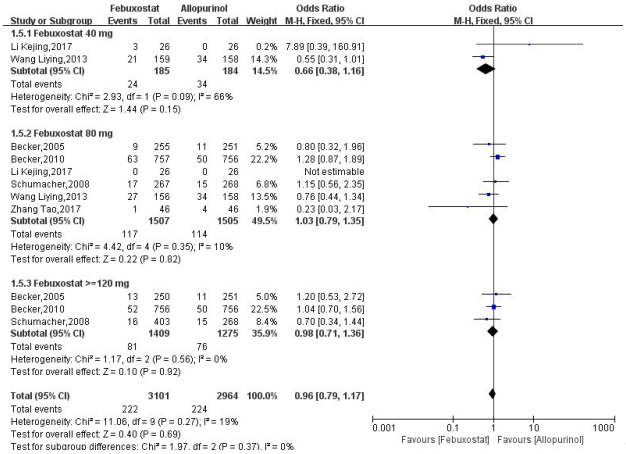

Fig. 8. Results of abnormal liver function in febuxostat and allopurinol.

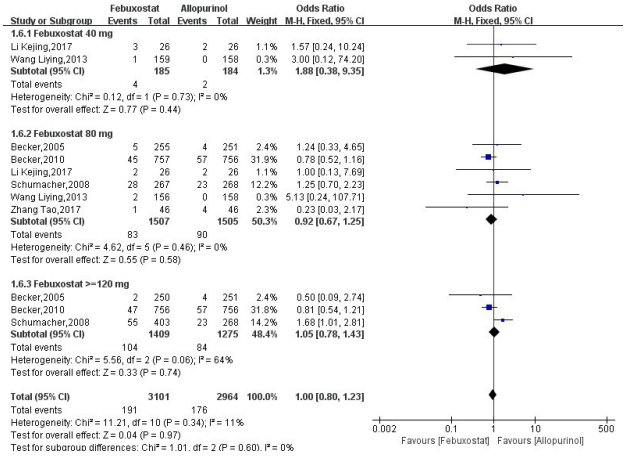

Fig. 9. Results of gastrointestinal adverse reactions induced by febuxostat and allopurinol.

DISCUSSION

Through the systematic evaluation of 11 studies, this analysis found that febuxostat and allopurinol had similar effects in reducing uric acid levels, but when the dose of febuxostat is 80 mg, the blood uric acid compliance rate of the subjects is significantly higher than that of those being administered allopurinol. In addition, daily administration of febuxostat 80 mg can significantly improve the expression of ET-1 in patients. In terms of drug safety, the incidence of adverse events, liver dysfunction and gastrointestinal adverse reactions in patients with gout taking febuxostat and allopurinol showed no statistically significant differences. As far as the authors know, this study is the first systematic evaluation study to compare the therapeutic effects and safety of different doses of febuxostat and allopurinol in patients with gout, thereby providing reference information for the medication management of these patients.

Febuxostat was launched in the United States in 2009 and approved for entry into China in 2013. Its launch has expanded clinicians drug choices for the treatment of gout and hyperuricemia, offering the opportunity to reduce the number of patients who are intolerant to existing oral uric acid-lowering drugs (Bardin and Richette, 2019). Febuxostat is a powerful uric acid-lowering drug, which has been confirmed by randomised controlled trials comparing it with allopurinol and placebos (Becker *et al*., 2005, 2010; Schumacher Jr *et al*., 2008). Different dosages of allopurinol will also lead to different therapeutic effects, but, at present, 300 mg/d is the most commonly used dosage (Becker *et al*., 2015; Reinders *et al*., 2009; Stamp *et al*., 2017a, b). The results of different dosages of febuxostat are quite different from those of allopurinol (300 mg/d). Compared with 300mg/d allopurinol, when the dosage of febuxostat is 40 mg, the effect of reducing serum uric acid concentration is not as good, and there is no significant difference in the standard rate of serum uric acid and ET-1 level. When the dosage was 80 mg, there was no significant difference in the effect of reducing serum uric acid concentration, but the standard rate of serum uric acid and levels of ET-1 were significantly improved. When the dosage was 120 mg, the rate of reducing serum uric acid was also significantly higher than that of allopurinol treatment, which is about 3.2% higher than that of 80 mg febuxostat treatment. Generally speaking, with a daily dose of 80 mg/120 mg, the clinical efficacy of febuxostat is better than that of allopurinol at a fixed dosage of 300 mg/d, and the safety of each dose is equivalent to that of the common treatment scheme (allopurinol at 300 mg/d). This finding is similar to that of another study (Zhang *et al*., 2019).

Uric acid plays an important role in inducing renal inflammation and renal injury, and ET-1 is a well-known crude fibrosis factor in the kidney. One study found that the increase in uric acid level promoted the expression of ET-1, which can lead to hyperuricemia and renal fibrosis (Romi *et al*., 2017). The results of the current study

showed that febuxostat 80 mg/d may have a positive effect on improving the expression of ET-1, but the mechanism between the two is still unclear. It is worth noting that several studies have shown that febuxostat has a higher risk of cardiovascular disease than allopurinol (Wang *et al*., 2021; Gao *et al*., 2021), which further suggests that not only the therapeutic effects of drugs in clinical practice should be considered, but their short-term and long-term outcomes are of equal importance.

This study has some limitations. Firstly, the 11 studies were mainly from China and the United States, so the extrapolation of their findings to different ethnic groups may be limited. Secondly, the small sample size of some of the studies may have led to potential bias in the results. Finally, the daily doses of febuxostat were mainly 40 mg, 80 mg and 120mg, and only one study used 240 mg/d, so the effect of higher doses of febuxostat was not explored; in contrast, the dose of allopurinol in the selected studies was only 300 mg/d, and there is no information about the effects of higher doses of allopurinol on improving serum uric acid levels in patients with gout.

In summary, febuxostat and allopurinol can both improve serum uric acid levels in patients with gout, and they both have good safety records. From the perspective of serum uric acid compliance rate, febuxostat has a better effect, and this effect appears to have a certain correlation with the dose. However, in clinical practice, it is necessary to pay attention to the effect of these drugs on the long-term outcome of patients with gout. In addition, due to the limitations of this study, a large number of multicentre, high-quality prospective studies are needed to further explore the effect of febuxostat and allopurinol on patients with gout and to clarify the relationship between drug dose and clinical effect.

CONCLUSION

Compared with allopurinol, a lower dose of febuxostat (40 mg) is not as effective at reducing the serum uric acid level of patients with gout, but the standard rates of serum uric acid and ET-1 levels after treatment are equivalent to those after allopurinol treatment. A higher dose of febuxostat (80 mg/120 mg) can reduce the serum uric acid level of gout patients in a similar way to allopurinol, but this dose is significantly better than allopurinol treatment in terms of the standard rate of serum uric acid and ET-1 levels. There is no significant difference in the incidence of adverse events between the patients with gout treated with different doses of febuxostat and those treated with allopurinol, suggesting that febuxostat is as safe as allopurinol.

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Ethical statement

This study was approved by the Ethics Committee of the Yichang Central People's Hospital (ethical batch number 2022-078-01)

Statement of conflict of interest

The authors have declared no conflict of interest.

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