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Original Article

Comparative Efficacy and Safety of Febuxostat and Allopurinol in the Treatment of Hyperuricemia: A Bayesian Network Meta-analysis

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Objective. The aim of this study was to assess the relative urate-lowering efficacy and safety of febuxostat and allopurinol in hyperuricemic patients with or without gout. **Methods.** Randomized controlled trials (RCTs) examining the efficacy and safety of febuxostat compared to allopurinol or placebo in hyperuricemic patients with/without gout were included in this Bayesian network meta-analysis. **Results.** Eight RCTs including 4,099 patients met the inclusion criteria. The number of subjects achieving a serum urate (sUA) level < 6.0 mg/dL was significantly higher in the febuxostat 120 mg and 80 mg groups than in the allopurinol (100 to 300 mg) group (odds ratio [OR] 7.17, 95% credible interval [CrI] 3.86 to 14.09; OR 3.49, 95% CrI 1.97 to 5.91, respectively). However, achievement of the target sUA level was comparable between febuxostat 40 mg and allopurinol. Ranking probability based on surface under the cumulative ranking curve (SUCRA) indicated that febuxostat 120 mg had the highest probability of being the best treatment for achieving the target sUA (SUCRA = 0.9973), followed by febuxostat 80 mg (SUCRA = 0.752), febuxostat 40 mg (SUCRA = 0.4289), allopurinol (SUCRA = 0.3217), and placebo (SUCRA = 0). In contrast, no significant difference in safety based on the number of withdrawals due to adverse events was observed among the 5 interventions. **Conclusion.** Febuxostat 80 mg and 120 mg were more efficacious than allopurinol (100 to 300 mg), and febuxostat 40 mg and allopurinol were comparable in urate-lowering efficacy. The safety of febuxostat at all doses was comparable with that of allopurinol. **(J Rheum Dis 2015;22:356-365)**

Key Words. Febuxostat, Allopurinol, Gout, Meta-analysis

INTRODUCTION

Hyperuricemia is defined as a serum urate (sUA) level exceeding the limit of urate solubility (6.8 mg/dL) that reflects supersaturation of the extracellular fluid with urate and predisposes to gout [1]. Gout is an inflammatory disorder characterized by hyperuricemia and consequences of urate crystal deposition, such as episodic gout flares, gouty arthropathy, tophi, and urolithiasis [1]. Hyperuricemia leads to monosodium urate crystal deposition in tissues, and increasing levels of hyperuricemia are correlated with increasing incidences of gouty arthritis and uric acid urolithiasis [2].

A primary goal in managing gout is to lower sUA levels to a subsaturating range (6.0 mg/dL) at which urate crystal formation and deposition are prevented or reversed [3]. Long-term achievement of this objective results in a decreased incidence of acute gouty attacks and dissolution of tophaceous deposits [4].

Allopurinol, a xanthine oxidase inhibitor, is the most commonly prescribed urate-lowering agent. Although the recommended doses of allopurinol range from 100 to 800 mg per day, titrated to sUA and creatinine clearance, the dose most commonly used in clinical practice is 100 to 300 mg per day [4]. Although allopurinol is generally safe, it may occasionally induce severe or life-threatening

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skin reactions and allopurinol-hypersensitivity syndrome, more often in patients with renal insufficiency [5,6]. Febuxostat is an orally administered selective inhibitor of xanthine oxidase in development for the treatment of hyperuricemia in patients with gout [7]. Febuxostat is being studied at daily doses of 40 to 120 mg for the management of hyperuricemia in patients with gout [8-15]. Dose reduction of allopurinol is needed in patients with impaired renal function due to the prolonged half-life (14 to 26 hours) of the major allopurinol metabolite, oxypurinol [16]. In contrast, febuxostat does not require dose adjustment for mild to moderate renal impairment, because febuxostat has minimal effects on other enzymes involved in purine and pyrimidine metabolism and is mainly metabolized in the liver [17].

Previous meta-analyses have shown that febuxostat is effective in hyperuricemic patients with gout and has a safety profile comparable to that of allopurinol [18]. However, data on the relative efficacy and safety of febuxostat with different dosages compared with allopurinol are limited, because it is difficult to integrate information regarding the relative efficacy and safety of all tested drugs at different doses due to the lack of multiple comparisons of classical meta-analysis.

Traditional meta-analysis compares only 2 treatments at a time [19,20]. On the other hand, network meta-analysis, also called multiple-treatments meta-analysis, simultaneously combines direct and indirect evidence of relative treatment effects [21]. Network meta-analysis can assess the comparative effectiveness of multiple interventions and combines evidence across a network of randomized controlled trials (RCTs) to help decision-making, even if there are no head-to-head comparisons [22]. The present study aimed to compare the efficacy and safety of febuxostat 40 mg, febuxostat 80 mg, febuxostat 120 mg, and allopurinol 100/300 mg daily in hyperuricemic patients with or without gout using a network meta-analysis.

MATERIALS AND METHODS

Identification of eligible studies and data extraction

We performed an exhaustive search for studies that examined the efficacy and safety of febuxostat in hyperuricemic patients with or without gout. A literature search was performed using PubMed, EMBASE, Cochrane Controlled Trials Register, and KoreaMed to identify available articles (up to May 2015). The following key words and subject terms were used in the search: febuxostat, hyperuricemia, and gout. All article references were reviewed to identify additional studies that were not included in the electronic databases. No restrictions were placed on language, race, ethnicity, or geographic area. RCTs were included if they met the following criteria: the study included hyperuricemic (sUA $>$7.0 mg/dL) adults (age $>$18 years) with or without gout defined by American Rheumatology Association preliminary criteria [23], the study compared febuxostat with placebo or allopurinol in the treatment of hyperuricemia for 4 weeks or longer, and the study provided endpoints for the urate-lowering efficacy and safety of febuxostat. The exclusion criteria were as follows: the study was an open-label extension trial, the study included duplicate data, and the study did not contain adequate data for inclusion. The outcome measure for efficacy was the number of patients that achieved an sUA level $<$6.0 mg/dL, and the outcome measure for safety was the number of patients withdrawn due to adverse events (AEs). Two independent reviewers extracted data from original studies. Any discrepancy between the reviewers was resolved by consensus or by a third reviewer. The following information was extracted from each study: first author, year of publication, country in which the study was conducted, febuxostat dose, length of follow-up time, and outcomes for efficacy and safety at the final visit. We quantified the methodological qualities of the four studies using Jadad scores [24]. The Jadad scale assesses random assignment, double blinding, and patient withdrawal and dropout rates. Jadad scores range from 0 to 5. Quality was classified as high (score of 3 to 5) or low (score of 0 to 2). We conducted a network meta-analysis in accordance with the guidelines provided by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [25].

Evaluations of statistical associations for network meta-analysis

For RCTs that compared multiple doses of febuxostat in different arms, the results from different arms were analyzed simultaneously. The efficacy and safety of febuxostat in different arms were ordered according to the probability of being ranked as the best-performing regimen. We used a Bayesian random-effects model for network meta-analysis using NetMetaXL [26] and WinBUGS statistical analysis program version 1.4.3 (MRC Biostatistics Unit, Institute of Public Health, Cambridge, United Kingdom). Bayesian approach provides greater flexibility to

use more complex models and different outcome types. Thus, Bayesian network meta-analysis permits simultaneous comparison of all treatment options. We chose a random effect model for network meta-analysis, because the model incorporates between-study variations and is a conservative method. The random network model was selected prior to statistical analysis. We used the Markov Chain Monte Carlo method to obtain pooled effect sizes [22]. All chains were run with 10,000 burn-in iterations followed by 10,000 monitoring iterations. Information on relative effects was converted to a probability that a treatment is best, second best, and so on, or the ranking of each treatment, called the surface under the cumulative ranking curve (SUCRA) [27], which is expressed as a percentage; the SUCRA is 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst. The league table arranges the presentation of summary estimates by ranking the treatments in order of the most pronounced impact on the outcome under consideration based on SUCRA [27]. We reported the pairwise odds ratio (OR) and 95% credible interval (CrI) (or

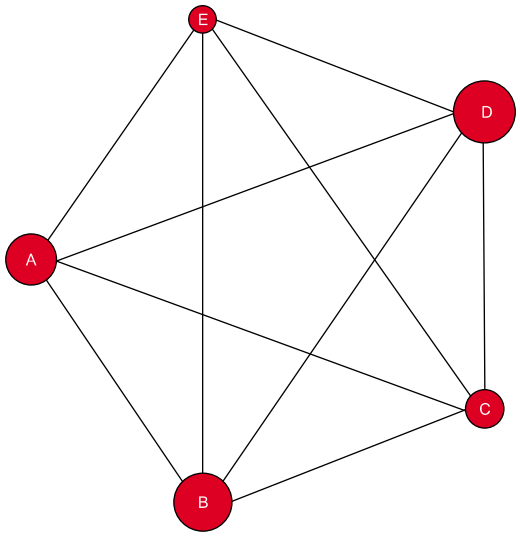

Figure 1. Evidence network diagram of network meta-analysis comparisons. The width of each edge is proportional to the number of randomized controlled trials comparing each pair of treatments, and the size of each treatment node is proportional to the number of randomized participants (sample size). (A) Febuxostat 40 mg. (B) Febuxostat 80 mg. (C) Febuxostat 120 mg. (D) Allopurinol. (E) Placebo.

Table 1. Characteristics of individual studies included in the meta-analysis and systematic review

Study	Country	Patient number	Hyperuricemia (mg/dL)	Gout (%)	Daily dose (number)	Follow-up period (wk)	Jadad score
Becker et al., 2005 [8]	USA	153	>8	100	Febuxostat 40 mg (37), febuxostat 80 mg (40), febuxostat 120 mg (38), placebo (38)	4	3
Becker et al., 2005 (FACT) [9]	USA	760	>8	100	Febuxostat 80 mg (256), febuxostat 120 mg (251), allopurinol 300 mg (253)	52	4
Schumacher et al., 2008 (APEX) [10]	USA	804	>8	100	Febuxostat 80 mg (267), febuxostat 120 mg (269), allopurinol 300 mg (268)	28	3
Becker et al., 2010 (CONFIRMS) [11]	USA	1,768	>8	100	Febuxostat 40 mg (757), febuxostat 80 mg (756), allopurinol 200/300 mg (255)	26	5
Kamatani et al., 2011 [12]	Japan	244	>8	46	Febuxostat 40 mg (122), allopurinol 100 mg (122)	8	3
Kamatani et al., 2011 [13]	Japan	121	>7	57	Febuxostat 40 mg (41), febuxostat 80 mg (42), placebo (38)	16	3
Kamatani et al., 2011 [14]	Japan	67	>8	49	Febuxostat 40 mg (34), placebo (33)	8	3
Park et al., 2013 [15]	Korea	182	>8	100	Febuxostat 40 mg (36), febuxostat 80 mg (36), febuxostat 120 mg (36), allopurinol 300 mg (37), placebo (37)	4	3

APEX: allopurinol- and placebo-controlled, efficacy study of febuxostat trial, COMFIRMS: the urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial, FACT: febuxostat versus allopurinol controlled trial, NA: not available.

Bayesian confidence interval) and adjusted for multiple-arm trials. Pooled results were considered statistically significant if the 95% CrI did not contain the value 1.

Tests for inconsistency and sensitivity

Inconsistency refers to the extent of disagreement between direct and indirect evidence [28]. Assessment of inconsistency is important for conducting a network meta-analysis [29]. We plotted the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to assess network inconsistency between direct and indirect estimates in each loop [30]. A sensitivity test was performed by comparing the random- and fixed-effects models.

RESULTS

Studies included in the meta-analysis

A total of 148 studies were identified by electronic or manual searches, and 17 were selected for a full-text review based on the title and abstract details. However, 9 of

Table 2. Characteristics of direct comparison

Comparison	Study number	Patient number
Febuxostat 40 mg vs. febuxostat 80 mg	4	1,449
Febuxostat 40 mg vs. febuxostat 120 mg	2	143
Febuxostat 40 mg vs. placebo	4	284
Febuxostat 80 mg vs. febuxostat 120 mg	4	998
Febuxostat 80 mg vs. placebo	4	479
Febuxostat 120 mg vs. placebo	3	432
Febuxostat 80 mg vs. allopurinol	4	2,164
Febuxostat 120 mg vs. allopurinol	3	969
Allopurinol vs. placebo	2	380
Febuxostat 40 mg vs. allopurinol	3	1,559

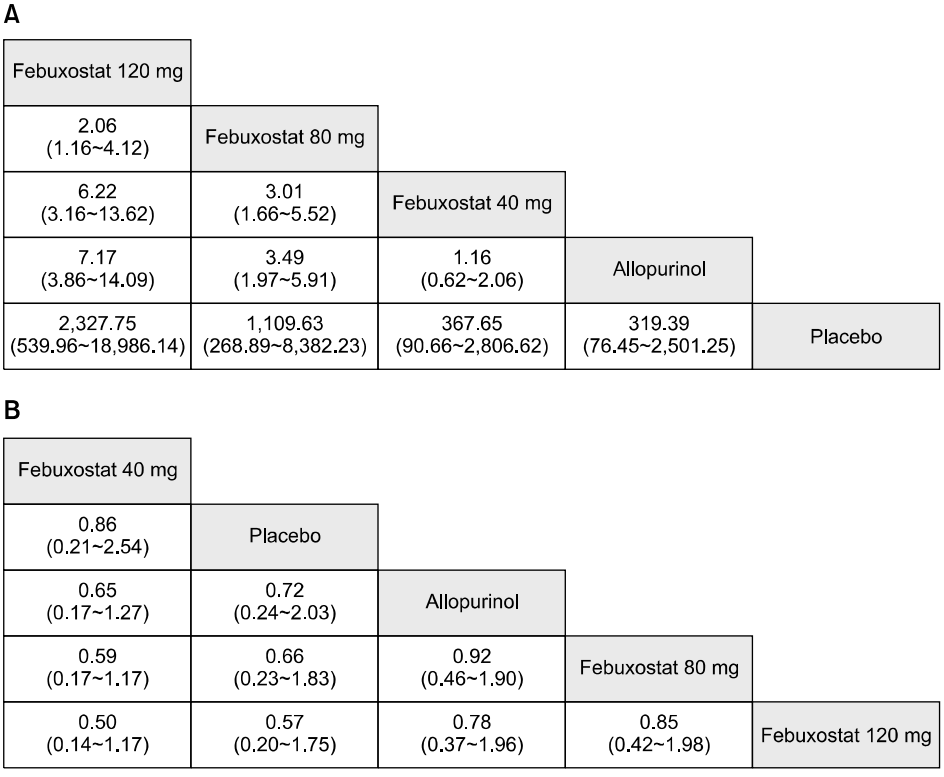

Figure 2. League tables showing the results of the network meta-analyses comparing the effects of all drugs including odds ratio (OR) and 95% credible intervals. (A) Efficacy; OR >1 means the top-left treatment is better. (B) Safety; OR <1 means the top-left treatment is better.

the 17 studies were excluded because they contained duplicate data [31-33], open-label data [34-36], or insufficient data [37-39]. Thus, 8 RCTs including 4,099 patients (2,108 events for efficacy and 291 events for safety) met the inclusion criteria [8-15] (Table 1).

The evidence network diagram shows data related to the number of studies performed comparing the different treatments, the numbers of patients in each treatment (Table 1 and Figure 1). There were 10 pairwise comparisons including 5 interventions for the network meta-analysis: febuxostat 40 mg, febuxostat 80 mg, febuxostat 120 mg, allopurinol 100/300 mg, and placebo (Table 1). Doses of allopurinol were 300 mg in 3 trials, 100 mg in 1 trial, and 200/300 mg in one study. Jadad scores of the studies were 3 to 5, indicating high study quality (Table 1). Relevant features of the studies included in the meta-analysis are provided in Tables 1 and 2.

Network meta-analysis of the efficacy of febuxostat in RCTs

Febuxostat 120 mg was listed in the top left of the diagonal of the league table (Figure 2) because it was associated with the most-favorable SUCRA for achieving an sUA level <6.0 md/dL, whereas placebo was listed in the bottom right of the diagonal of the league table because it was associated with the least-favorable results (Figure 2). The results are to be read from top to bottom and left to

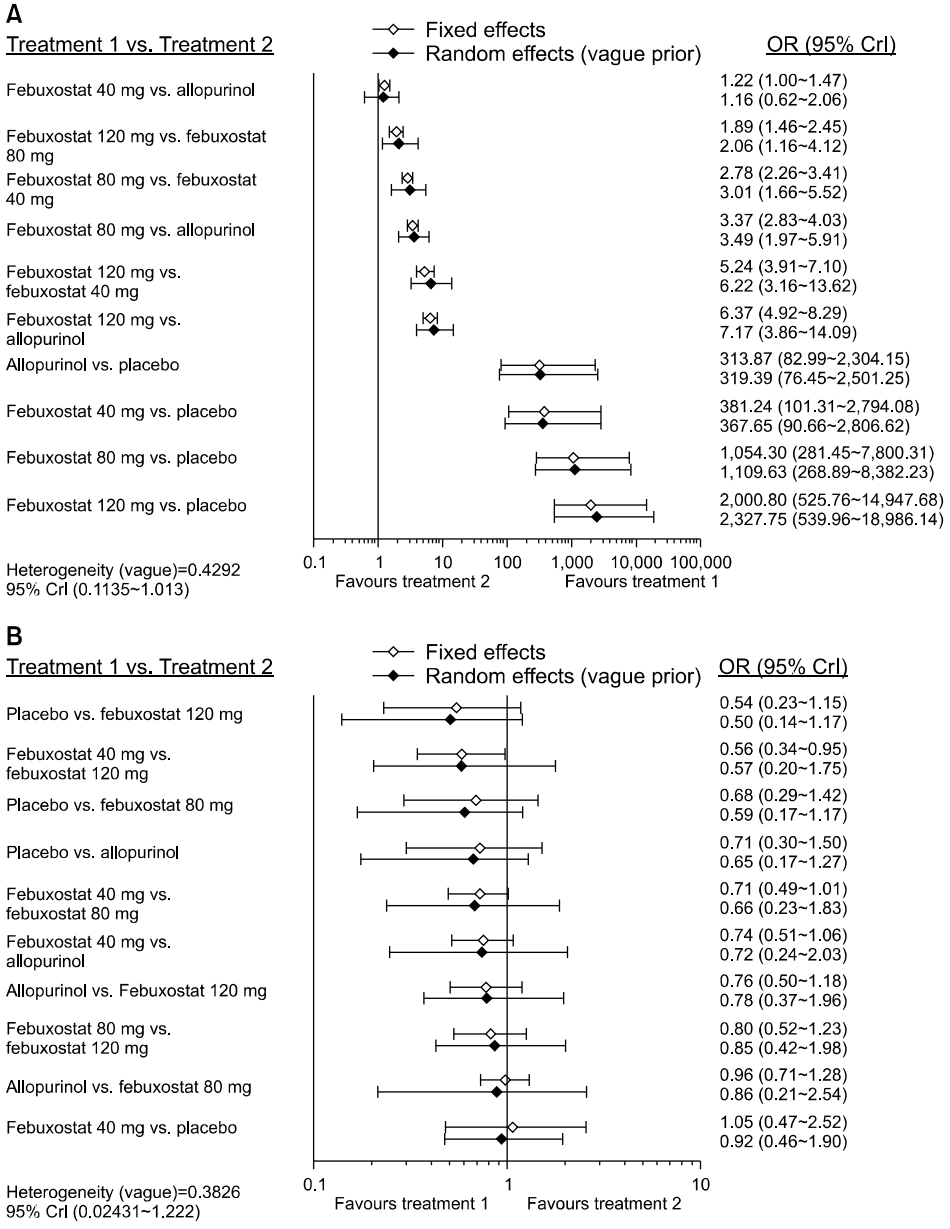

Figure 3. Bayesian network meta-analysis results of randomized controlled studies on the relative efficacy (A) and safety (B) of febuxostat, allopurinol, and placebo, respectively. CrI: credible interval, OR: odds ratio.

right. The proportion of patients achieving the target sUA level was significantly higher in the febuxostat 120 mg, febuxostat 80 mg, febuxostat 40 mg, and allopurinol (100 to 300 mg) groups than in the placebo group (Figures 2 and 3). The number of subjects with an sUA level < 6.0 mg/dL was significantly higher in the febuxostat 120 mg and febuxostat 80 mg groups than in the allopurinol group (OR 7.17, 95% CrI 3.86 to 14.09 and OR 3.49, 95% CrI 1.97 to 5.91, respectively) (Figures 2 and 3). Achievement of the target sUA level with febuxostat 40 mg was comparable with that with allopurinol (OR 1.16, 95% CrI 0.62 to 2.06) (Figures 2 and 3). Ranking probability based on SUCRA indicated that febuxostat 120 mg had the highest probability of being the best treatment for achieving the target sUA (SUCRA=0.9973), followed by febuxostat 80 mg (SUCRA=0.7520), febuxostat 40 mg (SUCRA=0.4289), allopurinol (SUCRA=0.3217), and placebo (SUCRA=0) (Table 3).

Table 3. Rank probability of febuxostat, allopurinol, and placebo*

Treatment	SUCRA	
	Efficacy	Safety
Febuxostat 120 mg	0.9973	0.1819
Febuxostat 80 mg	0.7520	0.3342
Febuxostat 40 mg	0.4289	0.8484
Allopurinol	0.3217	0.4352
Placebo	0	0.7002

SUCRA, surface under the cumulative ranking curve. *Efficacy based on the number of patients achieving a serum urate level of less than 6.0 mg/dL and safety based on the number of withdrawals due to adverse events.

Network meta-analysis of the safety of febuxostat in RCTs

We considered the number of patient withdrawals due to AEs as the safety outcome. The number of patients withdrawn due to AEs tended to be lower in the febuxostat 40 mg and placebo groups than in the allopurinol, febuxostat 80 mg, and febuxostat 120 mg groups (Figures 2 and 3). However, the number of patients withdrawn due to AEs did not differ significantly among the 5 interventions (Figures 2 and 3). Ranking probability based on SUCRA indicated that febuxostat 120 mg had the lowest probability of being the safest treatment (SUCRA=0.1819), followed by febuxostat 80 mg (SUCRA=0.3342), allopurinol (SUCRA=0.4352), placebo (SUCRA=0.7002), and febuxostat 40 mg (SUCRA=0.8484) (Table 3).

Inconsistency and sensitivity analysis

Some inconsistencies between direct and indirect estimates were found. Two points in both plots of the efficacy (placebo of Kamatani et al.'s study [13] and Kamatani et al's. study [14]) and safety (febusoxtat 120 mg of Becker et al. [8] study, febusoxtat 120 mg of Park et al. [15] study) appeared to have a higher than expected posterior mean deviance (Figure 4). However, sensitivity analysis removing the outlier studies did not meaningfully change the network meta-analysis results, i.e., OR for achieve-

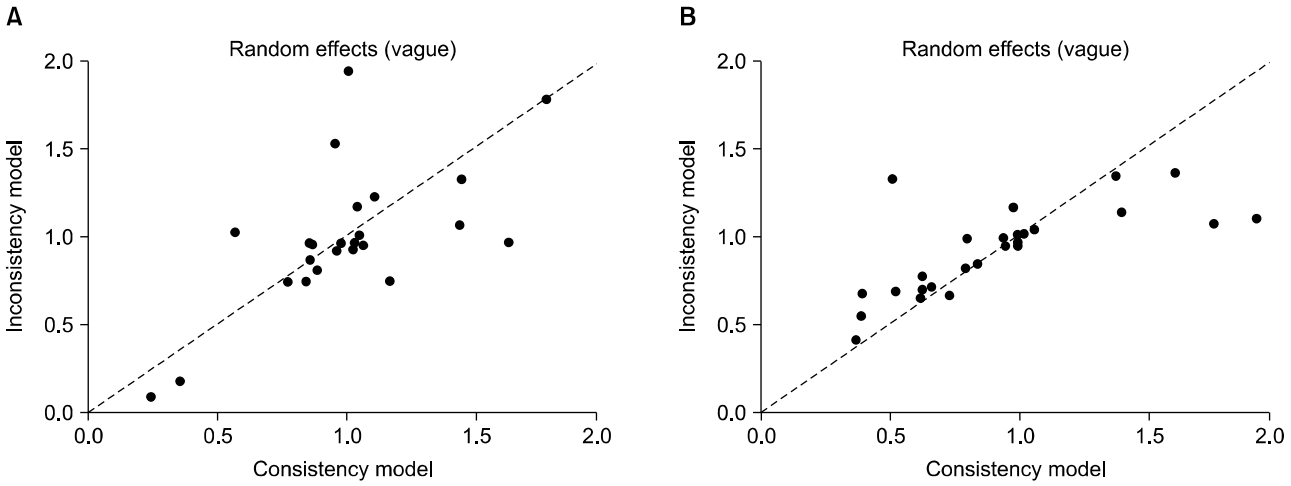

Figure 4. Inconsistency plots for efficacy (A) and safety (B) of febuxostat, allopurinol, and placebo. Plot of the posterior mean deviance contribution of individual data points for the consistency model (horizontal axis) and the unrelated mean effects model (vertical axis), along with the line of equality.

Table 4. Sensitivity analysis of the network meta-analysis comparing the random- and fixed-effects models

Comparison	Random-effects model		Fixed-effects model	
	OR	95% CrI	OR	95% CrI
Efficacy				
Febuxostat 40 mg vs. allopurinol	1.16	0.62～2.06	1.22	1.00～1.47
Febuxostat 120 mg vs. febuxostat 80 mg	2.06	1.16～4.12	1.89	1.46～2.45
Febuxostat 80 mg vs. febuxostat 40 mg	3.01	1.66～5.52	2.78	2.26～3.41
Febuxostat 80 mg vs. allopurinol	3.49	1.97～5.91	3.37	2.83～4.03
Febuxostat 120 mg vs. febuxostat 40 mg	6.22	3.16～13.62	5.24	3.91～7.10
Febuxostat 120 mg vs. allopurinol	7.17	3.86～14.09	6.37	4.92～8.29
Allopurinol vs. placebo	319.39	76.45～2,501.25	313.87	82.99～2,304.15
Febuxostat 40 mg vs. placebo	367.65	90.66～2,806.62	381.24	101.31～2,794.08
Febuxostat 80 mg vs. placebo	1,109.63	268.89～8,382.23	1,054.30	281.45～7,800.31
Febuxostat 120 mg vs. placebo	2,327.75	539.96～18,986.14	2,000.80	525.76～14,947.68
Safety				
Placebo vs. febuxostat 120 mg	0.50	0.14～1.17	0.54	0.23～1.15
Febuxostat 40 mg vs. febuxostat 120 mg	0.57	0.20～1.75	0.56	0.34～0.95
Placebo vs. febuxostat 80 mg	0.59	0.17～1.17	0.68	0.29～1.42
Placebo vs. allopurinol	0.65	0.17～1.27	0.71	0.30～1.50
Febuxostat 40 mg vs. febuxostat 80 mg	0.66	0.23～1.83	0.71	0.49～1.01
Febuxostat 40 mg vs. allopurinol	0.72	0.24～2.03	0.74	0.51～1.06
Allopurinol vs. febuxostat 120 mg	0.78	0.37～1.96	0.76	0.50～1.18
Febuxostat 80 mg vs. febuxostat 120 mg	0.85	0.42～1.98	0.80	0.52～1.23
Allopurinol vs. febuxostat 80 mg	0.86	0.21～2.54	0.96	0.71～1.28
Febuxostat 40 mg vs. placebo	0.92	0.46～1.90	1.05	0.47～2.52

CrI: credible interval, OR: odds ratio.

ment of the target sUA level with febuxostat 40 mg vs. allopurinol (OR 1.16, 95% CrI 0.62 to 2.06) did not change significantly after removing outlier studies (OR 1.13, 95% CrI 0.58 to 1.99). Same pattern of sensitivity analysis was also observed in the network meta-analysis of the safety, i.e., OR for the number of patients withdrawn due to AEs with febuxostat 120 mg vs. allopurinol (OR 0.78, 95% CrI 0.37 to 1.96) was not affected menacingly after removing the outlier studies (OR 0.71, 95% CrI 0.29 to 1.62). In addition, random- and fixed-effects model results also indicated that the results of this network meta-analysis are robust (Table 4).

DISCUSSION

Bayesian network meta-analysis synthesizes all available direct and indirect data to allow for simultaneous comparisons of different treatment options [21,22], whereas traditional meta-analyses do not rank the efficacy and safety of treatments and do not provide sufficient information to guide physicians' decision-making. We conducted a Bayesian network meta-analysis to compare the efficacy and safety of febuxostat at different doses in hyperuricemic patients with or without gout, because this analysis enables an indirect comparison of multiple treatments, which are either lacking in or have insufficient direct head-to-head comparisons.

The cornerstone of gout treatment is the achievement of a target sUA level <6 mg/dL [3]. This goal is based on the solubility of urate at 37°C (6.8 mg/dL), levels below which have been associated with a lower risk of gout flares and tophi [40]. This network meta-analysis assessed 5 types of interventions in hyperuricemic patients with or without gout based on the number of patients with an sUA level <6.0 mg/dL and the number of patients withdrawn due to AEs. In terms of efficacy, febuxostat at any dose and allopurinol were beneficial in achieving the target sUA level compared to placebo. Our network meta-analysis suggests that febuxostat 120 mg is the most effective in the treatment of hyperuricemia, followed by febuxostat 80 mg, febuxostat 40 mg, allopurinol (100 to 300 mg/d), and placebo. Febuxostat 120 mg and febuxostat 80 mg were effective in reducing sUA in hyperuricemic patients with or without gout compared with al-

lopurinol, whereas the urate-lowering efficacy of febuxostat 40 mg was comparable with that of allopurinol 100/300 mg (OR 1.16, 95% CrI 0.62 to 2.06). When target sUA levels are not achieved with febuxostat 40 mg daily or allopurinol 300 mg, the evidence suggests that dose titration to febuxostat 80 mg or febuxostat 120 mg may be a rational alternative to increasing allopurinol doses beyond 300 mg.

With respect to safety, febuxostat 120 mg had the lowest probability of being the safest treatment, based on the number of withdrawals due to AEs. This network meta-analysis suggests comparable safety among the different febuxostat dosages, allopurinol, and placebo, although there was a non-significant trend towards more withdrawals due to AEs from febuxostat 120 mg, to febuxostat 80 mg, allopurinol, placebo, and febuxostat 40 mg. Allopurinol is effective in the treatment of hyperuricemia, but it can occasionally induce severe adverse reactions, such as hematologic cytopenia, hepatitis, vasculitis, and the potentially life-threatening allopurinol hypersensitivity syndrome [5,6]. However, no severe rashes or hypersensitivity reactions were found with febuxostat use in previous clinical trials. Thus, febuxostat is considered as a potentially safe and efficacious alternative.

The results of this network meta-analysis, which combined evidence from both direct and indirect comparisons of the relative efficacy and safety of febuxostat and allopurinol, were in agreement with the result of a meta-analysis of direct comparisons; febuxostat 80 mg and febuxostat 120 mg provided a statistically significant improvement in the number of patients achieving an sUA level <6.0 mg/dL compared to allopurinol 100/300 mg and treatment discontinuation due to adverse reactions was not significantly different between febuxostat and allopurinol [18]. Additionally, our network meta-analysis ranked the efficacy and safety of treatments and provided evidence to optimally inform decision-making.

However, our results should be interpreted with caution because of the several shortcomings of our study. First, the follow-up times ranged widely, from 4 weeks to 52 weeks, with most being of short duration (<6 months). This might be too short for an evaluation of the long-term effects. Comparative studies with longer follow-up periods in the future are warranted. Second, there was heterogeneity in the design and patient characteristics of the included trials; thus, there is the possibility that these differences across studies affected the results of this network meta-analysis. Most patients included in this analysis (n=3,667) were hyperuricemic with gout, and 3 studies (n=432) included patients with hyperuricemia and some gout patients (46.3% to 57.0%) [12-14]. Asymptomatic hyperuricemia does not usually require treatment, and evidence of febuxostat in patients with hyperuricemia only is insufficient and needed. Third, this study did not comprehensively address the efficacy and safety outcomes of febuxostat and allopurinol in hyperuricemic patients with or without gout. This study only focused on effectiveness, based on the number of patients achieving an sUA level <6.0 mg/dL, and on safety, based on the number of patients withdrawn due to AEs, without assessing various outcomes. Specifically, the number of withdrawals due to AEs may not be sufficient to assess safety because of its low frequency.

Nevertheless, this meta-analysis has a number of strengths. The number of patients in each individual study ranged from 67 to 1,768, and this analysis included a total of 4,099 patients. Network meta-analyses synthesize all available data to allow for simultaneous comparisons of different treatment options that lack direct head-to-head comparisons [21,22]. In contrast with the individual studies, we were able to provide more accurate data by increasing the statistical power and resolution through pooling the results of independent analyses and ranking of the efficacy and safety of febuxostat at the doses tested and allopurinol.

CONCLUSION

In conclusion, by using a Bayesian network meta-analysis involving 8 RCTs comparing the urate-lowering efficacy of 5 different interventions, we found that febuxostat 80 mg and febuxostat 120 mg were more efficacious than allopurinol (100 to 300 mg) and that febuxostat 40 mg and allopurinol were comparable. The safety of febuxostat at all doses was comparable with that of allopurinol. Further long-term studies are needed to determine the relative efficacy and safety of febuxostat and allopurinol in a large number of hyperuricemic patients with gout.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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