Risk of Cutaneous Adverse Reactions Associated with Allopurinol or Febuxostat in Real-World Patients

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Background

- The risk of severe cutaneous adverse reactions (SCARs) associated with allopurinol has limited its use, and febuxostat, a novel xanthine-oxidase inhibitor, has become an alternative for patients with gout.
- Although there were no cases of SCARs in clinical trials of febuxostat, safety concerns have been raised after life-threatening febuxostat-related cutaneous adverse reactions identified during post-marketing surveillance.
  - According to reports from Taiwan National Adverse Drug Reactions Reporting System between March 1, 2012 to May 14, 2015, there were 25 cases of febuxostat-related cutaneous adverse reactions, including 4 cases of SCARs (Stevens-Johnson syndrome/ drug rash with eosinophilia and systemic symptoms).

Objective

- The aim of this study is to investigate the risk of cutaneous adverse reactions associated with allopurinol or febuxostat in real-world patients.

Methods

- Data source: Taiwan's National Health Insurance Research Database
- Study design: a nationwide cohort study
- Study population:
  - New users of allopurinol: patients received allopurinol prescriptions without prior use in the past 3 years, and those received febuxostat in the past 3 months were excluded
  - New users of febuxostat: patients received febuxostat prescriptions without prior use in the past 3 years, and those received allopurinol in the past 3 months were excluded
  - The date of the first prescription of allopurinol or febuxostat were defined as cohort entry date.
- Study outcome
  - Primary outcome: cutaneous adverse reactions
  - Secondary outcome: fatal cutaneous adverse reactions (mortality within 2 months after the cutaneous adverse reactions)
- Cutaneous adverse reactions:
  - Patients had diagnosis with ICD-9-CM code 693.0, 695.1, 695.89, and 695.9 within 3 months after the first prescription
  - No further use of the study drug within 6 months after the episode
  - The accuracy of the diagnostic codes have been validated in previous study using hospital system–based medical records[1]
- Study period: March 1, 2012 to June 30, 2015
  - Each patient was followed from cohort entry date until the earliest occurrence of the following:
    - Cutaneous adverse reactions
    - Discontinue use of allopurinol or febuxostat for more than 28 days
    - Switch between allopurinol and febuxostat
    - Death
    - 3 months after first prescription of the study drug
- Poisson regression was used to estimate the rate ratios (RRs) and 95% confidence intervals (CIs)

Results

- Febuxostat new users had older age, higher Charlson Comorbidity Index, and higher proportion with renal and liver diseases compared with allopurinol new users. Higher initial dosage, higher proportion prescribed by medical centers, and higher proportion prescribed by nephrologists were also found in the first prescriptions of febuxostat.
- There were 575 cases of cutaneous adverse reactions occurred during study period; 524 among allopurinol new users and 51 among febuxostat new users. Among patients developed cutaneous adverse reactions, 71 allopurinol new users and 4 febuxostat new users died within 2 months.
- Compared with febuxostat, allopurinol was associated with a 5-fold risk of cutaneous adverse reaction and a 13-fold risk of fatal cutaneous adverse reaction.

Conclusions

- In real world patients, febuxostat was associated with a lower risk of cutaneous adverse reactions compared to allopurinol.
- Nevertheless, continuous post-marketing surveillance is warranted as a few febuxostat related-fatal cutaneous adverse reactions were observed.

References

1. Yang CY, Chen CH, Deng ST, et al. Allopurinol use and risk of fatal hypersensitivity reactions: a nationwide population-based study in Taiwan. *JAMA Intern Med.* 2015;175(9):1550-1557.

Patient and Provider Characteristics of Allopurinol New users and Febuxostat New Users

	Allopurinol New Users		Febuxostat New Users		P-value [a]
	N	%	N	%	
Number of patients	187,337		51,569		
Sex					
Male	140,159	74.8	37,261	72.3	<0.0001
Female	47,178	25.2	14,308	27.7	
Age, year					
Mean (SD)	57.17 (17.22)		65.56 (15.65)		<0.0001
0-19	2,651	1.4	122	0.2	
20-39	31,350	16.7	3,783	7.3	
40-59	69,251	37.0	13,625	26.4	<0.0001
60-79	65,439	34.9	23,753	46.1	
80+	18,646	10.0	10,286	19.9	
CCI [b]					
Mean (SD)	1.43 (1.76)		2.73 (2.06)		<0.0001
0	79,478	42.4	8,309	16.1	
1	38,398	20.5	7,591	14.7	<0.0001
2	28,355	15.1	10,107	19.6	
3+	41,106	21.9	25,562	49.6	
Comorbidities [b]					
Renal disease	25,151	13.4	24,412	47.3	<0.0001
Liver disease	24,580	13.1	7,559	14.7	<0.0001
First prescriptions					
Initial dosage, DDD					
Mean (SD)	0.44 (0.33)		0.71 (0.53)		<0.0001
Low, ≦1DDD	181,878	97.09	35,307	68.47	<0.0001
High, >1DDD	5,459	2.91	16,262	31.53	
Hospital accreditation level of providers					
Medical center	29,166	15.6	21,577	41.8	
Regional hospital	45,202	24.1	17,725	34.4	<0.0001
District hospital	33,409	17.8	7,163	13.9	
Clinic	79,560	42.5	5,104	9.9	
Physician specialties of providers					
General medicine	36,272	19.4	5,432	10.5	
Family medicine	33,768	18.0	3,324	6.4	
Nephrology	15,838	8.5	20,182	39.1	
Orthopedics	26,408	14.1	1,359	2.6	<0.0001
Cardiology	11,765	6.3	5,306	10.3	
Rheumatology	10,628	5.7	6,196	12.0	
Others	52,658	28.1	9,770	18.9	

SD=standard deviation; CCI=Charlson Comorbidity Index; DDD=defined daily dose
a: Chi-square tests for categorical variables; t-tests for continuous variables
b: Within 3 years before cohort entry date

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	Allopurinol	Febuxostat	Crude RR (95%CI)	Adjusted RR (95% CI)
New users	187,337	51,569		
Person-years	31,761	11,247		
Cutaneous adverse reactions	524	51		
Incidence per 1000 person-years	16.50	4.53	3.64 (2.73-4.85)	4.96 (3.67-6.70) [a]
Fatal cutaneous adverse reactions	71	4		
Incidence per 1000 person-years	2.24	0.36	6.29 (2.30-17.21)	13.00 (4.62-36.59) [b]

RR=rate ratio, CI=confidence interval
a: adjusted for sex, age, initial daily dose, history of renal disease and liver disease
b: adjusted for sex, age, initial daily dose, Charlson comorbidity index, history of renal disease and liver disease

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