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
- 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