Allopurinol Use and Associated Cutaneous Adverse Reactions after Market Entry of Febuxostat

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Background

- Allopurinol has been widely used as first-choice urate-lowering therapy. However, its cutaneous adverse reactions (CARs) is notorious.
  - From 2008 to 2015, a total of 212 cases of suspected allopurinol-related CARs have been submitted to the Taiwan Drug Relief Foundation for compensations, and 42% of them were fatal cases.
- Febuxostat, a novel drug with lower risk of CARs reported in clinical trial, was approved by Taiwan FDA in 2011 and reimbursed by Taiwan's National Health Insurance (NHI) in 2012.

Initial reimbursement	*Reimbursement coverage expansion*
2012.04	*2014.03*
Criteria: patients who have used both allopurinol and benzbromarone and have experienced treatment failure or intolerance	*Criteria: patients who have experienced treatment failure with benzbromarone or had a history of chronic renal or liver diseases*

Objective

- To investigate the impact of the market entry of febuxostat on allopurinol use and associated cutaneous adverse reactions.

Methods

- Data source: Taiwan's National Health Insurance Research Database
- The study period was divided into 3 periods:

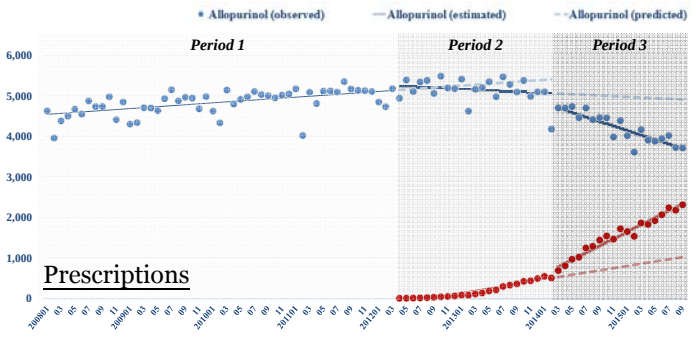
Period 1	*Period 2*	*Period 3*
2008.01-2012.03	*2012.04-2014.02*	*2014.03-2015.09*
before febuxostat reimbursed	*after the initial reimbursement of febuxostat*	*after the reimbursement coverage of febuxostat expanded*

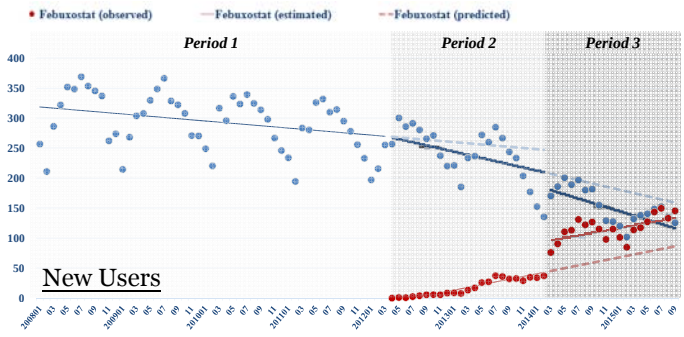
- Use of allopurinol and febuxostat (prescriptions and new users) were assessed monthly, and an interrupted time series design with segmented regression models was used to estimate level, trend, level changes, and trend changes in each period.
  - At the end of period 2 and period 3, relative changes were also calculated by comparing the estimated values to the predicted values (values estimated as if the reimbursement scheme had not changed).
- CARs among new users of allopurinol and febuxostat (number of cases and incidence rates) were assessed monthly, and a before-after design was used to compare the difference between periods.
- For more details about the definition of new users and cutaneous adverse reactions please refer to ***Poster no. 641***.

Results

- Allopurinol prescriptions and new users reduced by 6.3% and 15.2% respectively after the initial reimbursement of febuxostat (at the end of period 2), and further reduced by 24.8% and 27.4% respectively after the reimbursement coverage of febuxostat expanded (at the end of period 3).
- After the market entry of febuxostat, number of allopurinol associated CAR cases declined; however, incidence rates did not change apparently.

Trends in Prescriptions and New Users





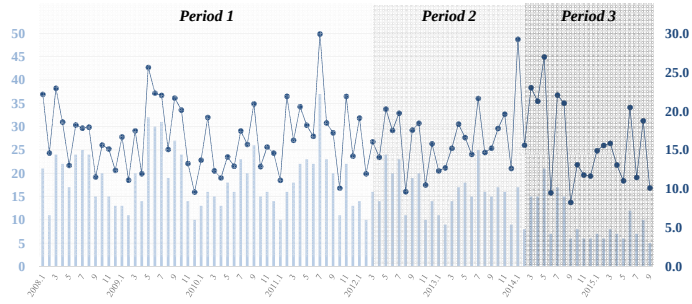
Allopurinol	Period 1		Period 2			Period 3		
	Level (*P*)	Trend (*P*)	Level change (*P*)	Trend change (*P*)	*Relative change (95% CI)* [b]	Level change (*P*)	Trend change (*P*)	*Relative change (95% CI)* [b]
Prescriptions [a]	4,532 (<0.05)	12 (<0.05)	+112 (0.13)	-20 (<0.05)	-6.3% (-10.5, -2.1)	-316 (<0.05)	-48 (<0.05)	-24.8% (-29.7, -20.0)
New users [a]	319 (<0.05)	-1 (<0.05)	+1 (0.86)	-2 (<0.05)	-15.2% (-23.2, -7.2)	-26 (<0.05)	-1 (0.25)	-27.4% (-42.5, -12.3)

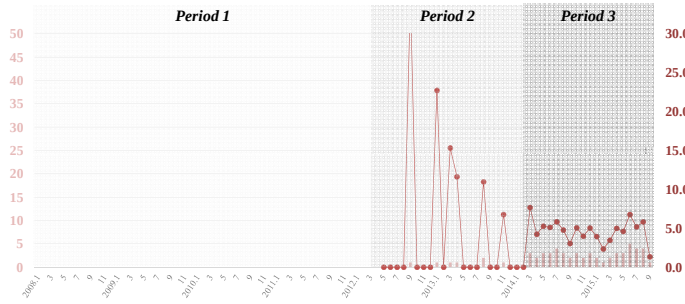
a: per million insured; b:relative changes were estimated at the end of period 2 and period 3

Febuxostat	Period 1	Period 2		Period 3		
		Level (*P*)	Trend (*P*)	Level change (*P*)	Trend change (*P*)	*Relative change (95% CI)* [b]
Prescriptions [a]		-131 (<0.05)	27 (<0.05)	+201 (<0.05)	+59 (<0.05)	+129.8% (+82.3, +177.3)
New users [a]		-10 (<0.05)	2 (<0.05)	+52 (<0.05)	-1 (0.47)	+55.0% (+34.5, +75.6)

a: per million insured; b:relative changes were estimated at the end of period 3

Trends in Cutaneous Adverse Reactions (CARs)





Allopurinol	Period 1	Period 2	Period 3
	Mean ± SD	Mean ± SD	Mean ± SD
No. of CAR cases [a]	18.78 ± 6.15	15.74 ± 4.67	9.68 ± 4.57
Incidence of CARs [b]	16.69 ± 4.26	16.50 ± 4.08	15.78 ± 5.25

a: per month; b: per 1000 person-years

Febuxostat	Period 1	Period 2	Period 3
	Mean ± SD	Mean ± SD	Mean ± SD
No. of CAR cases [a]	–	0.32 ± 0.55	2.79 ± 1.00
Incidence of CARs [b]	–	4.65 ± 9.02	4.65 ± 1.44

a: per month; b: per 1000 person-years

Conclusions

- New users of allopurinol substantially decreased after the reimbursement coverage of febuxostat expanded.
- Simultaneously, there was a decrease in the number of allopurinol related-CAR cases.
- However, no remarkable change in the incidence rates of allopurinol related-CARs was observed.

Acknowledgement : Funding for this project was provided by Food and Drug Administration, Ministry of Health and Welfare, Taiwan.
Conflict of Interest : All authors declared having no conflicts of interest that are directly relevant to the content of this study.
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