Characteristics of Febuxostat and Allopurinol Initiators and Utilization Patterns in Real-World Settings

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Disclosure

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- **Disclaimer:** The views expressed in this presentation are the author's and do not necessarily reflect the views of the U.S. FDA

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Overview

- CARES trial

- Objective and methods

- Results

- Discussion

- Conclusions

Background

Febuxostat (Uloric®) selective inhibitor of xanthine oxidase used in gout

- Lowers serum uric acid levels by inhibiting the conversion of xanthine to uric acid

- Concerns about cardiovascular (CV) safety in pre-approval studies

- Approved by FDA in February 2009
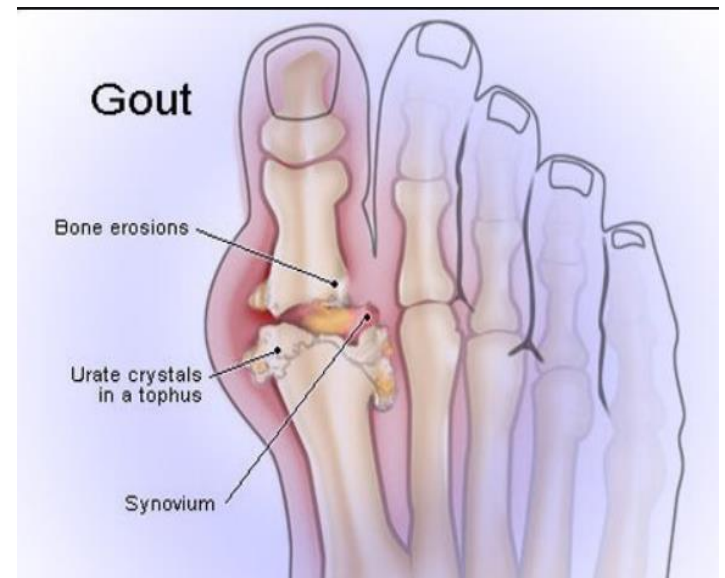
FDA required a post-market safety RCT to determine if febuxostat increased risk of serious adverse CV outcomes compared to allopurinol

Background
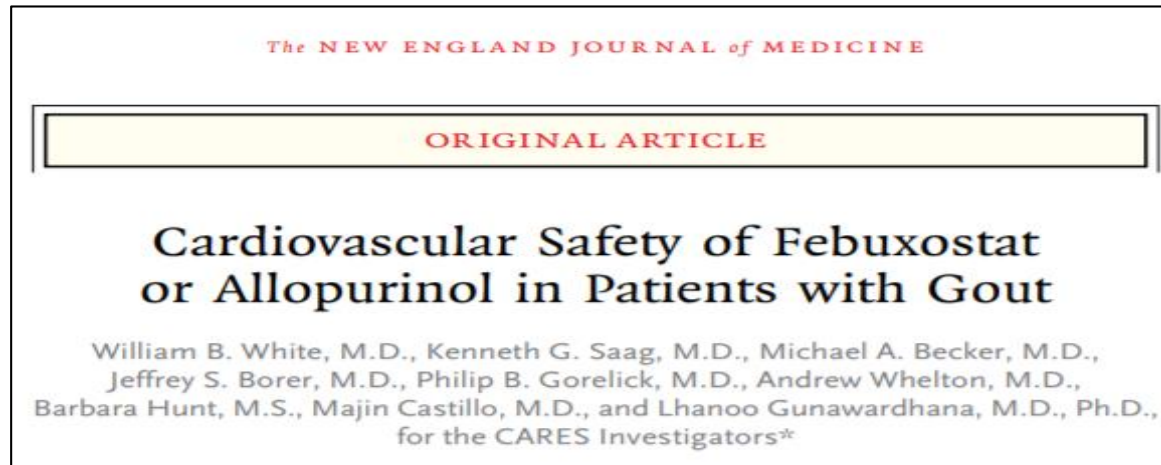
– Multicenter, randomized, double-blind, CV outcome safety study conducted in the U.S., Canada and Mexico

– Increased risk of

- *Cardiovascular mortality (HR 1.34 95% CI, 1.03 -1.73)*
- *All-cause mortality (HR 1.22 95% CI, 1.01-1.47)*

in febuxostat vs. allopurinol users

Background

- CARES study population enriched for CVD

- Concerns about generalizability of trial findings to gout patients in real world settings

Objective

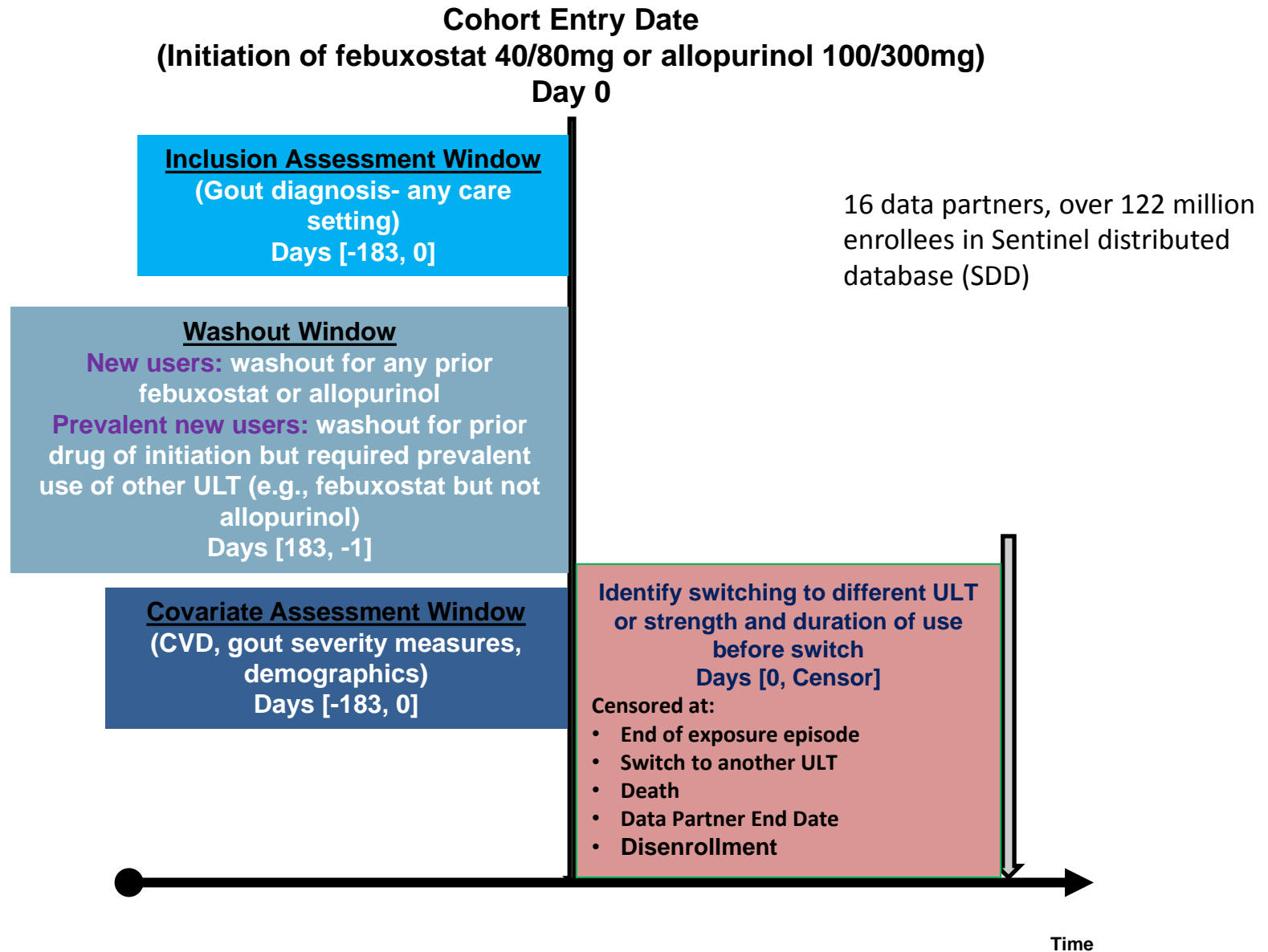- To determine if characteristics of patients and ULT utilization in the CARES trial reflect those in real-world settings using the Sentinel Distributed Database (SDD)

  1. *Characteristics of the gout population*
  2. *Characteristics, duration of use and switching patterns among both new users and prevalent new users of febuxostat and allopurinol*
  3. *Comparison with CARES population*

Methods

Figure 1. Retrospective cohort study in Sentinel January 1, 2009 to March 31, 2018

Cohort Entry Date
(Initiation of febuxostat 40/80mg or allopurinol 100/300mg)
Day 0

Inclusion Assessment Window
(Gout diagnosis- any care setting)
Days [-183, 0]

16 data partners, over 122 million enrollees in Sentinel distributed database (SDD)

Washout Window
New users: washout for any prior febuxostat or allopurinol
Prevalent new users: washout for prior drug of initiation but required prevalent use of other ULT (e.g., febuxostat but not allopurinol)
Days [183, -1]

Covariate Assessment Window
(CVD, gout severity measures, demographics)
Days [-183, 0]

Identify switching to different ULT or strength and duration of use before switch
Days [0, Censor]
Censored at:
- **End of exposure episode**
- **Switch to another ULT**
- **Death**
- **Data Partner End Date**
- **Disenrollment**

Time

Results

Characteristics of the Gout Population

	Patients with at least one gout diagnosis	
Number of unique patients	5,714,400	
	N	%
Demographics		
Age: 21-44	442,553	7.7
Age: 45-64	1,497,999	26.2
Age: 65+	3,773,848	66.0
Gender (Male)	3,579,534	62.6
Ever use of ULT following gout diagnosis		
Febuxostat	248,246	4.3
Allopurinol	2,644,794	46.3
Probenecid	94,443	1.7
Pegloticase	204	0.0

- *Most gout patients aged 65+*
- *More males than females were diagnosed*
- *Allopurinol was the most commonly used ULT following a gout diagnosis, febuxostat use appeared rare in comparison (4.3%)*

Characteristics of new users of Febuxostat and Allopurinol

	Febuxostat		Allopurinol	
	N	%	N	%
Number of unique patients	96,057		1,239,654	
Age: 21-44	7,505	7.8	102,413	8.3
Age: 45-64	24,570	25.6	333,515	26.9
Age: 65+	63,982	66.6	803,726	64.8
Gender (Male)	61,176	63.7	815,418	65.8

- *Slightly more febuxostat initiators were aged 65 years +*
- *Allopurinol initiators were slightly more likely to be male*

Characteristics of prevalent new users* of Febuxostat and Allopurinol

	Febuxostat		Allopurinol	
	N	%	N	%
Number of unique patients	83,034		27,331	
Age: 21-44	5,443	6.6	1,630	6.0
Age: 45-64	20,399	24.6	6,309	23.1
Age: 65+	57,192	68.9	19,392	71.0
Gender (Male)	53,357	64.3	17,652	64.6

- *Number of allopurinol users decreases dramatically as fewer gout patients were prevalent users of febuxostat that then switched to allopurinol*
- *Slightly more allopurinol users were aged 65 years +*

prevalent new use was defined using a 183 day washout with respect to the initiating drug but allowed prevalent use of other ULT in the prior 183 days

CVD History, Gout Severity and CKD in new users of ULT

	Febuxostat (n= 96,057)		Allopurinol (n=1,239,654)	
	N	%	N	%
Baseline cardiovascular history				
Myocardial infarction	1,507	1.6	19,393	1.6
Unstable angina	1,565	1.6	19,311	1.6
Stroke	2,644	2.8	36,635	3.0
Transient ischemic attack	671	0.7	9,242	0.7
Perpheral vascular disease	3,973	4.1	47,557	3.8
Diabetic macro- or microvascular disease	8,559	8.9	96,811	7.8
Baseline gout severity measures				
Tophi	14,974	15.6	112,377	9.1
Gouty arthritis	57,226	59.6	584,548	47.2
Kidney stones	10,931	11.4	114,833	9.3
Gout flares	74,833	77.9	862,060	69.5
Tophi and gouty arthritis	11,944	12.4	96,811	7.8
Chronic kidney disease	13,447	14.0	8,399	0.7

- *CVD at baseline was similar between initiators of febuxostat and allopurinol*
- *Initiators of febuxostat tended to have more severe gout than allopurinol initiators*
- *Febuxostat initiators were more likely to have CKD*

CVD History, Gout Severity and CKD in prevalent new ULT users

	Febuxostat (n=83,034)		Allopurinol (n= 27,331)	
	N	%	N	%
Baseline cardiovascular history				
Myocardial infarction	1,431	1.7	519	1.9
Unstable angina	1,511	1.8	517	1.9
Stroke	2,279	2.7	1,006	3.7
Transient ischemic attack	607	0.7	249	0.9
Perpheral vascular disease	3,631	4.4	1,491	5.5
Diabetic macro- or microvascular disease	8,320	10.0	3,051	11.2
Baseline gout severity measures				
Tophi	13,445	16.2	5,015	18.3
Gouty arthritis	52,145	62.8	17,824	65.2
Kidney stones	10,214	12.3	3,375	12.3
Gout flares	68,619	82.6	22,283	81.5
Tophi and gouty arthritis	10,973	13.2	4,117	15.1
Chronic kidney disease	12,762	15.4	4,555	16.7

- *CVD at baseline was similar between febuxostat and allopurinol users*
- *Gout severity measures more balanced compared to new users*
- *CKD was also similar*

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Discussion

Comparison with CARES Trial

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Comparison of demographics and clinical characteristics among CARES and SDD patients

	CARES		SDD prevalent new users		SDD new users	
	Febuxostat (n=3,098)	Allopurinol (n= 3,092)	Febuxostat (n=83,034)	Allopurinol (n=27,331)	Febuxostat (n=96,057)	Allopurinol (n=1,239,65)
Aged 65 years+ (%)	48.9	51.3	68.9	71	6.6	64.8
Male (%)	84.1	83.8	64.3	64.6	63.7	65.8
History of MI (%)	38.6	39.8	1.7	1.9	1.6	1.6
History of stroke (%)	14.8	13.3	2.7	3.7	2.8	3.0
Median duration of use (days)	728	719	150	151	120	147
CKD	92.1	92.5	15.4	16.7	14	0.7
Tophi	21.6	21.0	16.2	18.3	15.6	9.1

ULT users in the CARES trial

1. Younger than in real-world settings

2. More males than in real-world settings

3. Higher prevalence of both CVD and CKD than real-world settings

4. Had more severe gout

Conclusions

- Important differences in characteristics of ULT initiators in SDD compared to CARES trial

- In real world settings, ULT initiators were older and less likely to have recent CVD or CKD

- Persistence was poorer in the real-world settings

- Differences need to be considered in interpreting the generalizability of the CARES study

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Top switching patterns among new users

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Switching scenarios	New Users Switched (%)	Median time to switch in (days)
Allopurinol (100mg) to Allopurinol (300mg)	14	66
Febuxostat (any strength) to Allopurinol (any strength)	10	57
Febuxostat (40mg) to Febuxostat (80mg)	9	76
Allopurinol (300mg) to Allopurinol (100mg)	7	46
Febuxostat (40mg) to Allopurinol (100mg)	6	49

- *The proportion of new users that switched between ULTs was low (generally < 10%)*
- *The largest proportion of new user switches occurred from:*
  - *allopurinol 100 mg to 300 mg*
  - *febuxostat 40 mg to febuxostat 80 mg*
- *Median time to switch was longest for febuxostat 80mg to febuxostat 40mg*

Top switching patterns among prevalent new users

Switching scenarios	New Users Switched (%)	Median time to switch in (days)
Febuxostat (any strength) to Allopurinol (any strength)	24	42
Allopurinol (any strength) to Febuxostat (any strength)	19	31
Allopurinol (100mg) to Febuxostat (40mg)	15	30
Febuxostat (80mg) to Allopurinol (300mg)	15	46
Febuxostat (40mg) to Allopurinol (100mg)	14	39

- *The proportion of switches between ULTs higher among prevalent new users compared to new users*
- *The largest proportion of prevalent new user switches occurred from:*
  allopurinol 100 mg to febuxostat 40 mg
- *Median time to switch longest for febuxostat 80mg to allopurinol 300mg*