Clinical Rheumatology (2019) 38:263–265
https://doi.org/10.1007/s10067-018-4396-4

LETTER TO THE EDITOR

Gout lessons from 2018: CARES, a direct comparison of febuxostat vs allopurinol, and CANTOS, IL1 blocker for cardiovascular risk minimisation

Tim L. Th. A. Jansen[1] · Matthijs Janssen[1]

Received: 29 November 2018 / Accepted: 4 December 2018 / Published online: 12 December 2018

Abstract
In the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial conducted by White et al. (March 29 issue from NEJM), all-cause mortality and cardiovascular mortality are found to be higher among patients randomly assigned to febuxostat compared to allopurinol, but significant flaws are a clear lack of treat to target strategy with more powered treatment in the febuxostat arm, dysbalance with cardiovascular risk factors selectively in again the febuxostat arm, and discontinuation of the trial regimen in over 50% of patients with discontinuation of follow-up in about 45%. With these flaws, conclusions such as febuxostat-associated higher mortality are potentially if not probably incorrect, and thus febuxostat to be used not as first-line therapy may well be an invalid consequence? The paper here describes potential lessons to be taken.

Keywords Canakinumab · Dysbalance · Febuxostat · Gout · Mortality

In the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial conducted by White et al. (March 29 issue from NEJM) [1], all-cause mortality and cardiovascular mortality are found to be higher among 6190 patients randomly assigned to febuxostat compared to allopurinol; the 3098 patients who received febuxostat had lower serum urate levels up to month 72 than the 3092 patients receiving allopurinol. However, discontinuation of the trial regimen occurred quite frequently: 56.6% with discontinuation of follow-up in 45%. Still, these findings have led the authors to conclude that febuxostat is associated with a higher mortality, and have led others to conclude that febuxostat should not be used as first-line therapy [2].

The worse outcome in the febuxostat group is considered to be consistent with the hypothesis that depletion of uric acid, which accounts for about 50% of total plasma antioxidant capacity, may have unexpected deleterious effects [3]. In the National Health and Nutrition Examination Survey longitudinal study, the group with the level of serum urate in the lowest percentile had a trend toward increased cardiovascular mortality [4]. A previous longitudinal observational study in South Korea showed a similar U-shaped association between serum urate level and mortality [5]. With the exclusion of malnourishment, mortality and serum urate however have turned out to present a J-shaped association [6]. So, it would be premature to state that the lower serum urates are the cause of higher mortality, but additional factors such as malnourishment and possibly NSAID use are to be considered in such evaluations. This shows the complex properties of the metabolic parameter serum urate.

With a better look at the CARES data, many questions remain. In the CARES trial, the proportion of patients with a serum urate level below 5.0 mg per dl (0.30mmol/L) during treatment was approximately 50% higher among patients assigned to febuxostat than among those assigned to allopurinol, this is due to difference in potency of urate lowering capacity: allopurinol 600 mg QD is equipotent to 80 mg febuxostat, as stated before [7], see Table 1.

In the febuxostat group, 61% is exposed to a sub 80 mg febuxostat dose which is similar to allopurinol 100–500 mg QD with an exposure being 96% revealing the significant lower percentage of patients at a potent urate lowering dose, or the alternative perspective, 38% in the febuxostat arm is

✉ Tim L. Th. A. Jansen
tjansen@viecuri.nl; tljansen@fo.nl

[1] Department of Rheumatology, Viecuri MC, Venlo, The Netherlands

Table 1 Equipotent urate-lowering doses are given with 300 mg allopurinol about equipotent to 40 mg febuxostat with percentage of patients receiving the respective dose in CARES

Potency table regarding urate-lowering effect	Allopurinol	Febuxostat
	100 mg QD: 0%	na
	200 mg QD: 22%	na
	300 mg QD: 45%	40 mg QD: 61%
	400 mg QD: 25%	na
	500 mg QD: 4%	na
	600 mg QD: 4%	80 mg QD: 39%

na not applicable, *QD* per day, percentage of users

using the potent 80 mg QD febuxostat versus an equipotent allopurinol of 600 mg in only 4% in the allopurinol arm. The effect at a group level can be seen in the obtained serum urate levels, i.e. serum urate < 5.0 mg/dL in Fig. 1.

Whether this firmer reduction in the serum urate level in the febuxostat group was itself deleterious or whether it was due to combination or association with other deleterious factors is unclear, but it is speculative to correlate this with a more pronounced change in antioxidant capacity due to the absolute amount of urate being the explanation for increased mortality. An alternative explanation is already given in dysbalancing the treatment arms such as a more frequent exposure to non-steroidals or more non-aspirin in the potently treated febuxostat arm: in the appendixed tables, it is reported that non-steroidal use is 4.8% in febuxostat vs 2.2% in allopurinol group with a relative risk of 2.17 (p 0.032), and non-aspirin use 5.3% vs 2.7%, relative risk 1.99 (p 0.0001). Dysbalance is also found in percentage of patients exceeding a history of 10 years of being sufferer from gout, being obese with BMI > 30, being male, being over 65 years of age, colchicine use, or use of antihyperlipidemics, see Table 2.

Two major prognostic factors and seven additional negative factors are giving weight in the febuxostat arm and may thus contribute to the unfavourable outcome in the febuxostat arm. Final conclusions from CARES are not convincing on the issue of febuxostat being significantly worse for the all-cause or cardiovascular mortality, but clearly show a significant problem in study design: lack of treat to target with unbalanced dosing of XOi, many substeps for allopurinol, and only major steps for the powerful febuxostat.

Interpretation of a study where two arms are treated similarly i.e. equipotently to a predefined serum urate target would need equipotent dosing steps such as 300 mg QD and 600 mg QD allopurinol as opposed to 40 mg QD and 80 mg QD febuxostat. Secondly, such a study needs either a randomisation for NSAID use and colchicine/non-colchicine use, or an interleukin 1 inhibitor in both arms. It is an interesting scientific question to combine equipotent urate-lowering

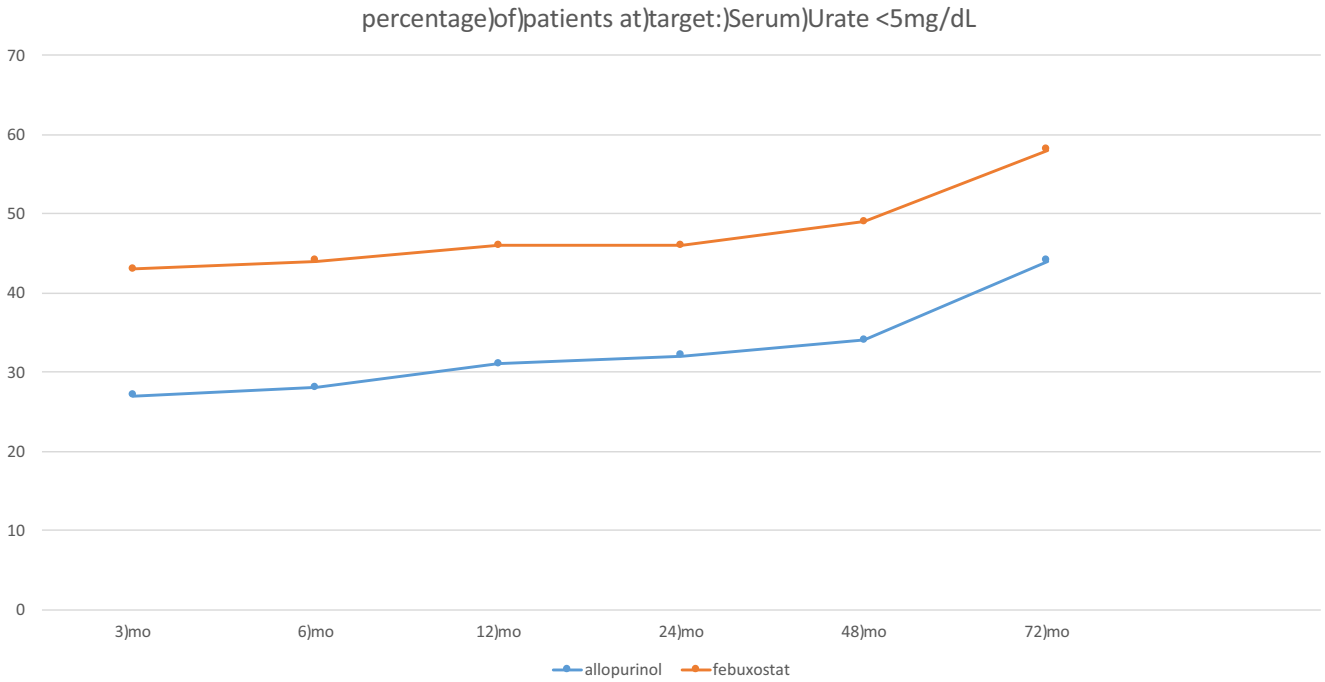

Fig. 1 Percentage of patients at 5 mg/dL (0.30 mM/L) serum urate target in allopurinol arm during treatment more than10% less than in febuxostat arm which is in line with 96% of allopurinol arm is treated with suboptimal dose whereas in febuxostat this is in 61%

Table 2 Dysbalance is found in the febuxostat vs allopurinol arms with > 2% difference in arms weighted as major and about 1% difference as minor, but altogether negative weighting for the mortality in febuxostat-treated arm

	Allopurinol arm (%)	Febuxostat arm (%)
Major factors		
NSAID use	2.2	4.8
Non aspirin use	2.7	5.3
Minor factors		
Age > 65 years	4.0	6.1
Male sex	3.4	4.5
BMI > 30	3.1	4.1
> 10 years gout sufferer	2.7	4.1
Baseline SU > 10 g/dL	6.2	7.0
DM in history	3.5	4.4
Hypertension	3.3	4.5

drugs for the duration of a prolonged period with an interleukin 1 inhibitor, as we already know the beneficial effects of anti-IL1: 50% reduction of attack rates with canakinumab in CANTOS [8, 9]. In combination with IL1 blocking agents, one may even question the need for treating the gout patient to a strict target such as 5 mg/dL (EULAR and BSR) or 6 mg/dL (ACR) [10].

Currently, it is premature to conclude that an increased cardiovascular or all-cause mortality is associated with febuxostat due to a problematic design and consequently unbalance in the arms of CARES etc. Xanthine oxidase inhibition via febuxostat probably still is a good option, probably most cost-effective after proof for allopurinol intolerance. IL1-blocking drugs are still not widely available despite positive cardioprotective effects predominantly due to pricing. Modern randomised controlled gout studies should be treating to a prespecified serum urate target as defined by EULAR and ACR and for these targets equipotent doses of allopurinol (with individual uptitration), should be compared with febuxostat, with an adequate prophylactic regimen excluding bias from NSAIDs. For prophylaxis, ideally an IL1-blocking regimen should be prescribed, or colchicine which is the drug ubiquitously available. If serum targets cannot be reached with XOi alone, one may well need to consider combination therapy with a uricosuric, as stated before [11].

Compliance with ethical standards

Disclosures None.

References

1. White WB, Saag KG, Becker MA, Borer JS, Gorelick PB, Whelton A, Hunt B, Castillo M, Gunawardhana L, CARES Investigators (2018) Cardiovascular safety of febuxostat or allopurinol in patients with gout. N Engl J Med 378:1200–1210
2. Choi H, Neogi T, Stamp L, Dalbeth N, Terkeltaub R (2018) New perspectives in rheumatology: implications of the cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular morbidities trial and the associated FDE public safety alert. A&R 70:1702–1709. https://doi.org/10.1002/art.40583
3. Yeum K-J, Russell RM, Krinsky NI, Aldini G (2004) Biomarkers of antioxidant capacity in the hydrophilic and lipophilic compartments of human plasma. Arch Biochem Biophys 430:97–103
4. Odden MC, Amadu A-R, Smit E, Lo L, Peralta CA (2014) Uric acid levels, kidney function, and cardiovascular mortality in US adults: National Health and Nutrition Examination Survey (NHANES) 1988-1994 and 1999-2002. Am J Kidney Dis 64:550–557
5. Kang E, Hwang S-S, Kim DK, Oh KH, Joo KW, Kim YS, Lee H (2017) Sex-specific relationship of serum uric acid with all-cause mortality in adults with normal kidney function: an observational study. J Rheumatol 44:380–387
6. Tseng WC, Chen YT, Ou SM, Shih CJ, Tarng DC, for the Taiwan Geriatric Kidney Disease (TGKD) Research Group, for the Taiwan Geriatric Kidney Disease (TGKD) Research Group, Tarng DC, Tseng WC, Ou SM, Yang CY, Lin YP, Chuang YF, Chen LK, Wang KY, Chen YH, Tsai MT, Shih CJ, Chen YT, Lin YS, Hung SC, Kuo KL, Hung TP, Hu FH, Chen NJ, Chen YC, Lin CH, Tsai TH, Hsieh SL, Wei YH, Hsu CC, Liu JS, Chang YK, Chiang MH (2018) U-shaped association between serum uric acid levels with cardiovascular and all-cause mortality in the elderly: the role of malnourishment. J Am Heart Assoc 10:7. https://doi.org/10.1161/JAHA.117.007523.
7. Jansen TL, Richette P, Perez-Ruiz F, Tausche AK, Guerne PA, Punzi L, Leeb B, Barskova V, Uhlig T, Pimentão J, Zimmermann-Górska I, Pascual E, Bardin T, Doherty M (2010) International position paper on febuxostat. Clin Rheumatol 29:835–840. https://doi.org/10.1007/s10067-010-1457-8
8. Ridker PM, Everett BM, Thuren T, MacFadyen J, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ, CANTOS Trial Group (2017) Anti-inflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 377:1119–1131
9. Solomon DH, Glynn RJ, MacFadyen JG et al (2018) Relationship of interleukin-1beta blockade with incident gout and serum uric acid levels: exploratory analysis of a randomized controlled trial. Ann Int Med 169:535–542
10. Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castañeda-Sanabria J, Coyfish M, Guillo S, Jansen TL, Janssens H, Lioté F, Mallen C, Nuki G, Perez-Ruiz F, Pimentao J, Punzi L, Pywell T, So A, Tausche AK, Uhlig T, Zavada J, Zhang W, Tubach F, Bardin T (2017) 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 76:29–42. https://doi.org/10.1136/annrheumdis2016U209707.
11. Jansen TL, Perez-Ruiz F, Tausche A-K, Richette P (2018) International position paper on the appropriate use of uricosurics with the introduction of lesinurad. Clin Rheumatol 37:3159–3165. https://doi.org/10.1007/s10067-018-4306-9