Diabetes Research: Open Access

Mini Review

DOI: https://doi.org/10.36502/2021/droa.6178

Up-To-Date Perspectives for Hyperuricemia, Cardiorenal Influence and Urate-Lowering Therapy (ULT)

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Received date: 26 March 2021; **Accepted date**: 17 April 2021; **Published date**: 27 April 2021

Citation: Bando H. Up-To-Date Perspectives for Hyperuricemia, Cardiorenal Influence and Urate-Lowering Therapy (ULT). Diab Res Open Access. 2021 April 27;3(1):16-19.

Abstract

Hyperuricemia is a clinical important problem and its prevalence has been increased. Latest topics are described. The guideline adequately managing gout was published from American College of Rheumatology (ACR). Various optimal uses of urate-lowering therapy (ULT) were presented. The cardiorenal effects of hyperuricemia have been investigated for years. Regarding the patients on chronic kidney disease (CKD) and high risk of progression, ULT with allopurinol did not show the decline in eGFR compared to the control. Recently, dotinurad that is a new selective urate reabsorption inhibitor (SURI) would be applied to medical practice. Low-dose dotinurad showed satisfactory pharmacological efficacy.

Keywords

Hyperuricemia, Urate-Lowering Therapy, Selective Urate Reabsorption Inhibitor, Chronic Kidney Disease, Preventing Early Renal Loss in Diabetes, American College of Rheumatology

Abbreviations

ULT: Urate-Lowering Therapy; SURI: Selective Urate Reabsorption Inhibitor; CKD: Chronic Kidney Disease; PERL: Preventing Early Renal Loss in Diabetes; ACR: American College of Rheumatology

For decades, chronic kidney disease (CKD) has shown increased its incidence, severity and prevalence [1]. From the tremendous health and financial burden, mitigation for CKD exacerbation would be crucial. Among them, hyperuricemia has been clinically important problems and its prevalence has increased. From UK National Health Service (NHS) Digital Hospital Episode Statistics, unplanned admission to hospital due to rheumatoid arthritis (RA) or gout was studied during 2006-2017 [2]. The result showed that RA incidence decreased from 8.6 to 4.3 per 100,000 population/year, while gout incidence increased from 7.9 to 12.5. Furthermore, provided prescriptions of allopurinol and colchicine have increased by 165.6% and 71.4%, respectively during this period. As regards to febuxostat, the prescription number has increased 20-fold for 7 years, when the data of prescription was possible. Thus, these situations suggest the necessity of aggressive target-driven treatment for controlling hyperuricemia and gout [2]. For this article, latest

topics are described for i) the latest guidelines, ii) the cardiorenal effects of gout and hyperuricemia and iii) uric acid-lowering drugs.

Firstly, the guideline for the management of controlling gout was published from ACR, which is known as American College of Rheumatology (ACR) [3]. The purpose was to give the adequate managements, such as optimal use for urate-lowering therapy (ULT), treatment for gout flares and recommendations for lifestyle and other medication. They used well-known GRADE methodology, meaning the Grading of Recommendations Assessment, Development and Evaluation. The results included 42 recommendations. Among them, some important items from strong recommendations are i) ULT is needed for all cases such as recurrent gout flares, radiographic damage due to gout, or tophaceous gout, ii) For ULT initiation, allopurinol is the preferred first-line including CKD stage >3, iii) starting low dose of allopurinol (≤100 mg/day, and lower in CKD) or febuxostat (<40 mg/day), iv) treat-to-target strategy with ULT would be uric acid value as < 6mg/dL [3].

Secondly, in order to estimate the efficacy of ULT, systematic review was performed [4]. The biomarkers included BP, GFR, renal failure events, mortality from all causes and MACE (major adverse cardiovascular events). The analyses included 6458 cases in 28 trials, associated with 506 MACE and 266 renal failure events. Overall benefits for risk ratio were 0.93 in MACE, 1.04 for mortality of all causes and 0.97 in renal failure without significant difference. In contrast, ULT attenuated the decreasing slope of GRF for 1.18mL/min/1.73 m^2 a year, systolic BP for -3.45 mm Hg. Significant difference did not exist for reverse event risks between therapy group and control group [4].

There was RCT for patients with CKD of stage 3-4, in which the influence of allopurinol for renal function has been evaluated [5]. Cases included 369 CKD patients, and they were divided into two groups for allopurinol vs control. The result showed that change in eGFR was not significantly different, which was -3.33 vs -3.23 ml/min/1.73m^2/year, respectively. Consequently, for patients associated with high-risk progression and/or CKD, ULT by providing allopurinol has not brought the reduction of eGFR in comparison with the control.

Hyperuricemia is observed in DKD, which has been recognized as diabetic kidney disease. As to multicenter trial study, Preventing Early Renal Loss in Diabetes (PERL) was conducted [6]. It included 530 Type 1 Diabetes mellitus (T1DM) cases and evaluated whether ULT on allopurinol would slow GFR loss in cases with DKD and T1DM. PERL determined clinical efficacy on allopurinol for mild-moderate DKD in Type 1 diabetes mellitus (T1DM). Hyperuricemia may increase the exacerbation risk for DKD. PERL study group evaluated renal function by ULT with allopurinol in T1DM [7]. Totally 530 cases were classified into allopurinol and control groups. Uric acid value decreased from 6.1 mg/dL to 3.9 mg/dL for the former, and stable at 6.1 mg/dL for the latter. The reduction of eGFR a year was -3.0 vs -2.5 mL/min/1.73m^2/year without significant difference. Consequently, meaningful benefits of ULT with allopurinol was not observed for T1DM and early-to-moderate DKD.

Some relationship may be present among MACE, all-cause mortality (mort), user or non-user (+/-) of xanthine oxidase inhibitors (XOIs) with allopurinol (Allo) and febuxostat (Febu). There was a retrospective cohort study analyzing the association of MACE and XOIS, and between mort and XOIS [8]. Participants was 13997, and ratio of XOI user (+/-) was 25.8%/74.2%. Both groups showed similar incidence of MACE/mort as hazard ratio (HR) 0.997/0.972. Feb user (n=276) showed similar MACE risk as Allo user (n=828), but decreased risk for heart failure-related hospitalizations (p=0.061).

As described above, ULT did not improve the cardiorenal outcome from some reports. Although it revealed the retrospective study, no increase in cardiovascular reverse events due to febuxostat have been found.

Thirdly, some tips for oral agents are described. Regarding febuxostat, pharmacokinetics for Asian race and body weight were investigated for 141 cases [9].

The result revealed that Asian people showed 1.64-fold higher of under the curve (AUC) of febuxostat than Caucasians, which was not related to weight or other covariates. These findings would be beneficial when deciding the beginning the doses for febuxostat in Asian people.

The risk for hypersensitivity reactions (HSRs) was evaluated with febuxostat, colchicine and also allopurinol for a population-based investigation [10]. The data were obtained from 5% of Medicare beneficiary sample for related patients of a newly given prescription for three agents. Regarding the obtained results, crude HSRs data showed febuxostat 30.7, allopurinol 23.7 and colchicine 25.6 statistically for 1000 person-years. When the standard prescription is to start allopurinol less than 200 mg/day, HR was 1.27 in allopurinol ≥300 mg/day. 1.21 in DM and 1.32 in female, respectively. HSRs occurred in outpatient setting for 69% [10].

A new selective urate reabsorption inhibitor (SURI), Dotinurad, was applied to medical practice recently [11]. It shows potent inhibitory efficacy at lower doses against the uptake of urate by urate transporter 1 (URAT1), which is situated at the apical membrane of renal proximal tubular cells. For pharmacological characteristic of Dotinurad, human distribution volume was 0.182 L/kg, and its oral clearance was 0.013 L/h/kg, respectively. These obtained data seemed to be lower, while plasma values were maintained enough at the higher levels. Furthermore, the differences among species were scarcely found with 94% of protein binding levels in the blood. Consequently, low-dose Dotinurad showed satisfactory pharmacological efficacy for a SURI [11]. Comparative clinical trials were conducted for dotinurad in hyperuricemia cases [12]. Subjects included 201 cases with hyperuricemia and/or without previous gout. Protocol included 102 of dotinurad and 99 of benzbromarone. Consequently, mean decreased percentage of UA level was 45.9% and 43.8%, respectively. In both groups, UA values decreased approximately from 9 mg/dl to 5 mg/dL. Non-inferiority for dotinurad 2mg were shown to benzbromarone 50mg [12].

In summary, current tips for hyperuricemia and ULT will be described. It will be hopefully useful for clinical actual practice and future research development.

Funding

There was no funding received for this paper.

Conflict of Interest

The author has read and approved the final version of the manuscript. The author has no conflicts of interest to declare.

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