Editorial
Volume 5:8, 2021

Clinical and Medical Case Reports

Open Access

Current Perspectives on Estimated Glomerular Filtration Rate (eGFR) and Urate-Lowering Therapy (ULT) for Chronic Kidney Disease (CKD)

Hiroshi Bando*

Tokushima University / Medical Research, Tokushima, Japan

Abstract

Recently, chronic kidney disease (CKD) has been a global health concern. Some problems related to CKD include decreased renal function, increased uric acid (UA) levels, urate-lowering therapy (ULT), allopurinol administration, and decreased estimated glomerular filtration rate (eGFR). Preventing Early Renal Loss in Diabetes (PERL) is a meaningful study, showing no evidence of apparent benefits of UA reduction with allopurinol on renal outcomes. Another significant study is CKD-FIX, which stands for the Controlled trial of slowing of Kidney Disease progression From the Inhibition of Xanthine oxidase. The change in eGFR was -3.33 vs -3.23 mL/min/1.73 m2 for allopurinol vs placebo, respectively.

Keywords: Chronic kidney disease (CKD) • Uric acid (UA) • Urate-lowering therapy (ULT) • Estimated glomerular filtration rate (EGFR)

Introduction

In recent years, chronic kidney disease (CKD) has been estimated as a global health concern worldwide. Especially, elderly people tend to have CKD more than expected [1]. Relationships among several factors have been in discussion including decreased renal function, increased uric acid levels, urate-lowering therapy (ULT), allopurinol administration, and decreased estimated glomerular filtration rate (eGFR) [2].

Latest report is a cohort study of the uric acid right for heart health (URRAH) Project [3]. Clinical cases (n=26,971) were analyzed by serum uric acid, eGFR, urinary albumin excretion, and others. The results showed that i) as eGFR is lower, hyperuricemia and gout are found higher, ii) compared to those with eGFR > 90 ml/min, subjects with < 60 ml/min show approximately 10 times higher of hyperuricemia, iii) the ratio of patients provided with allopurinol showed <2% in those who have GFR > 60 ml/min, 20% in those of CKD 3b and 35% in those with macroalbuminuria. These studies are progressing in the clinical practice and research, and the concept of rehabilitation for kidney disease has been emerged [4]. In this article, recent topics in this area will be described.

A variety of debate have exist concerning the pathophysiology of CKD. One is the perspective that serum uric acid levels rise as renal function declines [5]. The other is that renal function declines as a result of hyperuricemia. Conventionally, lots of observational studies are found. Among them, hyperuricemia has been known to be a risk factor for the development of CKD. On the other hand, there are few reports of medical administration for hyperuricemia and its intervention to improve the prognosis of renal function.

There was a meaningful investigation of feather trial [6]. It stands for febuxostat versus placebo randomized controlled trial regarding reduced renal function in patients with hyperuricemia complicated by chronic kidney disease stage 3, which was a multicenter, randomized, double-blind, and placebo-controlled trial. Subjects were 467 patients with CKD 3a/3b, and eGFR was observed between febuxostat group and placebo group. As a result, eGFR slope was 0.23 vs -0.47 mL/min/1.73 m^2/year (no significant difference p=0.1). Regarding gouty arthritis, the incidence was 0.91% vs 5.86% (significant difference p=0.007) [6].

Another study was found which showed the efficacy of febuxostat associated with delay of progression of renal dysfunction. It was freed study, which means febuxostat for cerebral and cardiorenovascular events prevention study [7]. Elderly patients with elevated uric acid were included 1070 cases, and febuxostat and non-febuxostat groups were observed for 36 months. As a result, UA level at endpoint was 4.50 mg/dL vs 6.76 mg/dL, respectively (p<0.001), and primary composite event rate showed hazard ratio (0.750, p=0.017) and renal impairment (HR 0.745, p=0.041). For this result, however, the soft end-point included combined 8 factors and no difference were found in the renal hard outcome such as the doubling rate of serum creatinine and the progression to end-stage renal disease (ESRD). Therefore, the interpretation of the conclusion is not easy.

Comparative study was conducted concerning febuxostat vs allopurinol, which was known as cares clinical trials [8]. Patients with hyperuricemia (n=6190) were treated by febuxostat vs allopurinol for 32 months in median. Primary end-point event was observed in 10.8% vs 10.4%, respectively. The former group showed higher all-cause and cardiovascular mortality (HR 1.22 and 1.34), which was analyzed in the modified intention-to-treat analysis. For gout patients associated with major cardiovascular coexisting conditions, febuxostat was noninferior to allopurinol in the light of adverse cardiovascular events.

In order to provide adequate urate-lowering therapy (ULT), American College of Rheumatology presented the guideline for the management of gout [9]. Meta-analyses with ratings of various evidence were summarized from the GRADE methodology, which stands for the grading of recommendations assessment, development and evaluation. There were 42 recommendations for standard therapeutic treatments. For those with CKD (stage >3), allopurinol would be preferred the first-line ULT, and starting dose would be <100 mg/day in allopurinol and <40 mg/day in febuxostat.

Based on the main evidence mentioned above, two important papers have recently been reported, which are PERL trial and CKD-FIX trial. Preventing early renal loss in diabetes (PERL) study is a recent mega study [10]. Subjects were patients with type 1 diabetes mellitus (T1DM), serum UA at least 4.5 mg/dL and eGFR of 40 to 99.9 ml/min/1.73m^2. Protocol included two groups of with allopurinol (n=267) or placebo (n=263) for 3 years. As a result, mean decrease in GFR was -3.0 vs -2.5 ml/min/1.73 m^2/year, which means the difference of -0.6 ml/min/1.73 m^2/year. It showed no evidence of apparent benefits of UA reduction with allopurinol on renal outcomes among T1DM and early-to-moderate diabetic kidney disease (DKD).

***Address for Correspondence:** Bando H, Tokushima University / Medical Research, Tokushima, Japan, E-mail: pianomed@bronze.ocn.ne.jp*

Received 09 August, 2021; **Accepted** 24 August, 2021; **Published** 31 August, 2021

CKD-FIX has been a double-blind, randomised, placebo-controlled trial [2013-2018], which means the controlled trial of slowing of kidney disease progression from the inhibition of xanthine oxidase [11]. Subjects were patients with CKD (stage 3 or 4) with no history of gout and urinary alb/cre ratio > 265 mg/g. eGFR decrease of > 3.0 ml/min/1.73 m^2/year. As a result, allopurinol group (n=182) vs placebo group (n=181) showed eGFR value as 31.6 vs 31.9 mL/min/1.73 m^2, respectively. The change in eGFR was -3.33 vs -3.23 mL/min/1.73 m^2, which showed no significant difference. Consequently, for patients with high progression risk, allopurinol did not slow eGFR decline in comparison with placebo.

From the results of PERL and CKD-FIX, allopurinol did not show the evidence for slowing the progression of CKD. Based on these results, there have been other various reports concerning urate-lowering therapy (ULT), and changes in eGFR. A latest report included a systematic review with 131 studies and 3.4 million patients [12]. Hyperuricemia is associated with worsening eGFR, albuminuria, CKD, and kidney failure. ULT use for ⩾1 year may improve kidney function. Hyperuricemia brings eGFR decline ⩾ 3 ml/min/1.73 m^2/year (OR 1.38), albuminuria (OR/HR 1.94), CKD (OR/HR 2.13), and kidney failure (HR 1.53). ULT use for ⩾1 year provides the significant improvements for eGFR (1.81 ml/min/1.73 m^2), serum creatinine (-0.33 mg/dl), and proteinuria (-5.44 mg/day), but no difference in kidney failure. This article will become hopefully some reference for development of nephrology.

References

1. Bando, H. "Up-To-Date Perspectives for Hyperuricemia, Cardiorenal Influence and Urate-Lowering Therapy (ULT)". *Diab Res Open Access*. 03; (2021):16-19.
2. Yen, FS., Wei JC, Chang CL, Yang CC, Hsu CC and Hwu CM et al. "Urate-lowering Therapy and Chronic Kidney Disease Development in Patients with Gout". *Int J Med Sci*. 18; (2021): 2599-2606.
3. Russo, E. "Working Group on UricAcid and Cardiovascular Risk of the Italian Society of Hypertension. Association of uric acid with kidney function and albuminuria: the Uric Acid Right for heArt Health (URRAH) Project". *J Nephrol*. (2021).
4. Kato, Y., Bando H and Kato Y. "Latest Perspectives Concerning Renal Rehabilitation for Chronic Kidney Disease (CKD)". *J Cardiol Cardiovascular Res*. 3; (2021): 112.
5. Watanabe, K., Nakayama M, Yamamoto T, Yamada G, Sato H and Miyazaki M, et al. Different clinical impact of hyperuricemia according to etiologies of chronic kidney disease: Gonryo Study. *PLoS One*.16; (2021):e0249240.
6. Kimura, K. "Febuxostat Therapy for Patients With Stage 3 CKD and Asymptomatic Hyperuricemia: A Randomized Trial." *Am J Kidney Dis*. 72; (2018):798-810.
7. Kojima, S., Matsui K, Hiramitsu S, Hisatome I, Waki M and Uchiyama K, et al. "Febuxostat for Cerebral and Cardiorenovascular Events Prevention Study". *Eur Heart J*. 40; (2019):1778-1786.
8. White, WB. "CARES Investigators. Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout." *N Engl J Med*. 378; (2018):1200-1210.
9. FitzGerald, JD., Dalbeth N, Mikuls T, Brignardello PR, Guyatt G and Abeles AM, et al. 2020 "American College of Rheumatology Guideline for the Management of Gout". *Arthritis Care Res (Hoboken)*. 72; (2020):744-760.
10. Doria, A. "PERL Study Group. Serum Urate Lowering with Allopurinol and Kidney Function in Type 1 Diabetes." *N Engl J Med*. 382; (2020):2493-2503.
11. Badve, SV. "CKD-FIX Study Investigators. Effects of Allopurinol on the Progression of Chronic Kidney Disease." *N Engl J Med*. 382; (2020):2504-2513.
12. Sharma, G., Dubey A, Nolkha N and Singh JA. "Hyperuricemia, urate-lowering therapy, and kidney outcomes: a systematic review and meta-analysis." *Ther Adv Musculoskelet Dis*. (2021).

How to cite this article: Bando, Hiroshi. "Current Perspectives on Estimated Glomerular Filtration Rate (eGFR) and Urate-Lowering Therapy (ULT) for Chronic Kidney Disease (CKD)". *Clin Med Case Rep* 5 (2021):165.