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Clinical Group

Archives of Renal Diseases and Management

ISSN: 2455-5495 DOI CC By

Filomena Panza, Chiara Ralli and Ennio Duranti*

UOC Nephrology and Dialysis Unit, Hospital of Arezzo, Italy

Dates: Received: 29 May, 2017; **Accepted:** 15 June, 2017; **Published:** 19 June, 2017

***Corresponding author:** Ennio Duranti, UOC Nephrology and Dialysis Unit, Hospital of Arezzo, Italy, E-mail: ennio.duranti@uslsudest.toscana.it

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Research Article

Effectiveness and Tolerability of Febuxostat vs Allopurinol in patients with Chronic Kidney Disease (CKD) on Conservative Therapy

Abstract

Uric Acid appears to be one of the most important prognostic markers and one of the principal risk factors for cardiovascular diseases. The aim of our study was to assess three groups of patients: a first group treated with Allopurinol (AL), a second group not adequately controlled by treatment with AL or allergic to AL switched to treatment with Febuxostat (AL/FB) and a third group of naive patients immediately treated with Febuxostat (FB). The effectiveness and tolerability of both drugs were therefore assessed over time.

Materials and methods: 44 patients, with CKD in conservative therapy, were divided into 3 groups. A group of 20 patients (AL) with well controlled uricemic values (serum uric acid < 6 mg/dl); a group of 12 patients (AL/FB) with not well controlled uricemic values (serum uric acid concentration > 6.0 mg / dl) and / or intolerant to AL that were switched to treatment with FB, then a group of 12 naive patients (FB) treated immediately with FB. At time 0,3,6,9,12,18,24 months, all patients were monitored as regards: serum uric acid, renal function parameters, serum electrolytes, hemoglobin, lipid profile, blood glucose, glycated hemoglobin, proteinuria 24 hours,parathyroid hormone (PTH), C Reactive Protein (CRP). The doses of anti-uric acid administered drug were also evaluated. All the patients underwent a monitoring of blood pressure (BP), heart rate (HR) and body mass index (BMI).

Results: Patients treated with AL started with serum creatinine values significantly lower, compared to patients of the two groups in FB, maintaining similar values for the entire period of observation. The glomerular filtration rate calculated using the CKD-EPI formula confirmed the behaviour. Serum uric acid was significantly lower (at 3 months $p < 0.003$ and at 12 months $p < 0.001$) in AL/FB group and FB group, compared to AL group. In addition, hyperuricaemia fell to values lower than 5mg / dl within 3 months of starting therapy with FB, while AL values remained around 6 mg / dl.Serum PTH showed no significant changes in any group. Serum CRP was more controlled in the two groups treated with FB, while AL values were always higher (at 3 months $p < 0.003$). Two patients resulted also intolerant to FB as well as to AL. The instrumental and clinical examinations revealed no alterations in any group.

Conclusions: Considering our data, Febuxostat, represents a valuable therapeutic approach, especially in controlling serum uric acid values (better < 5.5 mg /dl) and inflammatory markers (C Reactive Protein) of the patients with impaired renal function (CKD 3b-4).

Introduction

Multiple epidemiological studies have shown the close association between serum circulating levels of Uric Acid and cardiovascular diseases [1,2]. Hyperuricemia, initially known predominantly as inflammatory disease of the joints, in recent years has been increasingly associated with heart, brain and kidney diseases: ischemic heart disease, heart failure, stroke, dementia, and kidney failure. Therefore Uric Acid appears to be one of the most important prognostic markers and one of the principal risk factors for cardiovascular diseases [3,4]. The aim of our study was to assess three groups of patients: a first group with chronic kidney disese (CKD) on conservative treatment who showed hyperuricemia treated with Allopurinol (AL), a second group with serum Uric Acid values not adequately controlled by treatment with AL or allergic to AL switched to treatment with Febuxostat (AL/FB) and a third group of naive patients immediately treated with Febuxostat (FB). The effectiveness and tolerability of both drugs were therefore assessed over time.

Citation: Panza F, Ralli C, Duranti E (2017) Effectiveness and Tolerability of Febuxostat vs Allopurinol in patients with Chronic Kidney Disease (CKD) on Conservative Therapy. Arch Renal Dis Manag 3(1): 030-033. DOI: http://doi.org/10.17352/2455-5495.000023

Materials and Methods

They were enrolled 44 patients (Table 1), with CKD in conservative therapy, divided into 3 groups. A group of 20 patients (AL) with well controlled uricemic values (serum uric acid < 6 mg/dl); a group of 12 patients (AL/FB) with not well controlled uricemic values (serum uric acid concentration > 6.0 mg / dl) and / or intolerant to AL that were switched to treatment with FB, then a group of 12 naive patients (FB) treated immediately with FB. At time 0,3,6,9,12,18,24 months, all patients were monitored as regards: serum uric acid, renal function parameters, serum electrolytes, hemoglobin, lipid profile, blood glucose, glycated hemoglobin, proteinuria 24 hours,parathyroid hormone (PTH),C Reactive Protein (CRP). The weekly dose of anti-uric acid administered drug was also evaluated for the three groups. All the patients underwent a medical examination with monitoring of blood pressure (BP), heart rate (HR) and body mass index (BMI). Statistical differences were valued using Student's paired and non-paired t test.

Results

Patients treated with AL started with serum creatinine values (Figure 1) significantly lower (CKD stage 3a) compared to patients of the two groups in FB (CKD stage 3 b-4) and they maintained similar values for the entire period of observation. The behaviour was confirmed also by the glomerular filtration rate calculated using the CKD-EPI formula (Figure 2). The uric acid values (Figure 3) were significantly lower (after 3 months p <0.003 and after 12 months p <0.001) and thus better controlled in AL/FB group and FB group, compared to AL group. In addition, hyperuricaemia fell to values lower than 5mg / dl within 3 months of starting therapy with FB, while AL values remained around 6 mg / dl, a value that even if considered within the limits, in the course of CKD, can have a negative action on its evolution.Serum PTH (Figure 4) showed no significant changes among the three groups. Serum CRP (Figure 5) was more effectually controlled in the two groups treated with FB, while AL values were always higher (after 3 months p <0.003) highlighting a more significant anti-inflammatory effect of FB with respect to AL. Two patients resulted also intolerant to FB as well as, previously, to AL. The instrumental and clinical examinations revealed no alterations in the periods of observation in all three groups.

Table 1: Characteristics of the three groups.

Therapeutic regimen	AL	AL / FB	FB
Age years	71 ± 12	76 ± 7	74 ± 11
Sex M/F	17 / 4	9 / 3	8 / 4
BMI Kg/m2	27,7 ± 4,1	25,83 ± 4,57	27 ± 3
Drug Dose mg/week	832 ± 164	900 ± 0 AL 657 ± 165 FB	468 ± 295
Hypertensive n (%)	18 (90)	9 (75)	9 (75)
Diabetics n (%)	7 (35)	6 (50)	6 (50)
Cardiac ischemia n (%)	5 (25)	3 (25)	3 (25)
Kidney stones n (%)	3 (15)	2 (16)	0
Smokers n (%)	9 (45)	4 (33)	3 (25)
Vasculopathies n (%)	3 (15)	2 (16)	2 (16)
Dyslipidemia n (%)	7 (35)	6 (50)	7 (58)

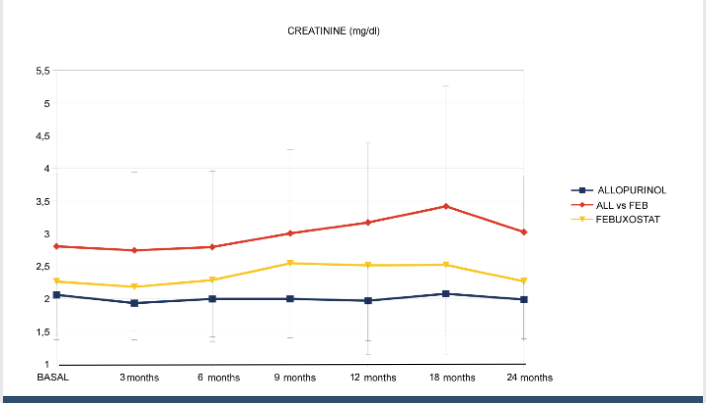

Figure 1: Creatinine trend in the three groups.

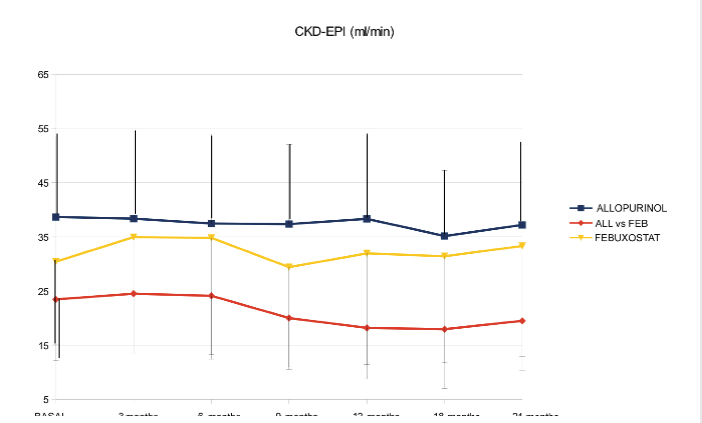

Figure 2: CKD-EPI trend in the three groups.

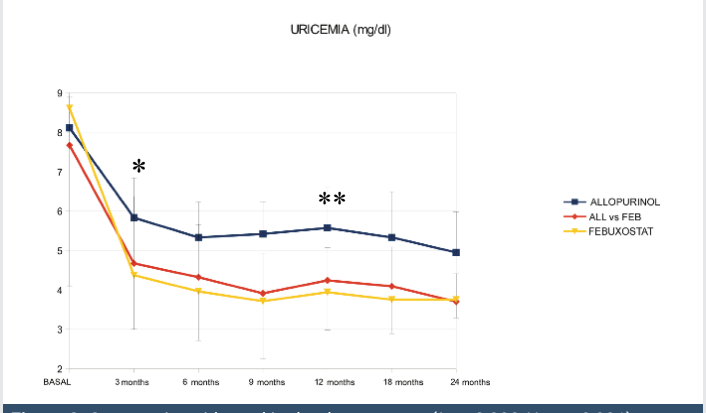

Figure 3: Serum uric acid trend in the three groups (* p <0,003 ** pp< 0,001).

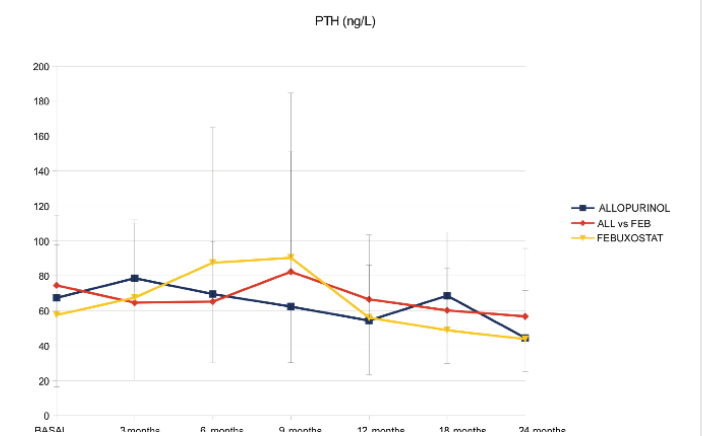

Figure 4: PTH trend in the three groups.

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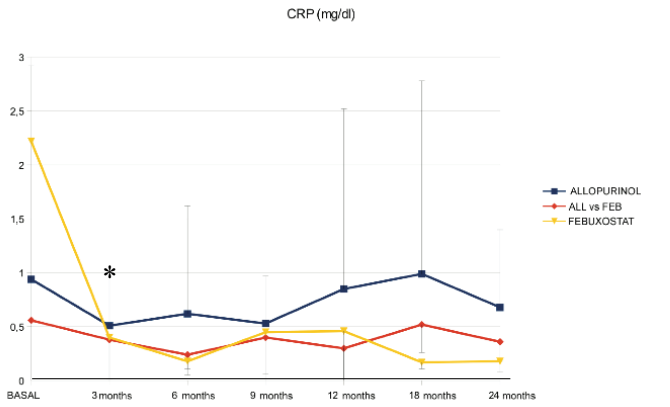

Figure 5: CRP trend in the three groups (* p<0,003).

Discussion and Conclusions

The population affected by CKD in conservative and replacement therapy represent, the most percentage at risk for cardiovascular complications that are, in fact, the leading cause of death. In the course of CKD, the excretion and therefore the clearance of uric acid is reduced, giving rise to an increase in its blood levels. The resulting buildup of uric acid causes an increase in the free radicals formation by generating a chronic inflammatory state that is associated with subsequent endothelial dysfunction [5,6]. The enzymatic reaction, catalyzed by the enzyme xanthine oxidase (XO), which transforms the hypoxanthine to xanthine and then to uric acid, also leads to the formation of reactive oxygen species, superoxide and hydrogen peroxide, which react with the nitric oxide forming peroxynitrite with double negative effect. The degradation of nitric oxide is accompanied by an imbalance of endothelial function in the proaterogenic, prothrombotic and vasoconstrictor sense. The peroxynitrite itself is a highly reactive species that amplifies the oxidative stress. Numerous studies have shown that FB is a potent, non-competitive and non-purine selective inhibitor of the XO, both in its reduced (XOR) and oxidized (XO) form. On the contrary AL is an analogue of the purine XO which is oxidized to oxipurinol, which greatly reduces the reactive oxygen species formation. FB also reduces the thickening of the renal arterioles, the expansion of the mesangial matrix and the glomerular hypercellularity induced in the rat by hyperuricemia [7] with a consequent reduction in glomerular hypertension and systemic arterial pressure. FB has a predominantly hepatic metabolism, which does not require dose adjustment in patients with mild to moderate CKD and in elderly patients.In addition in our experience neither renal impairment negatively influences the effectiveness of the drug, even if the efficacy and safety of FB have not been established in patients with GFR <30 ml / min [8]. FB has been shown in several studies [9-13] to have high efficiency in decreasing high serum uric acid values, with significant superiority compared to AL in achieving and maintaining, in the long term [12,13], the target serum uric acid concentration <6 mg / dl. High levels of uric acid, moreover, are associated with increased levels of serum inflammatory marker levels [14]. At this regard in our experience FB seems to have a more antiinflammatory effect compared with AL. The goal of uprate lowering therapy is the dissolution of urate crystals and over that to prevent their formation, and this can be achieved by maintaining the levels of serum uric acid below the saturation point of the monosodium urate < 6 mg/dl. It is important to monitor the levels of uric acid regularly, to keep them below the saturation point and to assess the compliance of patients to therapy. The results of our study showed that FB uric acid lowering activity is higher and faster than AL, confirming the results of several previous studies [15]. The FB tolerability was superior compared to AL. Moreover, even if FB is prescribed to patients with more compromised renal function (CKD stage 3b or 4) there have been no worsening of serum creatinine and GFR values. Ideally, in our view, the renal and cardiovascular prognosis could be better with a more strict control of serum uric acid values below 5.5 mg / dl.

In conclusion Febuxostat, represents a valuable therapeutic approach, especially in controlling serum uric acid values (better < 5.5 mg /dl) and inflammatory markers (C Reactive Protein) of the patients with impaired renal function (CKD 3b-4).

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