Internal and Emergency Medicine (2019) 14:903–905
https://doi.org/10.1007/s11739-019-02105-4

IM - COMMENTARY

Xanthine oxidase inhibitors in elderly patients with heart failure: useful or useless?

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Received: 9 April 2019 / Accepted: 3 May 2019 / Published online: 13 May 2019

Elevated serum uric acid levels have been progressively emerged as a powerful and independent risk factor for many cardiovascular diseases, including hypertension [1, 2], coronary artery disease [3, 4], stroke [5, 6] and congestive heart failure [7–9]. It has been also reported strong, positive and independent correlations between high-serum levels of uric acid and metabolic abnormalities, including hypercholesterolemia, atherogenic dyslipidaemia, obesity, metabolic syndrome, and diabetes [10, 11]. Additionally, high serum uric acid levels are able to predict progression from end-stage renal and heart failure and they have been related to worsen prognosis and increased risk of cardiovascular death in many observational studies [12]. On the other hand, several reports have demonstrated that reducing levels of serum uric acid levels with xanthine oxidase inhibitors was associated with better prognosis and improved event-free survival rate in different cardiovascular settings, including hypertension [13, 14], coronary artery disease [15, 16], and even congestive heart failure. On the basis of these consideration, high-serum levels of uric acid should never be neglected or ignored, independently by the clinical context or the clinical condition in which they are observed [17].

From a pathophysiological point of view, increased xanthine oxidase activity is able to produce high-serum levels of uric acid and abnormal concentration of reactive oxygen species (ROS) at both cardiac and circulating levels [18]. Increased ROS concentration may be responsible for peripheral vasoconstriction, abnormal excitation–contraction coupling, myocardial impairment, and development of left ventricular remodelling, and dysfunction. These maladaptive responses to oxidative stress can be frequently observed in the pathogenesis of congestive heart failure, and have been related to worsen prognosis and progression towards the end-stage of the disease. Thus, pharmacological interventions aimed at reducing high serum levels of uric acid should be paralleled by improved prognosis and better quality of life in patients with different degrees of congestive heart failure. Available evidence, however, reporting contrasting reports.

In the Efficacy and Safety Study of Oxypurinol Added to Standard Therapy in Patients With New York Heart Association Class III–IV Congestive Heart Failure (OPT-CHF) study, about 400 patients with New York Heart Association (NYHA) functional class III–IV heart failure due to systolic dysfunction on optimal medical therapy, were randomized to receive oxypurinol (600 mg daily) or matching placebo [19]. After 24 weeks of treatment, no significant differences were observed in the incidence of the composite endpoint, including heart failure morbidity, mortality, and quality of life, although post hoc analyses seem to suggest that some beneficial effects may be observed in those patients with baseline high levels of uric acid in a manner correlating with the degree of serum uric acid reduction [19].

In the La Plata Study, about 60 patients with NYHA functional class II to III heart failure, were randomized to receive oxypurinol (600 mg daily) or matching placebo. After 1 month of treatment, left ventricular ejection fraction was significantly higher, although only in those patients with reduced left ventricular performance at baseline, without relevant differences in walking capacity.

In the Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) study, about 250 patients with NYHA class III–IV heart failure and reduced left ventricular ejection fraction (less than 40%) were randomized to receive allopurinol (300 mg daily) or matching placebo [20]. After 24 weeks of treatment, there

Commentary on the manuscript entitled Effects of allopurinol and febuxostat on cardiovascular mortality in elderly heart failure patients.

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was no significant difference in clinical status and in the left ventricular ejection fraction between the two treatment groups [20].

More recently, 125 consecutive non-hyperuricemic patients with congestive heart failure were randomized to receive allopurinol 300 mg daily or placebo. After 6 months of treatment, cardiac function classification was improved, left ventricular end-diastolic diameter was diminished, left ventricular ejection fraction was increased, whilst plasma levels of brain natriuretic peptide and tumour necrosis factor-a were decreased ($p < 0.01$ for all parameters) [21].

In a recent analysis performed in 734 otherwise healthy adult untreated subjects enrolled in the last Brisighella population survey, serum uric acid levels resulted a strong and independent predictor of cardiac functionality parameters, including cardiac output ($B = -0.219$, $p < 0.001$) and stroke volume ($B = -3.684$, $p < 0.001$) [22]. In this issue of the Internal and Emergency Medicine, Cicero et al. [23] aimed at comparing the effects of two xanthine oxidase inhibitors on cardiovascular morbidity and mortality in elderly patients with congestive heart failure on top of optimal medical therapy. In this monocenter study, 255 patients with chronic heart failure with preserved ejection fraction and high levels of serum uric acid were randomized to receive either allopurinol 300 mg or febuxostat 80 mg daily [23]. After 8 years of follow-up, treatment with febuxostat was associated with a significantly improved survival rate from cardiovascular mortality compared to allopurinol ($p = 0.0046$).

These findings are of potential clinical interest, mostly in view of the recently available results of the CARES trial [24], which questioned the effectiveness and safety of febuxostat-based therapy in high-risk patients with gout. Although not comparable with the study performed by Cicero et al. [23], the CARES trial also included about 1250 patients with heart failure at baseline (20% of the overall population sample) and subgroup analysis for the presence or absence of heart failure did not shown significant difference in favour of either allopurinol or febuxostat [24]. In this trial, however, discontinuation rates from study drugs were relatively frequent [24], and this may at least, in part, explain the different outcomes observed in this trial compared to the one of Cicero et al. [23] in a setting of real practise.

Further clinical studies are needed to confirm this intriguing hypothesis that a pharmacological strategy based on a selective (febuxostat) or non-selective (allopurinol or its active metabolite oxypurinol) inhibition of the xanthine oxidase activity may improve endothelial function and ameliorate prognosis in patients with congestive heart failure, as well as in those with other cardiovascular diseases [25], such as hypertension, coronary artery disease or stroke.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statements on human and animal rights This article does not contain data derived by any current studies with human participants performed by any of the authors. The clinical studies mentioned were provided with specific ethical approval.

Informed consent For this type of study, formal consent is not required.

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