Internal and Emergency Medicine (2019) 14:949–956
https://doi.org/10.1007/s11739-019-02070-y

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Effects of allopurinol and febuxostat on cardiovascular mortality in elderly heart failure patients

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Received: 13 January 2019 / Accepted: 6 March 2019 / Published online: 12 March 2019

Abstract
Hyperuricemia is an emerging risk factor for the development of heart failure (HF) and is associated with a worsen prognosis of the disease. The effect of urate lowering drugs (ULT) and, in particular, the xanthine oxidase inhibitor in patients with HF is controversial. The aim of the study is to compare the effects of treatment with two different xanthine oxidase inhibitors (allopurinol or febuxostat) on cardiovascular mortality in elderly patients with chronic HF in a setting of clinical practice. In this observational trial, 255 elderly patients affected by chronic HF and treated with ULT on top of optimal medical treatment for HF. The sample included only outpatients with mild-to-moderate HF mainly secondary to chronic arterial hypertension or coronary artery disease and not previously hospitalized for HF. Patient treated with febuxostat (*N*. 120) and allopurinol (*N*. 135) were balanced for most of the baseline variables. In particular age, NYHA class distribution, drug treatment and renal function were comparable at the baseline and during the observation in both groups ($p > 0.05$). After a mean follow-up period of 5.1 years, the cumulative cardiovascular survival was 0.96 (95% CI 0.93–0.99) in febuxostat-treated patients and 0.89 (95% CI 0.84–0.93) in those treated with allopurinol. The between group difference, adjusted for the main confounding risk factors, was statistically significant ($p = 0.04$). Our study results suggest that possibility that febuxostat, a selective XO inhibitor, may favorably affect cardiovascular mortality in comparison with allopurinol in elderly patients with mild-to-moderate HF. This preliminary observation deserves further evaluation in the next future.

Keywords Allopurinol · Febuxostat · Heart failure · Hyperuricemia · Mortality

Introduction

Elevated serum uric acid (SUA) is an emerging risk factor that has been associated with an increased risk of disease progression and worsen prognosis in patients with heart failure (HF). A meta-analysis including five studies on the incidence of HF and 28 studies focused on the adverse outcomes of HF patients have demonstrated that for 1 mg/dL of increase in SUA the odd ratio for the new onset of HF, all-cause mortality and the composite endpoint (death + cardiac events) increases by 19% (HR 1.19, 95% CI 1.17–1.21), 4% (HR 1.04, 95% CI 1.02–1.06) and 28% (HR 1.28, 95% CI 0.97–1.70), respectively [1]. These results have been recently confirmed by a large post hoc analysis of the Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure (GISSI-HF) trial including 6683 outpatients with chronic HF with a median follow-up of 3.9 years [2]. The Oxypurinol Therapy for Congestive Heart Failure (OPT-HF) study [3] has demonstrated that the treatment with oxypurinol in comparison with placebo was associated with an improvement in clinical outcome (combined mortality, morbidity and quality of life) in sub-population of about 400 patients with HF and elevated levels of SUA.

Despite the conflicting nature of the available evidence [4], the existence of a strong correlation between elevated SUA and HF is strong supported by a number of pathophysiological mechanisms. Uric acid production involves

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the activation of XO resulting in an increase in the level of oxidative stress associated that can impair the nitric oxide production and the peripheral vasodilatory capacity [5]. SUA levels are associated with increased arterial stiffness, predominantly in patients with normal or slightly reduced renal function [6]. The impaired vasodilating capacity and the increased arterial stiffness can raise left ventricular post-loading and decrease ejection fraction [7]. Moreover, increased oxidative stress related to SUA production is associated with a significant increase of atrial fibrillation [8] and other tachyarrhythmias [9]. Interestingly, the association between hyperuricemia and poor clinical outcomes of HF seems to be more evident patients with preserved renal function [10, 11], suggesting a primary role for xanthine oxidase (XO) activity and uric acid production in the clinical progression of heart failure. This hypothesis has been recently confirmed by Japanese researchers demonstrating a significant increase in plasma XO activity in patients with more severe chronic HF [12]. Finally, an enhanced XO activity has been reported in patients with HF [13] and this can be responsible for an excessive production of SUA as well as for a depressive effect on left ventricular function.

However, despite all this consistent evidence supporting the negative role of the XO-uric acid axis in patients with HF, the potential therapeutic role for XO inhibitors in those patients is still matter of debate [14]. In particular, only few data have been published on the comparison between the clinical efficacy of different xanthine-oxidase inhibitors bearing different selectivity for the target enzyme.

The goal of the present study was to prospectively evaluate if the treatment with different xanthine-oxidase inhibitors (allopurinol and febuxostat) could have a different impact on cardiovascular mortality in elderly patients with chronic HF and hyperuricemia studied in a setting of daily clinical practice.

Methods

For the purpose of this study, we consecutively enrolled 255 elderly (> 60 years old) outpatients with chronic congestive HF, naïve of urate lowering drugs (no treatment in the last 12 months) and currently attending the HF clinic of the Department of Internal Medicine at the S. Orsola-Malpighi University Hospital of Bologna (Italy). The patients have been actively followed at a three-month interval in the period January 2012–December 2018. The study sample included only stable patients, without hospital admission for HF in the last 6 months and with mild-to-moderate (NYHA class I–II–III) HF due to chronic arterial hypertension or coronary heart disease, with the exclusion of patients with congenital and/or valvular heart diseases. We also excluded from the study patients with a diagnosis of gout, severe renal disease (eGFR < 30 ml/min/1.73 m^2) or malignancies in order to avoid SUA outliers. Ultimately, we excluded patients with large spontaneous variability of SUA level (> 20% in the last 3 samples), in order to avoid additional confounding conditions (Fig. 1).

This is an observational trial carried out in the setting of clinical practice. All the patients have been treated with allopurinol or febuxostat on top of optimal medical therapy for HF and according to country regulatory policy, history of renal dysfunction and medical history (previous AE's with one of the two drugs). Starting dose of allopurinol was 150 mg/day, up-titrated after 3 months to 300 mg if the target level of uric acid (< 6.0 mg/dL) was not reached. The starting dose of febuxostat was 80 mg/day, up-titrated to 120 mg/day, if target SUA level was not achieved [15].

All the laboratory data were collected after 12 hours of fasting and determined with a standardized methodology [16, 17] at the central laboratory of the S. Orsola-Malpighi University Hospital by trained personnel.

Plasma Brain Natriuretic Peptide (BNP) was measured using a microplate luminometer reader (Centro LB 960; Berthold Technologies GmbH & Co., Bad Wildbad, Germany) and a Shionoria BNP kit (Shionogi Company, Osaka, Japan). As the minimum and maximum detectable concentrations were 0.1 and 4000 ng/l, respectively, BNP levels < 0.1 ng/l were counted as 0.1 ng/l and BNP levels > 4000 ng/l were counted as 4000 ng/l in this study. The above tests were performed in our clinical laboratory, and inter- and intra-batch coefficient of variations were controlled within 5.5% and 3.5%, respectively. Estimated GFR was calculated by the application of the EPI-CKD formula that is considered more accurate in patients with chronic HF [18].

Blood pressure was measured by sphygmomanometer using an appropriately sized cuff, with the patient lying for 10 min. The systolic (SBP) and diastolic blood pressure (DBP) values were read to the nearest two mmHg. Three measurements were taken at two-minute intervals, and the average value was used to define office SBP and DBP, while mean arterial pressure (MAP) and pulse pressure (PP) were calculated thoroughly.

A standard M-mode two-dimensional Doppler echocardiographic evaluation was performed in all patients by the same well-trained operator unaware of the patient's SUA levels, and according to the main international guidelines [19]. Ultrasonographic imaging was obtained from the left parasternal long-, short-axis transducer position using a 2.5-MHz transducer; all tracings were recorded in the last phase of held expiration with the patient in the left lateral decubitus position and after 20 min of rest. Echocardiograms were recorded by simultaneous ECG tracings. In accordance with the recommendations of the American Society of Echocardiography, left ventricular ejection

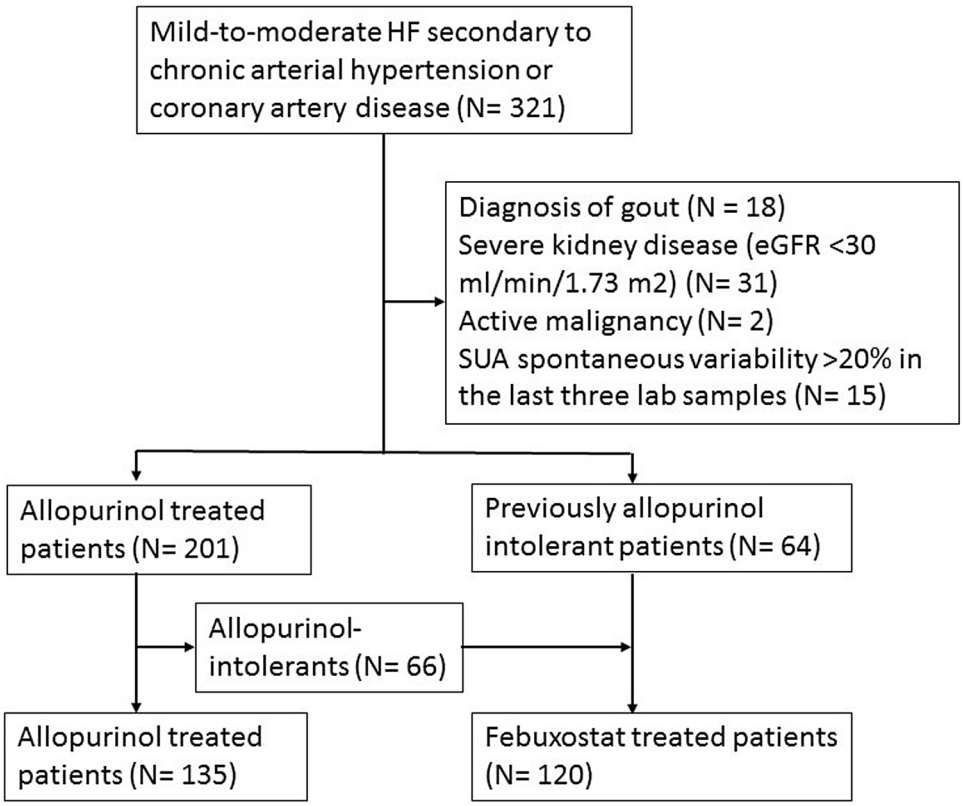

Fig. 1 Diagram of the study

fraction (LVEF) was calculated using the method of disks (modified Simpson rule) [20]. The within-study variability of individual measurements around the mean averaged ± 5%, with individual differences ranging from 1 to 12%. Heart rate (HR) was measured from the simultaneously recorded ECG tracing.

The study was preventively approved by the Ethical Committee of the S. Orsola-Malpighi University Hospital and was carried out in agreement with the declaration of Helsinki. All patients gave their written informed consent.

Reporting of the study conforms to STROBE, along with references to STROBE and the broader EQUATOR guidelines [21].

A descriptive analysis of all available variables was performed. Continuous and categorical variables were expressed as mean ± standard deviation (SD) or absolute figures, respectively. Continuous parameters were compared by using independent *T* test or Kruskal–Wallis Analysis of Variance. The cardiovascular mortality between the two groups was compared by Chi-square test Fisher. A 6-year Kaplan–Meier survival analysis was carried out per treatment group. The log-rank statistic (Mantel–Cox test) was used to estimate differences in the intergroup cardiovascular survival, after adjustment for baseline age, gender and ejection fraction. Every analysis was two-tailed. *P* values < 0.05 were always regarded as statistically significant.

Results

At enrollment, 135 patients have been treated with allopurinol 150 mg/day and 120 with febuxostat 80 mg/day. Twenty-eight subjects in the allopurinol group and 21 in the febuxostat required an increase in the dose of drugs during the follow-up period. During the observation period, three subjects treated with allopurinol and one treated with febuxostat experienced mild tolerable skin reactions, while three subjects in the allopurinol-treated group moved to the febuxostat-treated one because of more serious skin reactions. No one patient experienced severe worsening of renal function during follow-up.

The two populations of patients were well balanced at baseline for both categorical (Table 1) and continuous (Table 2) variables. In particular, no statistically significant difference has been observed in the distribution of cardiovascular risk factors, echocardiographic parameters and concomitant drug treatment.

NYHA functional class at baseline was evenly distributed in the two groups of patients treated with Febuxostat (class I: *n*.23/19.2%, class II: *n*.56/46.7% and class III: *n*.41/34.2%) and allopurinol (class I: *n*.18/13.3%, class II: *n*.74/54.8% and class III: *n*.43/31.9%) without significant difference between groups ($p > 0.05$).

Table 1 Categorical variables distribution among febuxostat- and allopurinol-treated subjects

	Febuxostat (*N.* 120)	Allopurinol (*N.* 135)
Gender (M:F)	79/41	81/54
Active smokers, *N* (%)	58 (48.3%)	72 (53.3%)
Hypertension, *N* (%)	114 (95.0%)	122 (90.4%)
Hypercholesterolemia, *N* (%)	78 (65.0%)	88 (65.2%)
Type 2 diabetes, *N* (%)	32 (26.7%)	39 (28.9%)
Chronic kidney disease, *N* (%)	65 (54.2%)	69 (51.1%)
Arrhythmias, *N* (%)	53 (44.2%)	67 (49.6%)
Coronary heart disease, *N* (%)	67 (55.8%)	84 (62.2%)
Cerebrovascular disease, *N* (%)	11 (9.2%)	18 (13.3%)
COPD, *N* (%)	45 (37.5%)	55 (40.7%)
ACE-inhibitors, *N* (%)	64 (53.3%)	69 (51.1%)
ARB's, *N* (%)	52 (43.3%)	64 (46.6%)
Beta-blockers, *N* (%)	90 (75.0%)	104 (77.0%)
Calcium-antagonists, *N* (%)	33 (27.7%)	31 (23.1%)
Loop diuretics, *N* (%)	73 (60.1%)	78 (57.8%)
Thiazides, *N* (%)	48 (40.0%)	56 (41.5%)
Potassium sparring diuretics, *N* (%)	51 (42.5%)	81 (60.0%)
Nitroderivatives, *N* (%)	8 (6.7%)	15 (11.1%)*
Antiplatelets, *N* (%)	78 (65.0%)	86 (63.7%)
Anticoagulants, *N* (%)	43 (35.8%)	53 (39.2%)
Statins, *N* (%)	67 (55.8%)	69 (51.1%)

COPD chronic obstructive pulmonary disease

*$p < 0.05$ versus Febuxostat-treated group

Table 2 Continuous variables distribution among febuxostat and allopurinol-treated subjects

	Febuxostat (*N.* 120)	Allopurinol (*N.* 135)
Age (years)	75.9 ± 8.9	78.1 ± 6.3
Body mass index (kg/m^2)	25.9 ± 2.9	26.1 ± 1.3
SBP (mmHg)	124.4 ± 10.5	127.2 ± 19.1
DBP (mmHg)	77.1 ± 4.7	76.0 ± 5.7
Pulse pressure (mmHg)	47.6 ± 3.4	51.8 ± 3.9
Heart rate (bpm)	71.4 ± 7.6	70.4 ± 6.9
Ejection fraction (%)	55.1 ± 7.2	52.7 ± 7.3
LVW (mm)	11.5 ± 1.6	12.2 ± 1.9
BNP (ng/L)	647.8 ± 84.2	697.2 ± 91.9
Hemoglobin (g/dL)	12.9 ± 1.9	12.7 ± 1.8
Fasting plasma glucose (mg/dL)	99.8 ± 15.3	102.0 ± 18.9
HDL-cholesterol (mg/dL)	44.6 ± 6.3	47.9 ± 6.1
LDL-cholesterol (mg/dL)	104.2 ± 16.9	98.2 ± 12.6
Triglycerides (mg/dL)	150.7 ± 26.9	136.6 ± 41.4*
Creatinine (mg/dL)	1.3 ± 0.4	1.3 ± 0.5
eGFR (ml/min/1.73 m^2)	55.0 ± 13.2	51.8 ± 12.0
Serum uric acid (mg/dL)	8.1 ± 2.1	7.5 ± 1.8

SBP systolic blood pressure, *DBP* diastolic blood pressure, *LVW* average thickness of left ventricular wall, *BNP* brain natriuretic peptide

*$p < 0.05$ versus Febuxostat-treated group

The target level for SUA at the end-of titration was achieved in the 75% and 82% of patients treated with allopurinol or febuxostat, respectively. At the end of the follow-up period, the mean SUA levels were 4.9 ± 0.9 mg/dL and 4.5 ± 1.0 mg/dL in allopurinol and febuxostat-treated patients despite a decrease in the individual adherence to treatment over time.

After a median follow-up period of 5.1 years, 20 (14.8%) patients in the allopurinol group and 8 (6.6%) in the febuxostat group died of cardiovascular causes. The cumulative cardiovascular survival was 0.96 (95% CI 0.93–0.99) in febuxostat-treated patients and 0.89 (95% CI 0.84–0.93) in allopurinol-treated patients (Fig. 2), and the difference achieved a statistical significance ($p = 0.04$). The result was confirmed by repeating the analysis by gender. In men, the cumulative cardiovascular survival was 0.97 (95% CI 0.95–0.99) in febuxostat-treated patients and 0.90 (95% CI 0.86–0.94) in allopurinol-treated patients ($p = 0.04$). In women, the cumulative cardiovascular survival was 0.95 (95% CI 0.93–0.98) in febuxostat-treated patients and 0.88 (95% CI 0.84–0.91) in allopurinol-treated patients ($p = 0.03$).

Discussion

HF patients require a complex and intensive management program including the improvement of all the known and reversible risk factors for rehospitalization [22].

Our results suggest a different effect of allopurinol and febuxostat in a mixed population of elderly outpatients with mild-to-moderate (NYHA class I–II–III) HF with either reduced or preserved left ventricular ejection fraction and followed a median follow-up period of 5.1 years. The cumulative survival was significantly higher in patients treated with febuxostat in comparison with allopurinol treatment. The results were comparable in men and women and after adjustment for a number of prognostic variables (SUA serum level, baseline kidney function, HF class and drug treatment).

Febuxostat has resulted to be more effective in terms of cardiovascular mortality and the difference may be explained by the peculiarities of the pharmacological profile of the drug when compared to allopurinol. In spite of their superimposable therapeutic indications, the two drugs bear different biological properties since both allopurinol and its active metabolite oxypurinol are substrates for many different enzymes whereas febuxostat is a selective inhibitor of xanthine oxidoreductase (XO) [23]. In patients with HF, several different mechanisms contribute to the production of SUA, including the increased availability and activity of XO, the larger conversion of xanthine dehydrogenase to XO and the augmented availability of XO substrate at the level of adenosine [24]. Circulating serum uric acid may actually reflect the activity of the XO, the key enzyme involved in the production of uric acid during purine metabolism that is upregulated in failing heart [25, 26] and could play an important role in the pathophysiology of HF, leading to increased oxidative stress, myocyte apoptosis and cardiac mechano-energetic uncoupling independently from renal function. [27, 28] Considering all this, it is plausible that the

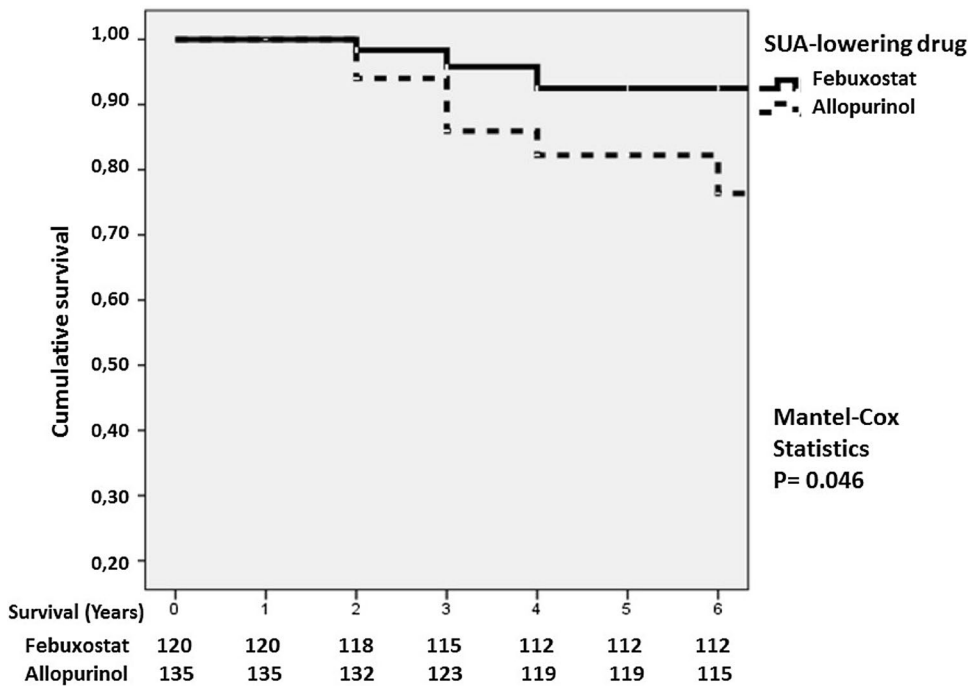

Fig. 2 Survival from cardiovascular mortality in heart failure patients treated with allopurinol and febuxostat

differences in pharmacological profile between allopurinol and febuxostat can have some effect on the clinical outcome of patients with HF even whether the results of the available studies have reported conflicting results.

In particular, our results largely differ from those of the CARES study, a larger, randomized study comparing the efficacy and safety of allopurinol and febuxostat in a population of obese patients with gout, and reporting an questionable increase in the risk of cardiovascular mortality (not including heart failure) in patients treated with febuxostat [29]. Conversely, our results are in agreement with those of Foody et al. [30] on a large population of patients including those with HF and studied in a setting of daily practice. This study has shown a better cardiovascular outcome in patients treated with febuxostat in comparison with allopurinol and the size of the benefit is greater than that observed in our study. As far as the other studies published in patients with elevated SUA and HF (OPT-HF, EXACT-HF) [3, 4], their results are not comparable with those reported in our study since only allopurinol or its derivative oxypurinol have been used and compared to placebo. Moreover, we mainly enrolled relatively young elderly and not frail elderly in which high SUA level could have a different clinical meaning, being protective versus some main health outcomes [31, 32].

On the other side, our study supports the hypothesis that the cut-off to identify a lower health risk related to SUA levels should be lower than the ones usually considered to be pharmacologically treated based on the gout risk [33].

Moving from single studies, a recent meta-analysis of 81 trials including 10,684 patients showed that XO inhibitors reduces the risk of total cardiovascular events (0.60, 0.44–0.82; serious cardiovascular events: 0.64, 0.46 to 0.89) [34]. However, the studies included in the meta-analysis had a median follow-up of 90 days (percentiles 25th, 75th: 60, 270 days; range 28–1095 days), while our observation on cardiovascular mortality is related to a remarkably longer follow-up.

Our study has some relevant limitations. First, it is an observational study, and its design is not double-blind nor randomized. However, we enrolled consecutively our patients to reduce as much as possible the selection bias. Moreover, the baseline characteristics of the patients were well balanced between the two groups. The allocation to treatment was largely based on the history of allopurinol intolerance and renal dysfunction, and this choice, largely based on clinical criteria, can increase the relevance of the observation in daily clinical practice. In the most part of cases, the change of treatment to febuxostat was done after the first 3 months of treatment with allopurinol, so that we do not believe that the first treatment has significantly influenced the outcome of the patients. In spite of the obvious limitations, our study has also some advantages. We have actively followed-up most of the patients (> 90%) which supports a suitable reliability of the results. Second, the population sample was relatively small, but representative of the whole cohort of outpatients attending our heart failure clinic. Third, we have decided to avoid any dietary standardization with the exclusion of salt intake considering that the effects of usual diet on SUA level are actually very limited. [35] Finally, the clinical nature of inclusion and exclusion criteria applied for the allocation of patients to treatment can contribute to better understand the role of xanthine-oxidase inhibitors in the general population of HF patients. A larger study, based on the same patient-oriented approach, is now warranted to identify whether this therapeutic approach can contribute to further improve the clinical prognosis of the heterogeneous population of patients with HF.

In conclusion, our study results suggest that possibility that febuxostat, a selective XO inhibitor, may reduce risk of cardiovascular mortality compared to allopurinol in elderly HF outpatients. These observations deserve further evaluation.

Funding This research was funded by institutional funding of the University of Bologna.

Compliance with ethical standards

Conflict of interest Prof. Claudio Borghi is scientific consultant for Menarini International, no one of the other authors have direct nor indirect conflict of interest in the publication of this paper.

Statements on human and animal rights The study was carried out in the setting of current clinical practice and has been carried out in agreement with the Declaration of Helsinki.

Informed consent The study was approved by the local ethical board and each subject signed an informed consent.

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