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Available treatment options for hyperuricemic patients

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Abstract

The negative impact of an elevated serum uric acid on the onset and/or progression of different diseases is well known. During the last decade, new forms of therapies were developed, with beneficial results on correcting hyperuricemia, but also with potential side effects that should not be overlooked as most of the hyperuricemic patients are presenting concomitant comorbidities that could influence the decision in prescribing a specific lowering serum uric acid drug. The review will describe recent treatment options, part of them available also in our country.

Keywords: hyperuricemia, xanthine oxidase inhibitors, uricosurics, adverse effects

INTRODUCTION

Hyperuricemia condition, physicochemical defined as an elevation of serum uric acid level more than 7 mg/dl, represents an important health problem that can contribute to the development and/or progression of different pathologies, such as chronic kidney disease, gout, insulin resistance syndrome, cardiovascular diseases, including hypertension etc. [1,2]. Furthermore, different studies concluded a significant increase of uricemia especially in high-income and economically developing countries, with a similar distribution between genders (21.2% in men, 21.6% in women, respectively) [3-6].

Considering all these aspects, including different factors that could contribute to the augmentation of serum uric acid (i.e. age, especially above 60 years old, kidney function, exogenous causes, mainly dietary habits, such as increased alcohol, processed food consumption etc.), there is a worldwide keen interest in determining the most suitable treatment approach in lowering elevated concentration of serum uric acid [7,8].

URIC ACID NORMAL PRODUCTION. POTENTIAL RISK FACTORS INCRIMINATED IN THE DEVELOPMENT OF HYPERURICEMIA

In order to comprehend the adequate drug therapy that could be considered as appropriate for this group of patients, it is important to understand the normal mechanisms of uric acid production, determined by the purine metabolism (Figure 1) [2,3].

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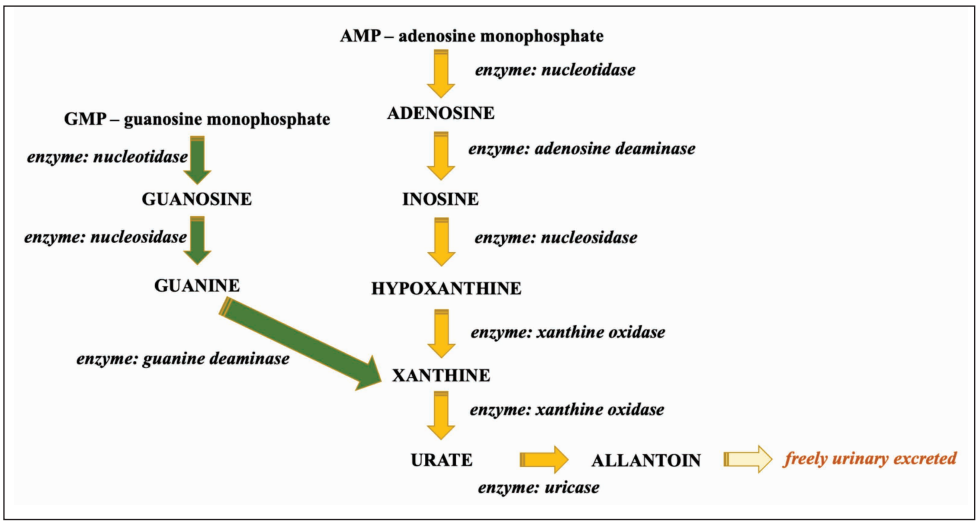

FIGURE 1. *Uric acid production via purine pathway – modified after [2,3]*

Considering the normal physiological pathway of uric acid production, there are several potential causes that could lead to the development of hyperuricemia, risk factors that are important to be acknowledged in order to apply the best treatment strategy in these patients (Table 1) [3,9-17].

Once the therapy management in lowering serum uric acid quantity is initiated, the physician should carefully monitor the serum level of uric acid as, nowadays, several studies reported a correlation between serum uric acid values below the normal range and the negative impact on different pathologies, such as multiple sclerosis, neoplasia, Parkinson's disease etc. [2,18-22].

AVAILABLE DRUG. TREATMENT STRATEGIES

Depending on their mechanism and site of action in lowering serum uric acid, the available drugs could be classified into reducing uric acid production through xanthine oxidase inhibition (i.e. Allopurinol, Febuxostat, Topiroxostat); inhibiting uric acid reabsorption (i.e. Benzbromarone, Probenecid, Lesinurad, Arhalofenate, Verinurad); increasing uric acid removal (i.e. Pegloticase); other drugs with potential uricosuric effect (i.e. sodium-glucose co-transporter 2 inhibitors, fenofibrate, losartan, vitamin C, salicylate/salicyclic acid and indomethacin), but further extensive clinical trials are required to validate their use in the treatment of hyperuricemia [3,7].

Allopurinol

Allopurinol represents the most common drug used in patients presenting hyperuricemia, being administrated orally or parenterally. It is metabolized to alloxanthine that inhibits the enzyme xanthine oxidase. Allopurinol is metabolized through the liver and has a biological half-life of 2-3 hours. The main adverse / side effects reported were: gastrointestinal complaints, skin rash, eosinophilia, intestinal nephritis, hepatitis. The daily dose can vary between 100 and 600 mg, but several studies reported that a dose lower than 300 mg/

TABLE 1. *Examples of potential risk factors incriminated in the development of hyperuricemia [3]*

Overproduction of urate			
Diet	Different pathologies	Genetic diseases	Drug administration
• Alcohol • Meat • Seafood • Fructose • Vitamins	• Obesity • Insulin resistance syndrome • Down syndrome • High cell turnover condition • Tissue hypoxia • Tissue ischemia	• Hypoxanthine-guanine phosphoribosyltransferase deficiency • Phosphoribosylpyrophosphate synthetase superactivity • Glycogen storage diseases	• Cytotoxic agents
Underexcretion of urate			
Diet	Different pathologies	Genetic diseases	Drug administration
• Alcohol • Fructose	• Chronic kidney disease • Obesity • Volume depletion • Small bowel disease	• Glomerulocystic kidney disease • Uromodulin variants	• Levodopa • Calcineurin inhibitors

day could be effective in decreasing the risk of cardiovascular events [7,23] and in addition, high doses of Allopurinol are contraindicated in patients diagnosed with chronic kidney disease, especially if they are under treatment with thiazides [7,24]. Allopurinol could interact also with other drugs, such as didanosine (an antiretroviral; major contraindication) [7,25], azathioprine (requiring lowering the dose of the immunosuppressive) etc. [7].

Febuxostat

Febuxostat is another xanthine oxidase inhibitor that is also metabolized through the liver, and could associate the following adverse / side effects: muscle pain, gastrointestinal complaints, increase of liver enzymes [7]. Its biological half-life is of 5-8 hours, and the daily dose is between 80 and 120 mg [7]. It is considered superior to Allopurinol as it presents a concomitant anti-inflammatory effect (on the endothelium) [7,26,27] and the possibility to decrease serum uric acid with lower doses (40 mg/day Febuxostat versus 300 mg/day Allopurinol) [7]. Nevertheless, recent studies highlighted the potential link between Febuxostat and the increase of cardiovascular mortality [7, 28], and, therefore, Allopurinol is recommended as first-line therapy in hyperuricemia [7, 29]. Regarding patients diagnosed with chronic kidney disease, there are trials that supported the use of Febuxostat, presenting a nephroprotective effect comparing with Allopurinol [7,30-32].

Topiroxostat

Topiroxostat, another xanthine oxidase inhibitor, hepatically metabolized, with a biological half-life between 4.5 and 7.5 hours, and with possible fewer adverse / side effects (polyarthritis, increase of hepatic enzymes), is considered to be safely used in chronic disease patients, undergoing or not hemodialysis – usual daily dose of 160 mg [7,33,34].

Probenecid

Probenecid represents another uricosuric that inhibits uric acid reabsorption. It has a biological half-life of 4-12 hours and the recorded adverse / side effects include gastrointestinal disorders, skin rash. The main concern regarding Probenecid administration is the renal toxicity (most of its metabolites are renal excreted), therefore, due to the lack of data related to drug safety in patients with a glomerular filtration rate below 50 ml/min/1.73 m^2, it should be avoided in this group of patients [7].

Other uricosurics that inhibit uric acid reabsorption

Benzbromarone has a biological half-life of 4-17 hours [7]. Due to its important hepatic toxic effect, it was withdrawn from several countries [7].

Lesinurad has a biological half-life between 9 and 10 hours, and can present the following adverse / side effects: nephrotoxicity, increase risk of cardiovascular mortality [7]. Therefore, it is contraindicated in patients with a serum creatinine level over 4 mg/dl, uncontrolled hypertension, recent myocardial infarction or diagnosed with heart failure NYHA class III / IV [7,35].

Arhalofenate presents a biological half-life of almost 50 hours, and could be associated with different adverse effects: increase in creatine kinase, kidney stones, angioedema, peripheral neuropathy [7]. It is considered the first choice of treatment for gout flares [7].

Verinurad represents an URAT1 inhibitor, currently under investigation, but with promising results in treating gout and asymptomatic hyperuricemia. It was correlated with the development and progression of renal impairment.

Pegloticase

Pegloticase is an intravenous uricosuric that determines an increase of uric acid removal [7]. It has a biological half-life time for 6.4-13.8 days, and its main adverse effects are: gastrointestinal complaints, dyspnea, headache, urticaria, acute gout attacks, decrease of blood pressure, methemoglobinemia etc. [7]. It is contraindicated in patients diagnosed with glucose-6-phosphate dehydrogenase deficiency [7,36] and due to development of anti-drug antibody during the treatment, concomitant immunosuppressive therapy should be considered [7,37].

CONCLUSIONS

Hyperuricemia, due to its multiple implications, is considered an important risk factor in the development and/or progression of different pathologies (i.e. renal, metabolic, cardiovascular diseases), should be effectively treated, but nevertheless, important aspects should be emphasized, such as the adequate type of drug elected in lowering serum uric acid, considering its potential adverse effects, the patients' comorbidities, and, in addition, an optimal assessment of serum uric acid concentration as a significant decrease could be correlated with several neurological or neoplasic diseases' poor outcome.

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