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Review article

Critical revision of the medical treatment of gout in Brazil

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ABSTRACT

Gout is considered the most common form of inflammatory arthritis in men over 40 years. The authors present a brief review of the current treatment of gout and discuss the existing pharmacological limitations in Brazil for the treatment of this disease. Although allopurinol is still the main drug administered for decreasing serum levels of uric acid in gout patients in this country, the authors also present data that show a great opportunity for the Brazilian drug market for the treatment of hyperuricemia and gout and especially for patients using private and public (SUS) health care systems.

Revisão crítica do tratamento medicamentoso da gota no Brasil

Palavras-chave:
Gota
Hiperuricemia
Tratamento
Artrite gotosa
Medicamentos

RESUMO

A gota é considerada a forma mais comum de artrite inflamatória em homens acima de 40 anos. Os autores apresentam uma breve revisão sobre o tratamento atual da gota e discutem as limitações farmacológicas existentes no Brasil para o tratamento desta enfermidade. Apesar de que o alopurinol ainda seja a principal medicação para a redução dos níveis de uricemia de pacientes com gota no país, os autores também apresentam dados que apontam para uma grande oportunidade para o mercado farmacológico brasileiro em relação ao tratamento da hiperuricemia e da artrite gotosa e especialmente para pacientes usuários de sistemas privados de saúde e do SUS (Sistema Único de Saúde).

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Introduction

Gout is a disease characterized by an accumulation of monosodium urate (MSU) crystals in the joints, synovial tissue, bone, and skin, regardless of the presence or absence of clinical manifestations.[1,2] This accumulation is a result of a persistent hyperuricemia.[1] The MSU crystals are the solid form of uric acid, the final product of purine metabolism; these crystals can accumulate in organic tissue.[3] The purines are a result of the breakdown of mononucleotides, substances derived from those nitrogenous bases that make up DNA and RNA. In the biological process of urate production, the compounds are, in their last stages, metabolized into xanthine which, in turn, is irreversibly oxidized to produce uric acid by the action of the enzyme xanthine oxidase,[4,5] which comprises the arsenal of peroxisomes in the majority of cells.[3] Circulating uric acid (UA) in the blood maintain its physiological levels at concentrations around 6.0 mg/dL,[6] and the excess is eliminated by the kidneys.[7] Under physiological conditions, circulating UA can take part in antioxidant, oxidant, and pro-inflammatory reactions; such participations are more evident when circulating UA is found in high serum concentrations.[5]

Hyperuricemia is defined as the high urate serum concentration, at approximately 6.8 mg/dL, which is the limit of solubility of the urate.[1] Above this level of solubility, MSU crystals may accumulate in the tissues, especially in a case of chronic, untreated hyperuricemia. In addition to disturbances in the generation or clearance of uric acid, hyperuricemia can be initiated or accelerated in patients with kidney and cardiac transplant, as these are usually associated with chronic kidney disease and the use of loop diuretics.[8] UA may be associated with different multifactorial disorders, whether dependently or independently. There is a direct relationship between UA levels and development and progression of cardiovascular disease.[9–15] There is also evidence of a positive association between UA levels and hypertension,[12,16] kidney disease,[16] and the risk of coronary events.[17] Furthermore, disorders of purine metabolism or in the process of elimination of uric acid, or an increase in protein intake[18] may contribute to the elevation of UA.

Gouty manifestations may occur in three phases: acute crises (1), intercritical period (2), which occurs between crises, is completely asymptomatic, and has a variable duration. At the beginning of the disease this period can last for years; however, it tends to become gradually shorter with the progression of the disease. Chronic arthropathy (3), the most advanced stage, is characterized by multiple and/or persistent crises.[8]

Several events can trigger acute attacks of gout, including excessive alcohol intake, metabolic stress (such as the observed in acute myocardial infarction or surgery) or, more commonly, sudden changes in UA levels, as occurs after the beginning urate reduction therapy, leading to a resorption of MSU crystals.[8] Acute gout is recognized as one of the most painful experiences, comparable to labor pains and visceral colic, such as nephritic colic.[19] A flare begins when macrophages present in the synovial fluid phagocyte the crystals and initiate the inflammatory cascade, releasing mediators and promoting neutrophil chemotaxis.[20]

The classical clinical presentation of gout is an acute inflammatory arthritis, which usually is a single-joint, recurrent, intense, self-limiting process.[8,19,21] In about 50% of cases, arthritis occurs in the first metatarsophalangeal joint, being known as podagra.[12,22,23] The joints of the ankle and knee are common sites of arthritis.[8] Oligoarticular and polyarticular impairment is less common,[24] but this can occur in patients with long-standing, untreated gout, as well as in patients with a marked and significant reduction of uric acid levels, arising from the urate-lowering therapy. Some prodromes, such as pain, discomfort, and limitation of movement, may indicate the onset of an acute gout episode.[8]

Tophi are macroscopic collections visible MSU crystals by clinical examination, and usually indicate a long-standing disease which has not been treated.[25,26] The presence of tophi is related to an increase of structural damage[27] and loss of joint function,[26] and its occurrence is directly related to increased serum urate levels.[25] The urate-lowering therapy is associated with a reduction of tophi formation, as well as to the regression of existing formations.[28] Chronic gout also leads to a restriction of joint mobility, joint swelling, and a radiologically apparent deformity.[8] Well-defined 'punched-out' type lesions, especially when showing an eggshell edge (overhanging bony edges – Martel signal) are characteristic radiologic findings indicating a longstanding, serious, untreated chronic gout.[29]

Epidemiology

Despite the wide variation of data between different countries, it is believed that the prevalence of gout has increased over the last six years.[16] The US study National Health Interview found an increase in the prevalence of self-reported gout, from 4.8/1000 in 1967[30] to 9.4/1996[31] in 1996. According to the Johns Hopkins Precursors Study, in 1991 the incidence of gout in the United States was estimated at 1.73 per 1000 population.[32] In Brazil, there is a lack of epidemiological studies in this area.

The reasons for the apparent increase in the incidence of gout over the last few years have not been clarified, although several risk factors have already been described. Hyperuricemia is directly linked to gout, since 10% of patients with hyperuricemia develop gout, and 90% of patients with gout have high concentrations of UA.[33] The Framingham study indicated an dose-dependent increase in the relative risk to gout development with increasing UA levels. Other risk factors related to gout indicated in the same study were alcohol intake, body mass index, and blood pressure.[16,24,32,34–39] It is known that both overweight and obesity can increase the endogenous production of uric acid.[40] The relative risk of incidence of gout is 1.95 in men with body mass index (BMI) between 25 and 29.9 kg/m^2, compared to the relative risk of 1.00 when BMI is between 21 and 22.9 kg/m^2. The same study noted an increase in the relative risk, to 2.97, when BMI is greater than 35 kg/m^2.[41] Other studies have added the consumption of purine-rich food and soft drinks sweetened with fructose as risk factors for hyperuricemia and gout. Conversely, dairy products, coffee, and vitamin C have been linked to a protective effect for developing gout.[36,42–45]

Diagnosis

The gold standard in the diagnosis of gout is the observation of monosodium urate crystals under compensated polarized light microscopy; for this examination, these crystals exhibit negative birefringence. The sample should be preferably collected from newly affected joints, as well as from previously affected joints.[12]

Nonetheless, in a typical clinical presentation, the clinical diagnosis is reasonably accurate, being acceptable in the absence of microscopy or rheumatologists. This diagnosis, however, is not definitive.[12]

Although a common clinical practice, the use of classification criteria for diagnostic purposes has evolved over the last decade.[46] Nevertheless, recently a diagnostic criterion for easy use, developed for primary care, showed good performance in secondary care, with a good positive predictive value in the diagnosis of gout when the analysis of synovial fluid is not available.[47]

After verification of the presence of MSU crystals in the joint environment, one must quantify this deposition, as well as its extent and the induced structural damage. In addition to history and physical examination, imaging studies such as X-rays, ultrasound, and dual emission computed tomography can be useful to assess the chronic phase of the disease and the damage done.[48] The differential diagnoses should always be considered, especially in oligoarticular or polyarticular presentation, which may mimic several diseases, such as rheumatoid arthritis and spondyloarthropathies. In the case of a monoarticular presentation, septic arthritis should always be discarded.[8]

Treatment

Basically, the treatment of gout can be divided into two stages: acute flare management and long-term therapy (Table 1). In the first stage, it is critical to relieve the pain, reducing inflammation and joint impairment; for this purpose, the patient must be treated with anti-inflammatory agents; in the second stage, the aim is to decrease UA concentrations, as well as to prevent new crises. Anti-inflammatories are no longer appropriate in this stage, where both pharmacological measures and non-pharmacological procedures should be adopted.[28,49–53]

Regarding drug prescription, both for the acute management and long-term therapy, some l variables can influence the choice of medication, such as availability, cost, efficacy, and clinical indications due to potential comorbidities of the patient. Hypertension, cardiovascular disease, chronic kidney disease, and diabetes are examples of commonly occurring conditions associated with gout that should be taken into consideration before the implementation of an appropriate treatment.[54]

Table 1 – Management of acute and chronic gout.

Management of gout	
Flare (acute)	Longstanding (chronic)
Objective	
• Pain relief	• Prevention of new attacks
• Inflammation decrease	• Reduction of the concentration of uric acid crystals
• Joint capacity restoration	
Management	
• Nonsteroidal antiinflammatory drugs	• Allopurinol
• Corticosteroids	• Febuxostat
• Colchicine	• Uricosuric agents
Consider an association if persistent pain or polyarticular involvement.	• Recombinant uricases
	Advise on modifiable risk factors.

Management of acute flares

For low- or moderate-intensity attacks (pain index ≤ 6 on a scale from 0 to 10) involving one to three small joints or one to two large joints, monotherapy is recommended. It can be initiated with both nonsteroidal anti-inflammatory drugs and colchicine or corticosteroids.[55]

The *nonsteroidal anti-inflammatory drugs* (NSAIDs) are the most widely used therapy for early treatment of acute gouty arthritis[56] and, due to the intensity of crisis, these agents can be administered in maximum dosages.[6] This class includes drugs of different pharmacokinetic and pharmacodynamic properties, but with a similar action: they exert an anti-inflammatory function by inhibiting the cyclooxygenase (COX) enzymes, which catalyze the conversion of arachidonic acid derived from membrane phospholipids to prostaglandins.[54,57] NSAIDs can be non-selective (such as ibuprofen, indomethacin, and naproxen), with inhibition of COX-1 and COX-2, or selective, with inhibition of COX-1 (such as aspirin) or COX-2 (like celecoxib and other "coxibs").[54,58] Among the NSAIDs commonly prescribed to patients with gout, indomethacin has been traditionally used.[59] However, there is evidence that any NSAID has a similar effect in reducing the acute inflammatory activity in gout.[19] Since gouty patients often have comorbid conditions and the prescribed dosages of anti-inflammatory drugs are high, proton pump inhibitors can be used in order to prevent gastrointestinal damage, such as ulceration, bleeding, and perforation. In this context, COX-2 inhibitors may have the same effect as COX-1 inhibitors, and may be a good option for patients with gastrointestinal disorders, such as gastroesophageal reflux disease and peptic ulcer.[60] However, due to their renal and cardiovascular toxicity, the use of these drugs should be carefully considered and individualized.

Colchicine, an alkaloid derived from meadow saffron extracts,[54] is also recommended in first-line treatment.[6,54,55] Several effects of this substance have already been reported, being the inhibition of cell division (by binding to tubulin of microtubules and prevent spindle formation) the best-known effect.[54] In gout, this function directly affects the activity of neutrophils by preventing diapedesis, Lysosomal mobilization, and degranulation, which releases not only pro-inflammatory substances, but also leukocytic chemotactic agents.[61] Moreover, colchicine inhibits the formation of inflamassome NLRP3 (intracellular multiprotein structure

important for the processing and release of inflammatory cytokines IL-1 and IL-18), induced by crystals of uric acid.[57,61] The metabolism of colchicine is processed by the cytochrome P450 family and thus this drug may interact with other drugs metabolized by this pathway.[54] Moreover, the renal and hepatic function of patients must be assessed before the use of colchicine.[19] Regarding dosage, the recommendations of the European League Against Rheumatism – EULAR[6] and those of the American College of Rheumatology – ACR are different.[62] The former organization recommends a maximum dose of 0.5 mg three times a day; conversely, the latter proposes a dose of 1.2 g, followed by another administration of 0.6 mg one hour later, repeated at 12 h. ACR guidelines also propose that the treatment with colchicine will lead to better results if started within 24 h of the onset of symptoms, not exceeding 36 h and remaining until the attack is suppressed. Intravenous administration of colchicine is extremely toxic and is not recommended.[6]

Anti-inflammatory steroids, or *systemic corticosteroids* (SC), have several known effects in suppression of the inflammatory response, such as suppression of the immune response, inhibition of prostaglandins and leukotrienes, direct inhibition of pro-inflammatory transcription factors, and inhibition of cytokines such as IL-1, IL-6, IL-8, and TNF-α.[54,63] In addition, SC upregulate genes for anti-inflammatory factors, involving phospholipase A2 blockers.[58] As to the administration route, there are several options for corticosteroids – oral, intravenous, intramuscular or intra-articular.[19] The oral use is indicated when there is a failure in treatment with colchicine and/or NSAIDs, or when these drugs are not indicated.[54] Evidence are lacking as to what is the ideal dosage for this treatment; Janssens et al. demonstrated that a daily dose of prednisolone 35 mg is equivalent to 500 mg of naproxen twice daily.[64] Intramuscular administration of steroids is an option; but its use is limited to intra-hospital environment and, moreover, there is also no consensus on the dose to be used.[19] An intra-articular corticosteroid injection after joint aspiration is considered the ideal treatment for acute gout, since the pain relief occurs quickly (due to a decrease in the intra-articular pressure caused by the inflammatory process), and the corticosteroid, with its minimal systemic absorption, promotes a larger local effect.[6]

Corticotropin (*ACTH*) is a hormone secreted by the pituitary gland, which directly influences steroids secretion by the adrenal glands, stimulating the production of cortisol, corticosterone, and androgens.[54,65] For a while, ACTH represented an alternative therapy in acute gouty arthritis when administered in intramuscular injections. The mechanism of action of this hormone in patients suffering gout is not established; It is known that the ACTH may inhibit peripherally gouty inflammation, by activating the melanocortin receptor type 3, which would be a secondary effect.[65,66] Axelrod and Preston concluded that patients treated with intramuscular ACTH experienced pain relief faster than those treated with oral indomethacin when comparing the effects of these drugs in patients with an acute gout attack.[67]

Another possible therapy target is IL-1, a cytokine involved in gouty inflammation. MSU crystals stimulate IL-1 production and secretion in synovial monocytes and mononuclear cells, and activate the inflammasome NLRP3, thus justifying the validity of inhibiting this interleukin in the treatment.[68–70] *IL-1 inhibitors* are anakinra, canakinumab, and rilonacept, all of which are biological.[20,70,71] These drugs should be prescribed only when all previously administered agents were discarded by failure or inability to treat. Nonetheless, this is still a high-cost treatment, especially when compared with NSAIDs, and these the medications are not licensed in most countries. Finally, there is evidence that ice packs applied to the inflamed site can be an adjuvant procedure for pharmacological treatment.[72]

Long-term gout therapy has two goals: to reduce circulating levels of urate to a level below the saturation point, keeping UA < 6.0 mg/dL, and to prevent the formation of new urate crystals.[6] The most effective method for achieving this goal is the urate-lowering therapy (ULT) and several classes of drugs can be used in current clinical practice. However, ULT should not be restricted only to drugs, as the non-pharmacological treatment of gout plays a significant role in the prevention of new crises.[73]

The first step after the resolution of an acute gouty arthritis episode is to explain to the patient the nature of the attack, making him/her aware of the possible etiology and the changes in lifestyle that can prevent new crises from happening. Therefore, it is essential to obtain a good medical history, centered on family history, clinical history, and lifestyle habits. Therefore, it can be said that the treatment of gout in its chronic form is an individualized task.[74] Therefore, patients should be informed of all non-modifiable risk factors that can accelerate gout, such as age, ethnicity, and gender. As for modifiable risk factors – such as hyperuricemia, obesity, hypertension, dyslipidemia, ischemic cardiovascular disease, diabetes mellitus, chronic kidney disease, dietary factors, and abrupt changes in the levels of urate – guidance on control measures, such as reducing body mass, alcohol consumption, consumption of purine-rich foods, such as red meat and seafood, and consumption of fructose-rich beverages and foods, such as apple and orange, is absolutely critical.[18,19,75]

The aforementioned comorbidities also deserve attention and should be controlled. A relevant topic is the attention to the medications used by the patient. Diuretics, both thiazides and especially loop diuretics, increase the risk of incidence of gout, including patients with stable disease.[76] Furthermore, Choi, H. et al., in an observational cohort study, demonstrated that beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers (with the exception of losartan) increase the level of UA by reducing the renal excretion of uric acid, whereas losartan and calcium channel blockers increase the renal excretion of uric acid.[77]

The exact time to start ULT is not well established; by consensus, ULT should be started when the gout is well established and in a relatively serious level, i.e. recurrent attack (two or more per year), or a flare in a patient with chronic kidney disease stage 2 or higher; the presence of one or more tophi on clinical or imaging examination[62]; joint damage, or nephrolithiasis. Several studies show that once started, ULT should not be discontinued because of the risk of recurrence of acute arthritis.[78,79]

The xanthine oxidase inhibitors are drugs that reduce the concentration of urate by inhibiting its synthesis. The enzyme

xanthine oxidase (XO) catalyzes the two last stages of purine metabolism in humans: conversion from hypoxanthine to xanthine and from xanthine to urate.[4,80] There are two drugs capable of inhibiting this enzyme: allopurinol and febuxostat.

Allopurinol is considered as a first-line drug in reducing urate, i.e., the drug is effective in up to 90% of patients.[73] Its use is well established and is administered only once daily; furthermore, it is inexpensive and relatively safe.[6] Thus, it is the most prescribed drug in ULT.[81] Both allopurinol as its main active metabolite, oxypurinol, are non-specific competitive inhibitors of hypoxanthine oxidase and xanthine oxidase, respectively. Therefore, both drugs are able to reduce the production of uric acid, leading to an increase of xanthine and hypoxanthine concentrations in extracellular fluid.[73,81,82] Oxypurinol accounts for 90% of the bioavailability of allopurinol and is preferably excreted via the kidneys.[81]

The allopurinol dose adjustment should be individualized, starting with 100 mg and increasing in that same amount each month until urate levels are under control (target for uricemia $\leq$ 6.0 mg/dL, or ideally 5.0 mg/dL) with a maximum of 900 mg.[55] The best established daily dose is 300 mg; however, in this dosage approximately half of the patients achieve disease control.[83,84] Side effects appear in up to 20% of patients, with gastrointestinal intolerance, nausea, and cutaneous rash being the most common events.[85] In 1984, hypersensitivity syndrome to allopurinol (now known as DRESS – drug reaction or rash with eosinophilia and systemic symptoms)[85] was described, involving fever, cutaneous rash, eosinophilia, hepatitis, progressive renal failure and death due to multiple-organ vasculitis.[58] Steven-Johnson syndrome and toxic epidermal necrolysis can join this clinical picture, or occur in isolation (known as SCAR – severe cutaneous adverse reactions).[85] These reactions occur more frequently in patients with pre-existing renal impairment, or taking diuretic drugs.[58] There is also evidence of increased risk for hypersensitivity reactions in those patients who started this therapy recently.[85]

Febuxostat is a highly specific inhibitor of XO; this drug is derived from tiazolocarboxycilic acid. Febuxostat selectively inhibits both the oxidized and reduced form of XO by competitive and non-competitive mechanisms. Its metabolism occurs mainly in the liver, with a little amount excreted in urine[34,41,86] (around 10%).[87] Due to this feature, febuxostat was shown to be a promising alternative for patients with chronic kidney disease. Moreover, compared with allopurinol, febuxostat does not require dose adjustments and has fewer drug interactions that may limit efficacy or safety.[34,41,86] Among the identified side effects, there are changes in liver function tests, and in some cases, a potential adverse cardiovascular effect. Therefore, febuxostat is not recommended in patients with an impaired heart failure.[19] Several studies confirm the effectiveness of febuxostat versus allopurinol at a dose of 300 mg, to the point several countries – among them United States, Canada, and 20 European countries – have already allowed its use at daily doses of 40, 80, or 120 mg.[84,88] Since 2012, febuxostat is recommended by the ACR as a first-line urate-lowering therapy.[89] Due mainly to its cost, its use is most suitable in case of failure or impossibility of using allopurinol.[90]

Uricosuric agents (*probenecid*, *benzbromarone*, and *sulfinpyrazone*) are weak organic acids whose main effect is to increase the renal excretion of uric acid by inhibiting anion transporters in the proximal convoluted tubule (URAT1), responsible for the resorption of urate. Probenecid is the only uricosuric agent currently available in the United States. Benzbromarone was widely available in European, Asian, and South American countries, but it was banned in 2003 following reports of severe liver toxicity and bone marrow suppression.[91] Uricosuric drugs are second-line agents in the treatment of gout, becoming first-line only in patients who cannot tolerate them, or when there is no indication for an XO inhibitor. In addition, these drugs increase significantly the concentration of uric acid in the collecting ducts, predisposing to stone formation.[62] The uricosuric properties of losartan and fenofibrate have also been described, albeit discreet.[92] A mild but persistent uricosuric effect was observed with the use of vitamin C at daily doses lower than 500 mg.[93] *Lesinurade* is a promising uricosuric agent, which is currently at a late stage of clinical development, and is a non-nucleoside reverse transcriptase inhibitor. Originally, this drug was developed to treat patients with HIV.[91]

Non-primate mammals and some birds do not have urate as an end product of purine metabolism, because in another enzyme, uricase, catalyzes the conversion of urate to allantoin, a soluble and readily excreted product.[94] *Pegloticase* is a porcine recombinant uricase linked to various ethylene chains to prolong their activity and reduce their immunogenicity.[94] UA levels decrease to very low or undetectable levels a few hours after intravenous administration of pegloticase 8 mg.[52] Furthermore, repeated infusions promote the resorption of MSU crystal deposits, having an efficient and quick action in the reduction in tophi.[95,96] There are reports of patients that produce antibodies against pegloticase, decreasing its activity and increasing the risk of hypersensitivity reactions.[97] Currently, pegloticase infusion is licensed in the United States for patients refractory to oral therapy.[6,62]

A summary of the final stages of purine metabolism, ending with the formation of uric acid, and of the enzymes involved in this process (XO: xanthine oxidase; XDH: xanthine dehydrogenase), is presented. In this process, febuxostat and allopurinol and its most active form, oxypurinol play a role. The excretion of uric acid occurs by renal filtration. Resorption in the loop of Henle, via URAT1 receptors, is the most important factor of urate return into the bloodstream. The uricosuric agents (probenecid, benzbromarone, and sulfinpyrazone) act by decreasing the resorption of urate. Lesinurade, a drug still in a testing process, and losartan would have similar effects. The excess uric acid predisposes to hyperuricemia and formation of urate crystals that, by accumulating in the tissues and joints, generate an intense local inflammatory response, controlled with colchicine, non-steroidal anti-inflammatory drugs, corticosteroids or, less commonly, with canakinumab, an anti-IL1monoclonal antibody. Another consequence of the hyperuricemia, demonstrated in the figure, is the formation of kidney stones. The enzyme uricase, which is not present in mammals, converts uric acid to allantoin, a slightly toxic product that is easily excreted by the kidneys. Pegloticase

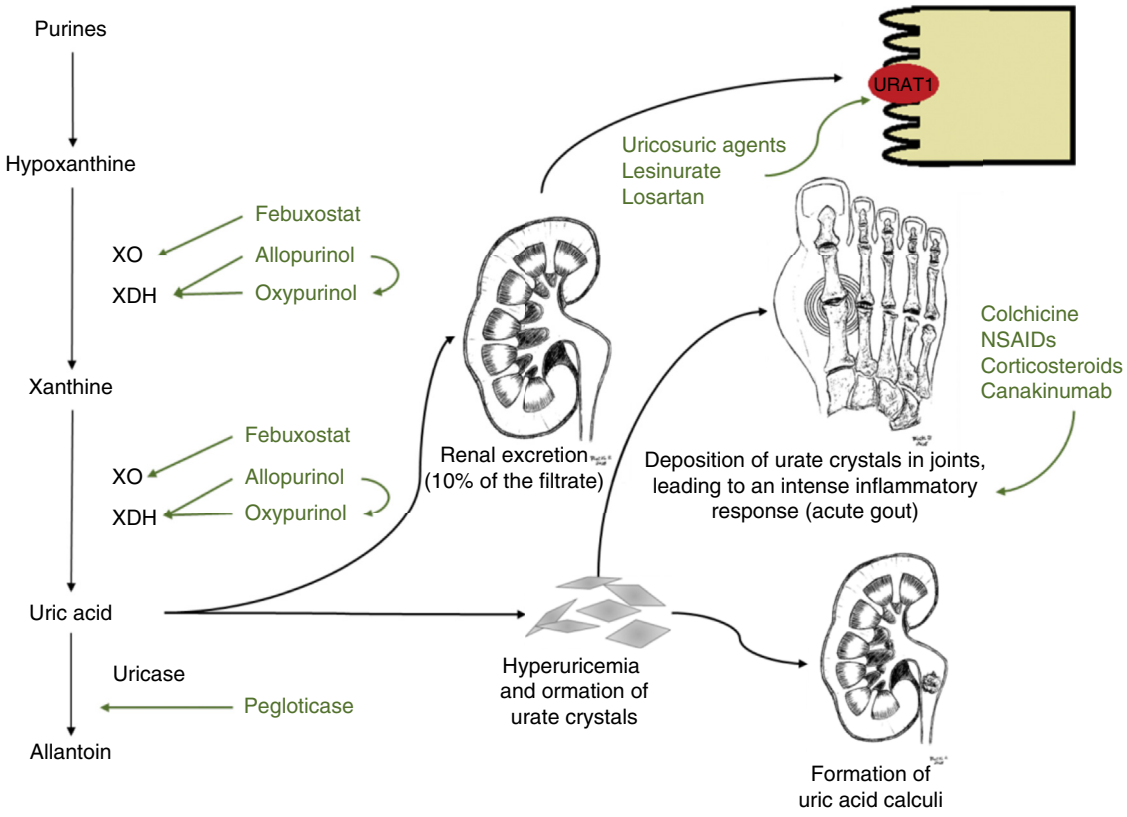

Fig. 1 – Pharmacologic agents and their mechanism of action for the treatment of gout.

(pegylated uricase) can perform the same functions of this enzyme (Fig. 1).

Options and limitations of the Brazilian drug market

Gout is considered the most common form of inflammatory arthritis in men aged over 40 years. Known since ancient times, the so-called "disease of kings" has attracted the attention of clinical investigators over several centuries. However, its treatment has remained largely unchanged for almost a century, until mid-2008, when the FDA advisory board approved the marketing of febuxostat, the first new drug in four decades for gout treatment. Since then, there is still no provision for the entry of this product in Brazil, and many patients with renal failure who would benefit from febuxostat need to import the medication with a medical prescription. In the treatment of an acute attack, colchicine, corticosteroids and a wide range of non-steroidal anti-inflammatory drugs are available in the Brazilian market, and these drugs are used in accordance with the experience of experts. Canakinumab is not a common therapeutic option for acute crises due to its high cost and also to the good response of the acute crises to traditional medications in most cases.

There is no set date for the arrival of Pegloticase, which can be used in patients with refractory chronic tophaceous gout, in the Brazilian market. Rasburicase, which is marketed in Brazil, is used in the prevention and treatment of tumor lysis syndrome, being only approved for use in adult patients with leukemia, lymphoma or solid tumors, who are subjected to cancer therapy, and who are at risk of presenting tumor lysis syndrome or an elevation of uric acid. Due to its off-label indication for tophaceous gout and also to the lack of convenience of its use (since the drug is used intravenously at daily intervals), rasburicase has not been routinely used in the treatment of gout. Furthermore, a precaution is required in patients with a history of atopy, as rasburicase can induce allergic responses. Clinical experience with this agent reveals that the patient should be closely monitored for the emergence of adverse events of an allergic nature, especially skin reactions, and bronchospasm. Nonetheless, a recent systematic review shows that in gouty patients with renal insufficiency, rasburicase, febuxostat, benzbromarone, and allopurinol in association with benzbromarone appear to be effective and safe.[98]

The use of benzbromarone is prohibited in the US market, but the therapeutic experience in Brazil has been positive, both in monotherapy or associated to allopurinol in refractory cases.[99] Although several national pharmaceuticals companies are producing this molecule, some patients complain of sporadic shortage of the product in the domestic market and often opt for a pharmacological manipulation of the product.[100]

There is no doubt that allopurinol has been the primary medication for reducing serum uric acid levels in gout patients in Brazil and recently a meta-analysis showed its impressive safety,[101] despite reported cases of toxic

Table 2 – Status of pharmacological drugs for the treatment of gout, according to the regulatory agency. ANVISA: Agência Nacional de Vigilância Sanitária (Brazil); FDA: Food and Drug Administration (United States); EMA: European Medicines Agency (Europe).

Drug	Regulatory agency		
	ANVISA	FDA	EMA
NSAIDs	Released	Released	Released
Colchicine	Released	Released	Released
Corticosteroids	Released	Released	Released
Canakinumab	–	Released	Released
Allopurinol	Released	Released	Released
Febuxostat	–	Released	Released
Probenecid	Released	Released	Released
Benzbromarone	Released	–	–
Sulfinpyrazone	–	Released	Released
Pegloticase	–	Released	Released

necroepidermyoisis[102] and death with the use of this product.[103]

Unfortunately, its active metabolite, oxypurinol, which is available on the European market, is also not available in the Brazilian market. However, questionnaire applied to rheumatologists in the 1990s indicated that colchicine was the most prescribed product for the treatment of gout in Brazil.[104]

Recent findings indicating that the elevation of uric acid is an important cardiovascular risk factor has forced a change of scenery in the treatment of patients with hyperuricemia, which should impact the treatment of gouty arthritis in Brazil, as has occurred in other countries.[105] Finally, for the next few years, the authors believe that there is a great opportunity for the Brazilian drug market for the treatment of gout and especially for patients using private and public (SUS) health care systems. Table 2 presents a comparison of the presence of these medicines in the European, US, and Brazilian markets.

Conflicts of interest

Dr. Valderilio Feijó Azevedo, Dr. Eduardo dos Santos Paiva and Dr. Geraldo da Rocha Castelar Pinheiro declare their participation in the advisory board of Astra Zeneca. The other authors declare no conflicts of interest for this publication.

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