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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:
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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]

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