ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Rapid induction of oral tolerance to allopurinol: a case report

Indução oral rápida de tolerância a alopurinol: um relato de caso

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ABSTRACT

Continuous oral allopurinol use is the first-line treatment for hereditary glycogen disorders. While hypersensitivity reactions to allopurinol are uncommon, they can pose challenges when this medication is the only available option for the long-term treatment of the underlying disorder. In such cases, desensitization emerges as a viable alternative. We report the case of a patient with glycogen storage disease type I who developed a generalized pruritic rash due to allopurinol. Drug intolerance was successfully managed using a rapid oral desensitization protocol, which allowed an uneventful long-term use of allopurinol.

Keywords: Drug hypersensitivity, immunologic desensitization, glycogen storage disease.

RESUMO

O alopurinol, de uso contínuo oral, é o tratamento de escolha para os distúrbios hereditários do glicogênio. Apesar de não ser comum, a reação de hipersensibilidade ao alopurinol se torna um problema quando esta é a única medicação disponível para o controle da doença de base. Nestes casos, a dessensibilização é uma alternativa viável. No presente relato, descrevemos o caso de um paciente com diagnóstico de doença de depósito de glicogênio tipo I, com exantema pruriginoso generalizado ao alopurinol, tratado com um protocolo de dessensibilização oral acelerado. Este tratamento permitiu o uso contínuo deste medicamento sem novas reações em longo prazo.

Descritores: Hipersensibilidade a drogas, dessensibilização imunológica, doença de depósito de glicogênio.

Introduction

Glycogen storage diseases (GSDs) are hereditary metabolic disorders resulting from defects in glycogen synthesis or degradation.[1] Of various known subtypes, glycogen storage disease type I (GSD I) is so named as it was the first to have its mechanism identified. It has an autosomal recessive inheritance pattern, with an incidence of 1 per 100,000 population. Its underlying etiology is a deficiency of one of two enzymes, either glucose-6-phosphatase (subtype GSD-Ia) or glucose-6-phosphate translocase (subtype GSD-Ib). GSD-I may present with growth restriction, intermittent hypoglycemia, hepatomegaly, progressive renal failure, hyperlactatemia, hyperuricemia, hyperlipidemia, anemia, and neutropenia.[2] Around 71% of those affected will develop metabolic changes, including hyperuricemia, which occurs secondary to decreased renal clearance and increased production of uric acid as a byproduct of adenine nucleotide degradation.[3] Given the well-established association of hyperuricemia with kidney

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disease, cardiovascular diseases, diabetes, and gout, treating this condition is key to preventing or at least mitigating such complications.[4,5] The current treatment of hyperuricemia consists of dietary restrictions (with various types of diet being studied, including the DASH diet, the Mediterranean diet, and a low-purine diet) and allopurinol.[6]

Allopurinol is widely used in the treatment of patients with hyperuricemia and/or gout. It is inexpensive and is considered a first-line therapy of choice. Most of the action of allopurinol is the result of its main active metabolite, oxypurinol, inhibiting xanthine oxidase, the enzyme responsible for catalyzing the oxidation of hypoxanthine and xanthine into uric acid; inhibition decreases production of uric acid and, consequently, reduces its levels in blood and urine.[7,8] Although widely used and generally well tolerated, allopurinol can lead to hypersensitivity reactions, and is a significant cause of severe cutaneous adverse reactions worldwide. Allopurinol-related reactions can range from a mild maculopapular rash to life-threatening severe cutaneous reactions such as the Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS).[7] In recent decades, investigators have attempted to identify a relationship between genetic predispositions and allopurinol-induced adverse cutaneous drug reactions. One study with Chinese patients demonstrated a strong relationship between HLA markers and the risk of developing SJS/TEN.[9] To date, some risk factors identified for this association are female sex, advanced age, chronic kidney disease or cardiovascular disease, initiation of therapy at high doses of allopurinol, and HLA-B 58:01 carrier status.[7]

An adverse drug reaction (ADR) can be defined as any non-therapeutic effect resulting from the use of a drug in usually therapeutic doses. ADRs can be classified as predictable or unpredictable. Predictable, or type A, reactions are those caused directly by the medication administered. Unpredictable, or type B, reactions are those not directly related to the effects of the medication, but rather due to intolerance or hypersensitivity; these may be allergic or result from a direct interaction of the drug with immune cell receptors. Hypersensitivity ADRs are due to stimulation of the immune system by potentially immunogenic particles. In some cases, a small-molecule drug – a hapten – binds to a carrier protein, thus forming an allergenic complex. Allergy to beta-lactams is one example of this mechanism. Pseudoallergic reactions are mediated by activation of inflammatory mechanisms without involvement of the adaptive immune system, causing a clinical picture resembling that of IgE-mediated reactions. This process occurs through activation of cellular inflammation receptors or inhibition of enzymes leading to an increase in pro-inflammatory mediators. Examples include direct activation of Mas-related G protein-coupled receptor-X2 (MrgprX2) in mast cells and the inhibition of cyclooxygenase by non-steroidal anti-inflammatory drugs (NSAIDs). The pharmacological interaction with immune receptors (p-i) concept describes a phenomenon that occurs through non-covalent bonding between a drug and immune-system cell receptors (HLA or TCR), eliciting a T cell-mediated immune response and triggering alloimmune hypersensitivity. This mechanism does not require a second signal to trigger a strong T cell-mediated reaction. Some ADRs to allopurinol are an example.[10,11]

Treatment of ADRs involves immediate discontinuation of suspected medications, symptom management, and supportive care as necessary. In anaphylaxis, epinephrine is the only treatment with proven effectiveness and must be administered promptly. Drug desensitization should be considered in patients with confirmed or high likelihood of a hypersensitivity reaction to a medication whose use is essential and where no other treatment options are available. Desensitization involves administering the culprit medication in increasing doses until the therapeutic dose is reached.[12] When treatment with allopurinol is necessary and the initial hypersensitivity reaction is not severe, desensitization may be an appropriate therapeutic option.[13]

The present report describes oral desensitization to allopurinol with a rapid protocol, designed to ensure that effective treatment can be resumed promptly in patients for whom this medication is indispensable.

Case report

A 31-year-old white man diagnosed with GSD-I was referred to our service after developing a generalized pruritic maculopapular rash 1 hour after oral intake of 300 mg allopurinol. As allopurinol is the only medication available for the treatment of hyperuricemia associated with his underlying disease, we considered drug desensitization the best option for this patient.

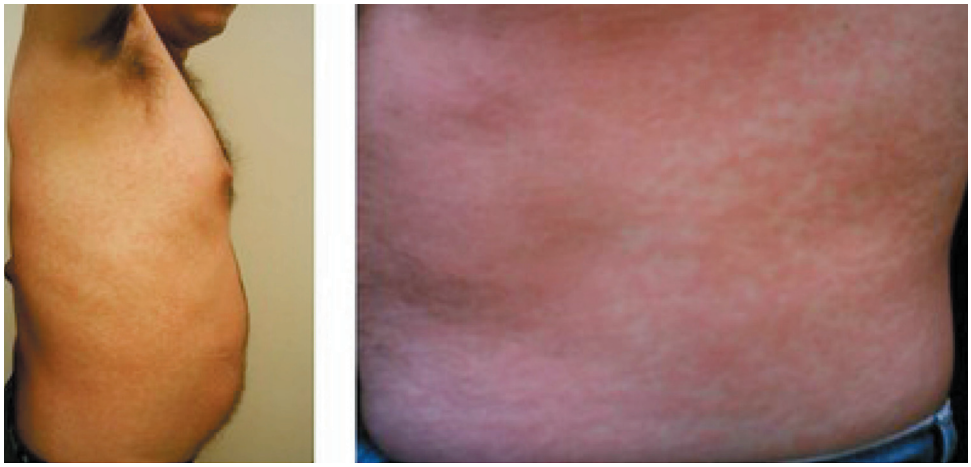
We initially proposed oral desensitization based on a 30-day protocol[14] involving daily administration of the medication at 3-to-5-fold dosage increments from one day to the next. The starting dose was 0.01 mg, with the aim of reaching 300 mg on day 30 of the protocol. However, at the 1-mg dose, the patient developed slightly pruritic erythema on his hands, and at 3 mg, the rash spread to his feet. These reactions were adjudicated as mild, and the decision was made to continue the protocol. Upon reaching the 100-mg dose, the patient developed a generalized pruritic maculopapular rash, although it was mild in severity. The 300 mg dose was reached and maintained for 1 week, at which point the rash worsened and the patient discontinued daily allopurinol (Figures 1 and 2). The rash was treated with a 21-day course of prednisone 60 mg once daily plus fexofenadine 180 mg twice daily. Prednisone was then tapered off uneventfully.

At the time we encountered this patient, there was only one report in the literature of a rapid desensitization protocol for allopurinol[15]; however, it required intravenous allopurinol, which is no longer commercially available. Therefore, we decided to adapt the reported protocol to use the oral formulation instead, administered in a hospital environment. The rapid protocol consisted of administering progressive doses of allopurinol at 15-minute intervals, with a starting dose of 0.01 mg and a target dose of 100 mg, as shown in Figure 3.

At first, the patient was advised to continue allopurinol at 300 mg per day, divided into 3 doses (100 mg every 8 hours), so as to keep the interval between doses under 12 hours. However, only a few hours later, the patient again developed a generalized pruritic rash. We then decided to continue allopurinol 100 mg every 8 hours but add on prednisone 40 mg daily and cetirizine 10 mg twice daily. After 3 days, the patient reported complete resolution of the rash.

After 2 weeks of the aforementioned regimen, a prednisone taper was started at a decrement of 5 mg/week. Once a daily dose of 20 mg prednisone was reached, the tapering rate was reduced to 2.5 mg per week. However, upon reaching a dose of 15/10 mg every other day, the rash recurred once more. This required an increase in prednisone dose back to 40 mg daily for 1 week, then 30 mg daily for another week and, finally, 20 mg daily for a further 2 weeks. From this point onwards, the dose was tapered more slowly, at a rate of 2.5 mg every 3 weeks. Once the patient had been stable on 2.5 mg every other day for 3 weeks, prednisone was discontinued. Two months later, cetirizine was also discontinued.

The patient has had no further recurrences of the rash since 2009. He has taken allopurinol 100 mg every 8 hours uninterruptedly since, and at the time of writing has not required corticosteroids or antihistamines. Laboratory tests, including complete blood counts and liver enzymes, were performed



Figures 1 and 2
Generalized pruritic maculopapular rash after a daily dose of 300 mg allopurinol

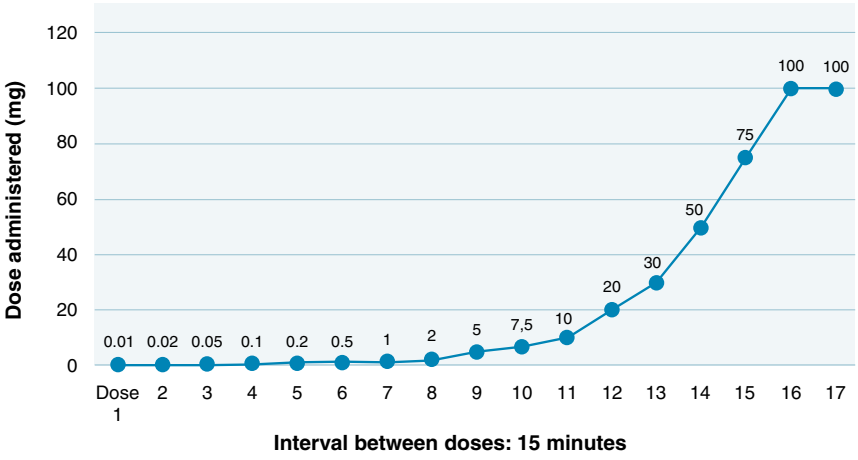


Figure 3
Rapid allopurinol desensitization protocol

periodically. All remained within normal limits before, during, and after the desensitization period. Figure 4 shows the extent of the patient's articular involvement before starting treatment, while Figure 5 shows the reduction in tophi after long-term allopurinol therapy.

Discussion

Drug desensitization is a procedure performed with the aim of temporarily reducing hypersensitivity, whether to allow chronic (continuous) drug treatment or to allow completion of a time-limited regimen or course of therapy.[16] Various mechanisms have been implicated in drug tolerance achieved through desensitization, such as hapten inhibition, IgE consumption, depletion of mast-cell and basophil mediators, and mast-cell desensitization.[17]

Although intolerance to allopurinol is uncommon, approximately 2% of patients who take this medication experience hypersensitivity reactions. Newer medications for the treatment of hyperuricemia have been developed, but access is difficult in Brazil, and options thus remain limited. Desensitization should be considered for most patients with hypersensitivity to allopurinol, except those who presented with severe reactions.[17] For the patient described in this report, we chose to pursue desensitization as his reactions were mild and there were no alternative treatments available.

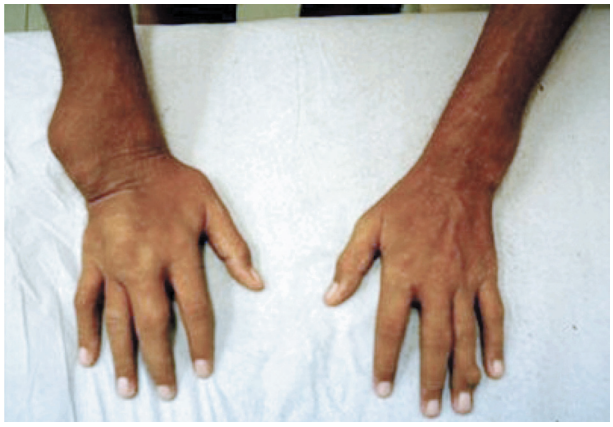


Figure 4
Articular findings before institution of long-term allopurinol therapy

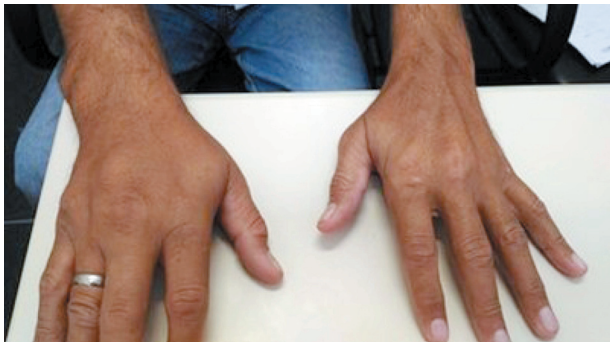


Figure 5
Reduction in gouty tophi after long-term allopurinol therapy

We found several allopurinol desensitization protocols in the literature, ranging from 28 to 81 days in duration until the desired therapeutic dose is reached. Such prolonged protocols aim to minimize potential risks; however, if there is an urgent clinical need to resume therapy with the culprit drug, they can be adapted.[17]

At the time of our treating this patient, there was only one published report of rapid desensitization with intravenous (IV) allopurinol, but IV formulations are no longer commercially available.[15] Therefore, we decided to adapt the rapid IV protocol for the oral route. Allopurinol was administered orally under medical supervision in a hospital setting, initially at a dose of 0.01 mg, increasing progressively at 15-minute intervals so a final target dose of 100 mg could be reached in a single day. The patient was then instructed to continue this 100-mg dose every 8 hours, thus avoiding the risk of a prolonged interval off the dose achieved during desensitization.

Drug desensitization protocols generally involve the administration of increasing doses of the culprit medication at regular intervals to reduce the frequency and severity of reactions. Although our patient developed several reactions throughout the desensitization process, none was considered serious. Furthermore, he responded well to the anti-allergy measures instituted during these mild reactions, which allowed desensitization to proceed safely. The impact of ceasing allopurinol treatment on his gout and known risk of involvement of other vital organs secondary to hyperuricemia was also taken into account.[18] On the basis of these considerations, pursuing desensitization proved to be the best option despite repeated reactions. The protocol was subsequently re-adapted to the patient's needs, in order to minimize reactions and increase tolerance, with administration of antihistamines and systemic corticosteroids for as long as necessary until clinical stability was achieved with oral allopurinol at the desired dose. It bears stressing that regular, ongoing intake of the drug is of the utmost importance to prevent loss of the tolerance induced by desensitization.

Most published protocols for desensitization to oral allopurinol are slow and gradual, with the 28-day oral protocol being that most frequently employed and tolerated by patients. The maintenance dose achieved with this protocol is 100 mg/day.[13,19] Contrary to what is reported in these studies, our patient developed a reaction to low-dose oral allopurinol during the conventional long (30-day) protocol we initially pursued[14], before we decided to attempt the adapted rapid protocol. Although it is still rarely used, rapid desensitization in a hospital environment (or even in an outpatient setting when appropriate) should be considered, with risks and benefits weighed on a case-by-case basis.[20]

More recently, other authors have reported induction of tolerance to oral allopurinol using accelerated protocols, with the objective of reaching the desired dose in a shorter time. The duration of desensitization in these reports ranged from 1 to 16 days, with no increase in the frequency of reactions.[17,21]

Conclusion

In glycogen storage diseases, treatment of hyperuricemia is essential to preventing metabolic and cardiovascular complications and improving quality of life. In patients intolerant to allopurinol where no alternative treatment is available, desensitization should be considered. When carried out in a safe environment by a team of specialized, experienced professionals, it can allow adaptation of therapy so that optimal treatment is provided. The rapid desensitization protocol with oral allopurinol proved successful in the case described herein, allowing treatment to resume, and enabling short- and long-term clinical stability.

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