Desensitization to Allopurinol in Localized and Systemic Hypersensitivity Reactions

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Abstract

Introduction: Allopurinol is, by far, the most frequently prescribed drug for the treatment of hyperuricemia, and the lack of alternatives makes, in case of a reaction, a desensitization procedure to be considered. With this survey, we aimed to do a characterization of patients with hypersensitivity (HS) reactions to allopurinol, who endured desensitization procedures.

Material and methods: Retrospectively, we analyzed the medical files of a group of patients that fit into our objective and were observed in our Department of Immunoallergology of Coimbra University Hospital, between 2007/2012. Demographic data, pathology underlying all prescriptions and concomitant diseases/regular medication, the desensitization protocol and all adverse reactions were taken into consideration.

Results: Six out of seven patients were male, aged from 37 to 79 (mean age of 64 ± 14 years) when undergoing the procedure. As far as the kind of reaction was concerned, three of the patients presented a fixed erythema, two urticaria with/without angioedema, one anaphylaxis and another one maculopapular rash at the time of desensitization. Five of them had gouty joint pathology, one hyperuricemia with chronic renal failure and another had both. Six among all of them presented associated cardiovascular pathology and were polymedicated.

The desensitization protocol used was adapted from Umpiérrez, with an initial dose of 10 µg up to 300 mg/day, adjusted in case of adverse reaction. There were no complications in three patients and the remaining had mild/moderate skin reactions. In four patients with HS reaction during desensitization, only three needed to decrease the dose. The maintenance dose was achieved by extending the length of desensitization, between sixteen to twenty-two days.

Conclusion: In this series, the majority of patients had HS reactions during desensitization protocol and dose adjustment was necessary. However, we managed to achieve a maintenance dose in all of them.

Keywords: Desensitization; Allopurinol; Hyperuricemia; Localized and systemic hypersensitivity

Introduction

Allopurinol (4-hidroxicirazol piramidine) is the first line therapy employed to treat hyperuricemia. It is an inhibitor of the enzyme xanthine oxidase which is responsible for the successive oxidation of hypoxanthine and xanthine, resulting in the production of uric acid [1]. In addition to blocking uric acid production it may also inhibit purine synthesis [2]. Although it is a well-tolerated drug, there are descriptions of HS reactions to treatment with variable degree of incidence and severity. The most frequent reactions are morbilliform rash/pruritic erythematous maculopapular rash (2%) [3,4], and, less frequently, patients may experience life-threatening dermatological conditions like DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) (0.4%) [5], SJS (Stevens-Johnson syndrome) or TEN (Toxic Epidermal Necrolysis) [6].

Recent studies have demonstrated the association between human leukocyte antigen (HLA) B*58:01 allele and allopurinol-induced severe cutaneous adverse reactions, this aspect might explain ethnic differences in incidence [7]. In allopurinol HS, there are data suggesting that the starting dose may be relevant for the development of HS [8].

In some countries, the uricosuric drugs (probenecid, benzbromarone and sulfinpyrazone), which increase the excretion of uric acid in the urine, are utilized in the chronic treatment of gout but they are not available in the Portuguese market [9]. Thereby we have very limited alternatives in treating patients with gout and allopurinol hypersensitivity, and a desensitization procedure must be considered.

The first description of desensitization to allopurinol was reported by Meyrieri [10]. In the next decades, several case reports with oral and intravenous protocols were published [10-17]. We emphasize the cases series from Fam et al. [18] and Lopes da Silva et al. [9] which included a higher number of patients, 32 and 9 patients, respectively.

The mechanisms involved in the desensitization to allopurinol are not well understood and several pathways were proposed. Teraki and Shiohara [11] reported a patient with fixed erythema submitted to allopurinol desensitization; the authors showed that intraepidermal CD8+ T cells in the attained skin are the main cells present before the desensitization, whereas a significant number of CD25+CD4+ T cells were present after the procedure, supporting that, probably these cells may be involved in the induction of desensitization. The HS reactions to allopurinol may be immunologically mediated (via T cell response to oxipurinol or allopurinol [19-21] or secondary to immune complexes and so considered true HS allergic reactions, or be associated with toxic effects resulting from accumulation of oxipurinol and allopurinol [19-21].

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The aim of this study was to perform a retrospective analysis of patients with allopurinol HS reactions who underwent a desensitization procedure in our Immunoallergology Department from 2007 to 2012.

Material and Methods

Patient population

We analyzed, retrospectively, the medical files of patients with allopurinol HS reactions who underwent desensitization, observed in our department in a six-year period (January 2007 to December 2012). The study included seven patients, with severe gouty arthritis or other hyperuricemic states requiring urate-lowering therapy with allopurinol. These patients had a well-documented recurrent history of HS reaction to allopurinol recorded by the examining physician, which resolved after discontinuation of the drug, and who, subsequently, underwent oral desensitization to allopurinol.

Patients with severe reactions to allopurinol, like DRESS, TEN or SJS, were not submitted to desensitization. Based on data of other studies [12,18], patients did not undergo desensitization if their hemoglobin value was <9.0 g/dL, total leukocyte count <4000 cells/mm³, platelet count was <100000 cells/mm³, liver function tests 2-fold elevated.

The demographic data, pathology that motivated prescription of allopurinol and concomitant diseases/medications were evaluated. Demographic data included age at the time of the desensitization, clinical manifestations of delayed HS reaction, indication for allopurinol therapy (primary diagnostic), concomitant diseases, chronic medication and complementary diagnostic exams performed (before and after desensitization process).

Desensitization procedure

Patient’s informed consent was obtained. The desensitization protocol used was adapted from Umpiérrez et al. [27]. It is a 16 days protocol with increasing allopurinol dosage beginning with 10 µg up to a dose of 300 mg (Table 1). This protocol was adjusted if an adverse reaction occurred, repeating the last tolerated dose after treating the reaction, consequently increasing the desensitization timing procedure.

A suspension of allopurinol was prepared by our hospital’s pharmacy with a 200 µg/ml allopurinol concentration. Unit doses containing 25 mg, 50 mg and 100 mg were prepared. Successful desensitization was defined as the ability to tolerate allopurinol at a dosage ≥ 100 mg/day.

| Day  | Dose  |
|------|-------|
| 1st  | 10 µg | 20 µg | 30 µg |
| 2nd  | 40 µg | 50 µg | 60 µg |
| 3rd  | 70 µg | 80 µg | 90 µg |
| 4th  | 100 µg| 200 µg| 400 µg|
| 5th  | 600 µg| 800 µg| 1 mg  |
| 6th  | 2 mg  | 4 mg  | 8 mg  |
| 7th  | 16 mg | 25 mg | 35 mg |
| 8th  | 50 mg | -     | -     |
| 9th  | 75 mg | -     | -     |
| 10th | 100 mg| -     | -     |
| 11th | 125 mg| -     | -     |
| 12th | 150 mg| -     | -     |
| 13th | 175 mg| -     | -     |
| 14th | 200 mg| -     | -     |
| 15th | 250 mg| -     | -     |
| 16th | 300 mg| -     | -     |

Table 1: Desensitization protocol adapted from Umpiérrez et al. [27]; 1 h interval between doses.

Table 2: Demographic characteristics of the 7 patients who underwent allopurinol.

| Feature                          | Frequency (Total=7) |
|---------------------------------|---------------------|
| Age, mean (range) years         | 64 (37-79)          |
| Sex (men/women)                 | 6/1                 |
| Indication for desensitization  |                     |
| Tophi and chronic tophaceous    | 6                   |
| gouty arthritides               |                     |
| Chronic renal failure           | 2                   |
| Uric acid nephropathy           | 1                   |
| Serum urate mean (range) mg/dL   | 10.2 (7.2-14.0)     |
| Serum creatinine (range) mg/dL   | 0.7-2.48            |

No patient experienced any serious hypersensitivity reactions, significant abnormal laboratory findings, or required emergency department care.

The overall success rate of desensitization was 100%, since the maintenance dose therapy (at least 100 mg/day) was achieved in all
patients; 5 patients reached to 300 mg/day; one to 200 mg/day and another to 150 mg/day.

After the protocol patients were evaluated by our clinic. One patient was lost from the consultation. The remaining six patients have improved clinically, decreasing the number of gouty attacks and had a lower urate level [mean 6.95 mg/dL; range 3.7-9.8 mg/dL (previous: mean 10.2; range 7.2-14.0)].

Discussion

Although the allopurinol is a well-tolerated drug, 2% of the patients develop a pruritic maculopapular rash. More severe systemic reactions, such as DRESS, SJS or TEN are scarcer, with an incidence of only 0.4%. The pathophysiological mechanisms underlying these reactions are not well understood and may be immunologically mediated and/or of toxic nature. When we have a reaction to allopurinol, we can consider desensitization in patients with confirmed hypersensitivity to the molecule and there is a need for hypouricemic therapeutic.

We chose this protocol for its success rate as previously described by others [9,27]. We did not reach the final dose of the protocol (300 mg) in all patients because the individual effective dose was previously defined by patient's assistant physician.

Even though this protocol was initially created for desensitization of patients with local skin reactions (fixed erythema), we observed that it was also effective in desensitization of patients with systemic reactions, thus saving time comparing with the protocol used by Fam et al. [18] whose duration was at least a month.

However, more than half of the patients (57%) had skin reactions during the induction phase. Two patients with fixed erythema experienced recurrence of symptoms during protocol. We had to adapt protocol both patients with success. None of them needed corticosteroids or other preventive therapy to achieve maintenance dose, like the patient reported by Kelso and Keating [15] who received low-dose prednisone during desensitization procedure. One patient with urticaria after the intake of allopurinol also had recurrence of symptoms during the induction phase and this patient needed pre-medication with anti-histamine in order to achieve maintenance dose. This was the most problematic patient of our case series and the only one who needed pre-medication.

The largest number of complications was at the 6th and 7th day of the protocol corresponding to a cumulative dose of 14 mg and 51 mg of allopurinol, respectively. These reactions lead to individual management of the protocol increasing the time of the procedure. In Lopes da Silva et al. [9] series, in two of three patients who suffered a reaction, this occurred in the 8th day of the protocol.

The frequency of reactions during the protocol demonstrates the difficulty and risks of this procedure. Furthermore, the risk of adverse reaction and its severity is increased by the patient's age and by the concomitant pathology. Another risk factor in these patients is the difficulty and risks of this procedure. Furthermore, the risk of adverse reaction and its severity is increased by the patient's age and by the concomitant pathology. Another risk factor in these patients is the chronic medication including beta-blockers. It is for the physician to decide whether the benefits obtained with desensitization outweigh the risks of stopping this medication.

Comparing the present study with other studies in the literature, the works of Fam et al. [18] and Lopes da Silva et al. [9], our success rate was higher (100% versus 66.7% and 87.5% respectively). There were no severe reactions or significant abnormal laboratory findings that led to

| Patient | Age | Sex | Primary diagnostic | Concomitant diseases | Chronic medication | HS reaction | Final dose (mg) | Complications |
|---------|-----|-----|-------------------|---------------------|-------------------|-------------|----------------|--------------|
| 1       | 73  | M   | Gouty joint pathology | HBP | Losartan Colchicine | Fixed erythema | 300            | 2nd day: Fixed erythema (oral antihistamine and topical corticosteroid) |
| 2       | 76  | M   | Hyperuricemia with chronic renal failure | HBP | Colchicine Trimetazadine Candesartan/HCTZ Carvedilol,ercandipine Fibrate Alprazolam Clopidogrel | Fixed erythema | 100            | 3rd and 6th days: Fixed erythema |
| 3       | 57  | M   | Gouty joint pathology | HBP | Colchicine Valsartan Bisoprolol Clopidogrel Statin AAS | Late onset anaphylaxis | 300            | 0            |
| 4       | 78  | M   | Gouty joint pathology | HBP NIDDM Valvulopathy | Furosemide Perindopril Metformin Sitagliptine Colchicine Carvedilol Oxazepam | Urticaria | 300            | 0            |
| 5       | 62  | M   | Gouty joint pathology | HBP DVT | Eterocoxib Trimetazadine Diclofenac Glucosamine | Urticaria | 300            | 4th and 6th days: Urticaria 7th and 9th days: Fixed erythema (IM antihistamine, daily antihistamine after) |
| 6       | 80  | F   | Gouty joint pathology | HBP Dyslipidemia | Alprazolam Trimetazadine Statin AAS Candesartan Glucosamine | MPE | 150            | 7th day: MPE (IM antihistamine and IV corticoid) |
| 7       | 37  | M   | Gouty joint pathology and uric nephropathy | HBP | Losartan Fenofibrate | Fixed erythema | 200            | 0            |

Table 3: Clinical characteristics, hypersensitivity reaction to allopurinol and adverse reactions during desensitization procedure.
discontinuation of treatment but the number of mild reactions during the protocol was higher (57% versus 34.3% in Fam et al. [18]) and in 33.3% of patients in the series of Lopes da Silva et al. [9]. However in our work as well in Lopes da Silva et al. [9] there is an important limitation based on small sample compared to the Fam et al. [18] (7 and 9 versus 32).

**Conclusion**

The absence of uricosuric drugs in Portugal increases the need for desensitization to allopurinol in patients with hyperuricemia and HS to the drug. Our work showed that desensitization is effective despite the fact that adverse reactions during the protocol are frequent. However these reactions are minor and do not imply suspension of the procedure. Further studies are needed to investigate the mechanisms of HS reactions to allopurinol as well as those underlying the desensitization process to the drug.

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