Efficacy and Safety of Desensitization to Allopurinol following Cutaneous Reactions

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Objective. **To evaluate the long-term efficacy and safety of slow oral desensitization in the management of patients with hyperuricemia and allopurinol-induced maculopapular eruptions.**

Methods. **A retrospective evaluation of an oral desensitization regimen using gradual dosage-escalation of allopurinol in 32 patients (30 with gout and 2 with chronic lymphocytic leukemia) whose therapy was interrupted because of a pruritic cutaneous reaction to the drug.**

Results. **Twenty-one men and 11 women with a mean age of 63 years (range 17–83 years), a mean serum urate level of 618 μmoles/liter (range 495–750) (or, mean 10.4 mg/dl [range 8.3–12.6]), and a mean serum creatinine level of 249 μmoles/liter (range 75–753) (or, mean 2.8 mg/dl [range 0.8–8.5]) were studied. Desensitization failed in 4 patients because of unmanageable recurrent rash. Twenty-eight patients completed the desensitization procedure to a target allopurinol dosage of 50–100 mg/day, 21 without deviation from the protocol for a mean of 30.5 days (range 21–56 days) and 7 requiring dosage adjustments because of a recurrent rash over 53.8 days (range 40–189 days). Seven of these 28 patients developed late cutaneous reactions 1–20 months postdesensitization, 4 responding to dosage modification and 3 discontinuing the drug. Twenty-five of the 32 patients (78%) continued to take allopurinol; their mean duration of followup was 32.6 months (range 3–92 months) and the mean postdesensitization serum urate level was 318 μmoles/liter (range 187–452) (or, mean 5.3 mg/dl [range 3.0–7.5]).**

Conclusion. **The study confirms the long-term efficacy and safety of slow oral desensitization to allopurinol in patients with maculopapular eruptions, particularly in those with gout, who cannot be treated with uricosurics or other urate-lowering drugs. Although pruritic skin eruptions may recur both during and after desensitization, most of these cutaneous reactions can be managed by temporary withdrawal of allopurinol and dosage adjustment.**

Allopurinol is an effective urate-lowering drug which has been the mainstay of treatment of hyperuricemia and gout for the last 36 years (1). The drug is well tolerated by the majority of patients, and serious side effects are rare (1–4). However, an estimated 2% of patients receiving allopurinol therapy, particularly those with chronic renal insufficiency, may experience a pruritic maculopapular rash that precludes further administration (1–4). This poses an obstacle to the treatment of hyperuricemia, particularly in patients with gout and renal insufficiency, which renders uricosurics ineffective (5), and in patients receiving chemotherapy for myeloproliferative or lymphoproliferative diseases, in whom uricosurics are not recommended.

Desensitization procedures (6), including both true immunologic desensitization (e.g., to penicillin) and test-dosing or tolerance-induction protocols (e.g., "desensitization" to sulfasalazine [7], trimethoprim/sulfamethoxazole [8], and ciprofloxacin [9]), have been successfully used for the management of drug-induced cutaneous reactions. In 1992, we reported our experience with desensitization to allopurinol, using a schedule of graded dosages, in a group of 9 patients with gout and renal impairment who had their therapy interrupted because of a maculopapular eruption in response to the drug (10). Findings from the study indicated that slow oral desensitization to allopurinol is a feasible and

acceptably safe approach to therapy, particularly in patients who cannot be treated with other urate-lowering drugs (10). Other investigators have reported similar results with allopurinol desensitization (11–17), including rapid intravenous desensitization in 1 patient (18), re-desensitization after initial failure in 1 patient (19), and desensitization of 2 siblings with allopurinol-induced rash (20). Recently, desensitization to allopurinol-induced fixed drug eruptions has also been described (21–23). However, only a small number of patients have been studied, and there is limited information regarding the long-term outcome of allopurinol desensitization.

The present study (24) retrospectively evaluates the outcome, safety, and long-term clinical utility of allopurinol desensitization in a larger group of patients with hyperuricemic disorders (mainly gout) and cutaneous reactions who were desensitized during the period 1991–1998, with a further followup of the original 9 patients who underwent desensitization from 1980 to 1990 (10). A secondary objective of the investigation was to define the indications and dosing guidelines for allopurinol desensitization.

PATIENTS AND METHODS

Patient population. Sunnybrook Health Science Centre is a tertiary referral teaching hospital. Preparation of the allopurinol suspension and the protocol for desensitization were established by the Ambulatory Patient Pharmacy since our initial publication in 1980 (25) and the larger study in 1992 (10). Patients were either referred to our unit or the desensitization schedule was prescribed by their physicians and dispensed by the pharmacy at Sunnybrook. A computer printout generated by the Ambulatory Patient Pharmacy was used to identify all patients for whom allopurinol suspension was prescribed for desensitization during 1991–1998. Desensitization was the only indication for allopurinol suspension in this setting. No patient was inadvertently excluded, as verified by reviewing the pharmacy's computer records. A list was also compiled of the original 9 patients who had undergone desensitization from 1980 to 1990 (10). Study approval was granted by the Research Ethics Board of Sunnybrook Health Science Centre.

Patients received a consent form approved by the Research Ethics Board describing the nature of the study and requesting permission to review personal medical records and, if necessary, participate in a telephone interview. The study included patients with gouty arthritis or other hyperuricemic states requiring urate-lowering therapy with allopurinol who had a well-documented recent history of a pruritic, erythematous maculopapular or morbilliform eruption occurring following initiation of allopurinol, which resolved after discontinuation of the drug, and who subsequently underwent oral desensitization to allopurinol, as recorded in the pharmacy computer. In all patients, the rash was documented in the

outpatient chart or hospital record by the examining physician and verified to be temporally related to allopurinol administration.

Based on data from the original study (10), patients did not undergo desensitization if their hemoglobin value was <90 gm/liter, total leukocyte count was <4.0 × 10^9/liter, platelet count was <100.0 × 10^9/liter, or findings of liver function tests were >2-fold elevated, or if they had experienced toxic epidermal necrolysis or other catastrophic reaction associated with allopurinol.

Clinical data included age, sex, indication for allopurinol therapy, presence of renal impairment, hypertension, alcoholism, heart failure, or history of nephrolithiasis, concomitant medications (including diuretics, low-dose aspirin, and cyclosporine), a description of the original cutaneous reaction to allopurinol and any history of inadvertent reexposure, and other therapies for acute and chronic gout.

Results of the following studies performed before, during, and after desensitization were recorded: complete blood cell count, urinalysis, serum creatinine (normal <120 μmoles/liter [or, <1.5 mg/dl]), serum urate (normal for men 180–450 μmoles/liter [or, 3–7 mg/dl] and for women 150–360 μmoles/liter [or, 2–6 mg/dl]), alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, bilirubin, and albumin, as well as a pretreatment 24-hour urinary urate excretion study while eating a regular diet (normal <4.76 mmoles/day [or, 800 mg/day]).

Desensitization procedure. Desensitization was performed as previously described (10). Briefly, a suspension of allopurinol was prepared by the outpatient pharmacy as follows: two 100-mg tablets of allopurinol were crushed in a mortar, and 33 ml of 1% methylcellulose solution was slowly added to make a slurry. Both 4 ml of cherry flavor and simple sugar were then added and mixed to a volume of 100 ml to yield a concentration of allopurinol of 10 mg/5 ml. Ten milliliters of this suspension was further diluted with the same ingredients to 100 ml, yielding a 1 mg/5 ml (200 μg/ml) concentration.

Using the high- and low-concentration suspensions, unit doses containing 10 μg, 25 μg, 50 μg, 100 μg, 200 μg, 500 μg, 1 mg, 5 mg, 10 mg, and 25 mg of allopurinol were prepared; 50-mg and 100-mg doses were then administered as one-half and whole 100-mg tablets, respectively. Predesensitization intradermal tests using a solution of allopurinol and oxypurinol were not performed. The desensitization procedure and its potential risks were discussed with each patient and after obtaining the patient's informed consent, the *standard protocol* was administered as follows (Table 1): an initial dosage of 50 μg of allopurinol/day, which was progressively and cautiously increased every 3 days to 100 μg, 200 μg, 500 μg, 1 mg, 5 mg, 10 mg, 25 mg, and finally to a target dosage of 50–100 mg of allopurinol/day. Further dosage increments were based upon the individual patient's serum urate and creatinine levels, aiming at reducing and maintaining serum urate levels at <300–350 μmoles/liter (or, <5–6 mg/dl), which is well below the levels at which urate saturates the extracellular fluid (~404 μmoles/liter [or, 6.8 mg/dl] at 37°C).

A *modified desensitization protocol*, with initial daily doses of allopurinol of 10 μg and 25 μg, and a dosage change every 5–10 days or longer, was initially prescribed for frail, elderly patients with multiple comorbid medical conditions,

Table 1. Standard allopurinol desensitization protocol*

Daily dose	Preparation†	Days (approximate)
50 μg	0.25-ml suspension (1 mg/5 ml)	1–3
100 μg	0.5-ml suspension (1 mg/5 ml)	4–6
200 μg	1-ml suspension (1 mg/5 ml)	7–9
500 μg	2.5-ml suspension (1 mg/5 ml)	10–12
1 mg	5-ml suspension (1 mg/5 ml)	13–15
5 mg	2.5-ml suspension (10 mg/5 ml)	16–18
10 mg	5-ml suspension (10 mg/5 ml)	19–21
25 mg	12.5-ml suspension (10 mg/5 ml)	22–24
50 mg	One-half a 100-mg tablet	25–27
100 mg	One 100-mg tablet	28+

* For high-risk patients, a modified desensitization protocol, with initial allopurinol doses of 10 μg and 25 μg (0.05 ml and 0.12 ml of 1 mg/5 ml suspension, respectively), and a dosage escalation every 5–10 days or longer, is recommended.
† Two concentrations of allopurinol suspension were used: 1 mg/5 ml and 10 mg/5 ml, depending on the dosage required.

including renal impairment, as well as for patients with more widespread, confluent, allopurinol-induced eruptions, particularly when associated with facial or tongue swelling, fever, stomatitis, or eosinophilia.

All patients undergoing desensitization were cautioned about possible severe reactions and were instructed to stop allopurinol and consult their physician if an adverse reaction, such as fever, pruritus, or skin eruption, occurred. In such an event, allopurinol was withheld until the reaction had resolved, reintroduced cautiously at one-half the previously tolerated dosage, and the rate of dosage escalation was slowed to every 5–10 days or longer.

Outcome assessment. Followup data were collected through active clinic assessments, chart review, and if necessary, by telephone interview. Short-term and long-term assessments of outcome were made. In the short-term outcome assessment, successful desensitization was defined as the ability to tolerate allopurinol at a dosage of 50–100 mg/day. The time taken to reach the target dosage and the occurrence of recurrent rash or other adverse events during desensitization were documented. In the long-term outcome assessment made after desensitization, we evaluated the control of hyperuricemia, the effects of treatment on the frequency of gouty attacks, as confirmed by interview with the patients and review of their medical records, and on the number and size of tophi, as documented by the treating physician, late cutaneous reactions, and discontinuation of allopurinol for any reason.

RESULTS

Patient population. The clinical characteristics of the 32 patients who had undergone desensitization to allopurinol are outlined in Table 2. This patient group consisted of 9 previously described patients who had been desensitized to the drug between 1980 and 1990 (10) and an additional 23 patients who were consecutively enrolled between 1991 and 1998.

Thirty patients had gout, and 2 had chronic

lymphocytic leukemia. All patients with gout experienced recurrent gouty attacks, and 21 had tophi and disabling chronic tophaceous gouty arthritis. Eight of the patients with gout had a history of renal calculi. Indications for allopurinol desensitization in patients with gouty arthritis included renal insufficiency, which renders uricosurics ineffective, in 26 patients, intolerance to uricosurics in 3 patients, and contraindication to uricosuric therapy in 1 patient because of nephrolithiasis and hyperuricosuria of 5.6 mmoles/day.

Allopurinol therapy had been withdrawn in all patients because of a pruritic maculopapular or morbilliform eruption, which in the majority of patients (24 of 32, or 75%) developed within 3 months of initiating treatment. The rash was associated with fever in 6 patients, 3 of whom also had eosinophilia and facial swelling, and with stomatitis in 1 patient. None of these individuals had experienced a severe allopurinol hypersensitivity reaction (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, acute hepatitis, or acute interstitial nephritis) or had previously failed desensitization to the drug. In 4 patients, inadvertent reexposure to allopurinol prior to desensitization resulted in recurrence of the rash, which resolved following withdrawal of the drug.

Twenty-two of the 32 patients undergoing desensitization had been referred to our unit; in the remaining 10 patients, desensitization was initiated by their physi-

Table 2. Clinical characteristics of 32 patients undergoing allopurinol desensitization for cutaneous reactions

Feature	Frequency
Age, mean (range) years	63 (17–83)
Sex, no. of men:no. of women	21:11
Indication for allopurinol desensitization, no. positive/total	
Gout and renal insufficiency	26/32
Gout and intolerance/ contraindication to uricosurics	4/32
Chemotherapy for chronic lymphocytic leukemia	2/32
Serum urate, mean (range) μmoles/ liter	618 (495–750)
Twenty-four–hour urinary urate, mean (range) mmoles/day*	2.3 (0.5–5.6)
Serum creatinine, mean (range) μmoles/liter	249 (75–753)
Patients with gout, no. (%)†	
Recurrent gouty arthritis	30/30 (100)
Tophi and chronic tophaceous gouty arthritis	21/30 (70)
Renal calculi	8/30 (27)

* Represents 13 of 32 patients.
† Represents 30 patients.

cians. Allopurinol dosages prior to the cutaneous reaction were not always appropriate for the degree of renal impairment: 21 of 26 patients with renal insufficiency were receiving 300 mg/day, and 4 were maintained on 200 mg/day. Only 1 patient with advanced renal disease was receiving 100 mg of allopurinol daily.

The mean serum urate concentration before desensitization was 618 μmoles/liter (range 495–750) (or, 10.4 mg/dl [range 8.3–12.6]), with a mean of 631 μmoles/liter (or, 10.6 mg/dl) in men and 594 μmoles/liter (or, 10.0 mg/dl) in women. The mean 24-hour urinary urate level in 13 of 32 patients was 2.3 mmoles/day (range 0.5–5.6) (or, 390 mg/day [range 80–940]). The mean predesensitization serum creatinine concentration was 249 μmoles/liter (range 75–753) (or, 2.8 mg/dl [range 0.8–8.5]).

Risk factors in the 30 patients with gout included renal insufficiency in 26 patients (88%), hypertension in 25 (83%), chronic diuretic therapy in 22 (73%), cardiac failure in 8 (25%), long-term low-dose aspirin in 8 (25%), cyclosporine following renal transplantation in 3 (10%), family history of gout in 3 (10%), and ethanol abuse in 2 (7%).

Drug therapies for acute gouty attacks included corticosteroids in 18 patients, colchicine in 13, and nonsteroidal antiinflammatory drugs (NSAIDs) in 8. None of the patients were receiving long-term NSAIDs. Twelve patients were treated with uricosurics (sulfinpyrazone in 8 and probenecid in 4) but with little benefit in 9 and intolerance in 3 patients. No data were available on individuals with cutaneous reactions to allopurinol who declined desensitization.

Desensitization and outcome of therapy. The immediate and long-term outcomes of allopurinol desensitization are summarized in Table 3. Twenty-three individuals underwent desensitization as outpatients, and in 9 patients, the desensitization procedure was initiated in the hospital.

Short-term outcome. The dosage of allopurinol was escalated every 3 days (standard protocol) in 23 patients and every 5–10 days or longer (modified protocol) in 9 patients. Four patients (12.5%) were unable to complete the desensitization procedure because of recurrent rashes (Table 3): 1 patient also had nausea and oral ulcers, 1 had nausea and facial swelling, 1 refused to continue with further desensitization, and 1 developed an unmanageable rash despite repeated dosage adjustments.

Twenty-eight patients (87.5%) completed the desensitization protocol to a target allopurinol dosage of 50–100 mg/day. Desensitization was achieved in 21

Table 3. Short-term and long-term outcome of allopurinol desensitization in 32 patients

	Number (%) of patients	
Outcome	Continued administration	Drug withdrawal
Short-term outcome (n = 32)*		
Reactions during desensitization (n = 11)		
Recurrent rash (n = 9)†	7	2
Rash, nausea, and oral ulcers (n = 1)	0	1
Rash, nausea, and facial swelling (n = 1)	0	1
Completion of desensitization protocol	28 (87.5)	4 (12.5)
Long-term outcome (n = 28)‡		
Postdesensitization reactions (n = 7)		
Recurrent rash (n = 7)†	4	3
Overall outcome (n = 32)	25 (78)	7 (22)

* Percentage success rate of desensitization and adverse events.
† Two patients had rashes both during and after desensitization.
‡ Postdesensitization long-term tolerance to allopurinol for 32.6 months (range 3–92 months).

patients (75%) without any adverse reaction or deviation from the set protocol, with dosage escalation every 3 days in 19 patients and every 5 days in the other 2. The mean duration of desensitization in this group of patients was 30.5 days (range 21–56 days). The other 7 patients (25%) required single (6 patients) or repeated (1 patient) dosage modifications because of a transient recurrent rash. These cutaneous reactions occurred at allopurinol dosages of <5 mg/day in 5 patients, 50 mg/day in 1, and 100 mg/day in 1. These patients required a slower rate of desensitization, with dosage changes every 5–10 days or longer (*modified desensitization protocol*), with a mean duration of the desensitization procedure of 53.8 days (range 40–189 days).

Long-term outcome. Followup was complete through 1999, with an observation period of 902 patient-months, or a mean of 32.6 months per patient (median 24 months, range 3–92 months per patient). Seven of 28 patients (25%) developed late, postdesensitization, recurrent cutaneous eruptions, 2 of whom also had "early" rash occurring during the desensitization procedure. These late cutaneous reactions occurred at a mean of 6 months (range 1–20 months) following desensitization. Four of the 7 patients responded to dosage adjustment, but the other 3 discontinued allopurinol treatment because of either an unmanageable recurrent rash (1 patient) or an unwillingness to continue treatment (2 patients).

Thus, the overall success rate of desensitization was 25 of 32 patients, or 78% (Table 3). In the remaining 7 patients (22%), failure of allopurinol desensitization was the result of unmanageable recurrent rashes that occurred during (4 patients) and after (3 patients) desensitization. No patient experienced any serious hypersensitivity reactions, significant abnormal laboratory findings, or required hospitalization, emergency department care, or medications other than diphenhydramine for recurrent pruritic rash.

Maintenance dosages of allopurinol following desensitization in the 25 patients who remained evaluable for long-term tolerance were notably lower than predesensitization dosages: 100 mg/day in 8 patients, 150 mg/day in another 8 patients, 200 mg/day in 6 patients, and 300 mg/day, 250 mg/day, and 50 mg/day in 1 patient each. Twenty-three patients with gout improved clinically, with complete (n = 14) or partial (n = 9) cessation of gouty attacks. The mean postdesensitization serum urate level in 20 of the 25 long-term–evaluable patients was 318 μmoles/liter (range 187–452) (or, 5.3 mg/dl [range 3.0–7.5]), with only 2 patients having levels above 350 μmoles/liter (or, 6.0 mg/dl). Resolution of tophi, which occurred in 16 of 18 patients, was complete in 4 patients and partial in 12.

Two patients inadvertently stopped taking allopurinol for about a week at 3 and 6 months following successful desensitization. In both patients, the drug was successfully reintroduced at one-half the previously tolerated dosage, followed by gradual escalation of the dosage to its previous level.

Reasons for late, postdesensitization withdrawals included death from unrelated causes in 11 patients (3–84 months postdesensitization due to heart failure in 2, myocardial infarction in 2, metastatic carcinoma in 3, chronic lymphocytic leukemia in 1, aplastic crisis secondary to systemic lupus erythematosus in 1, stroke in 1, and septic shock in 1), loss to followup in 4 patients (11–24 months postdesensitization), improvement of gout following renal transplantation in 1 patient (42 months postdesensitization), and improvement of gout with home hemodialysis in 1 patient (49 months following desensitization).

Eight patients were receiving allopurinol at 13–92 months postdesensitization (mean 44 months, median 36 months); the mean serum urate level in 7 of these patients was 353 μmoles/liter (range 267–412) (or, 5.9 mg/day [range 4.8–6.9]); only 1 patient had a serum urate level of 412 μmoles/liter (or, 6.9 mg/dl). Six patients reported complete cessation of gouty attacks, and 2 reported less frequent attacks. Five of these 8 patients had tophi, which resolved completely in 3 patients and partially in 2 patients.

DISCUSSION

An estimated 2% of patients receiving allopurinol experience a pruritic maculopapular rash, sometimes associated with fever, facial swelling, or eosinophilia (1–4). More severe reactions, including toxic epidermal necrolysis, erythema multiforme or exfoliative dermatitis with leukocytosis, acute hepatitis, and/or acute interstitial nephritis with renal failure (allopurinol hypersensitivity syndrome), are rare (~0.4% of patients) (26–28). The exact pathogenesis of these hypersensitivity events, whether immune-mediated and/or toxic in nature, are unclear. Accumulation of oxypurinol (principal metabolite of allopurinol) due to renal impairment or coadministration of thiazide diuretics (26–28), genetic factors (20,29), abnormal T lymphocyte–mediated immune responses to oxypurinol, and to a lesser extent, allopurinol (30,31), and formation of immune complexes (28,32) have been implicated. A recent study suggests that in vitro allopurinol-induced release of interferon-γ from peripheral blood T lymphocytes may be a useful test in the diagnosis of Stevens-Johnson syndrome and other sensitivity reactions to allopurinol (33). Skin testing with either allopurinol or oxypurinol is less specific and has yielded conflicting results (18,28,30).

Many of those who experience allopurinol hypersensitivity are elderly patients with renal impairment in whom the dosage of the drug has not been reduced appropriately (26–29). In the present study, 26 of the 32 patients (81%) who underwent desensitization had renal insufficiency; 18 of them (69%) were taking concomitant diuretics, and 21 (80%) were receiving 300 mg of allopurinol daily—an inappropriate dosage for their degree of renal insufficiency. Recent reports indicate that allopurinol, at a "standard" dosage of 300 mg/day, is the most frequently prescribed urate-lowering drug (34,35) and that not all physicians adjust the initial dosage according to the degree of renal insufficiency (35). In this study, daily allopurinol dosages following desensitization were considerably lower than the predesensitization dosages, further emphasizing the importance of dosage reduction in patients with renal impairment (26).

The occurrence of cutaneous reactions to allopurinol severely limits the ability to manage hyperuricemia, particularly in individuals who cannot be treated with an alternative, equally effective, urate-lowering

Table 4. Indications for desensitization in patients with allopurinol-induced pruritic maculopapular eruptions

Patients with gout and renal insufficiency, and those requiring concomitant cardioprotective low-dose aspirin, which renders uricosurics ineffective (5,36–38)

Patients with gout, "overproduction" hyperuricemia, hyperuricosuria, and nephrolithiasis in whom uricosurics can increase the risk of stone formation, renal colic, and renal failure (36–39)

Patients with gout and "underexcretion" hyperuricemia who are either allergic or intolerant to both probenecid and sulfinpyrazone

Patients with malignancy-associated hyperuricemia due to cytolytic therapy for myeloproliferative or lymphoproliferative disorders; the resulting massive uricosuria precludes the use of a uricosuric agent (40)

drug. Table 4 lists the indications for desensitization in patients with such reactions to allopurinol. In the present study, we evaluated allopurinol desensitization as a potential therapy for patients in whom long-term control of hyperuricemia has proved difficult to achieve because of a pruritic maculopapular reaction to the drug. Overall, desensitization was successful in 78% of the patients (95% confidence interval 63–93%), enabling them to tolerate long-term allopurinol therapy (up to 92 months) as effective treatment for hyperuricemia and gout. To our knowledge, this is the largest reported series of patients who have undergone allopurinol desensitization.

Although the present study was limited by its retrospective, uncontrolled, open-label design, a number of observations can be made. First, cautious reinstitution of allopurinol, through reexposure to graded oral doses (test dosing or tolerance induction strategy) is a viable, acceptably safe approach to therapy in patients with allopurinol-related rash in whom other urate-lowering drugs are ineffective, poorly tolerated, or contraindicated (Table 4). We were unable to identify any antecedent clinical or laboratory parameter(s) that was predictive of either the immediate or long-term outcome of desensitization. Second, while transient pruritic rashes may recur both during (about one-third of patients) and after desensitization (about one-fourth of patients), more than 60% of the cutaneous reactions in the present study were managed by temporary withdrawal of allopurinol until the rash had subsided, followed by cautious reintroduction of the drug at one-half the previously tolerated dosage, and a slower rate of incremental dosage change. Medication compliance is important, since it is unclear whether the loss of sensitivity in these individuals is temporary or permanent. In the present investigation, 2 patients inadvertently interrupted their allopurinol treatment for about a week, and

it was possible to reintroduce the drug at one-half the previously tolerated dosage, followed by gradual dosage escalation. However, it is not known whether a longer lapse of therapy would require a full re-desensitization procedure. Third, while no severe cutaneous reaction, hepatitis, interstitial nephritis, or hematologic toxicity was encountered in any of the 32 patients who underwent allopurinol desensitization, the procedure can occasionally result in life-threatening reactions (15,19). To minimize such a risk, timely recognition of any sign of intolerance, such as pruritus, cutaneous erythema, fever, or oral ulcers, and prompt withdrawal of allopurinol are essential.

A major obstacle to the management of hyperuricemia in allopurinol-intolerant patients is the limited availability of suitable, equally effective, alternative urate-lowering drugs, particularly in patients who are refractory to treatment with or are intolerant of uricosuric drugs. Oxypurinol at a dosage of 100–600 mg/day has been used to treat allopurinol-sensitive individuals, but cross-hypersensitivity with allopurinol has been reported in up to 40% of these patients (41–43).

Urate oxidase, or uricase, is an enzyme that catalyzes the conversion of uric acid into allantoin, which is 10 times more soluble than uric acid and is more readily eliminated by the kidneys (40,44–48). Humans and certain primates lack this enzyme activity (48). When given parenterally, urate oxidase is a more potent and faster acting urate-lowering drug than is allopurinol (40,44–48). Uricozyme, a nonrecombinant urate oxidase derived from cultures of *Aspergillus flavus,* has been used in Europe since 1974 as a short-term adjunct to cytolytic therapy for childhood leukemia and other myeloproliferative and lymphoproliferative disorders (40,44,45). It is not available in the United States or Canada, and its use for prolonged therapy of gout is limited by the need for parenteral administration, its potential immunogenicity, and its side effects (allergic rash, anaphylaxis, bronchospasm, and hemolytic anemia) (40,44,45). Recently, recombinant urate oxidase, a complementary DNA clone derived from *Aspergillus flavus* and biosynthesized in the yeast strain *Saccharomyces cerevisiae* (Sanofi-Synthelabo, New York, NY) has been utilized in the prophylaxis and treatment of chemotherapy-associated hyperuricemia in patients with leukemia and lymphoma (47). However, its long-term parenteral use in allopurinol-sensitive patients with chronic gout and renal insufficiency has not been examined.

As renal function deteriorates, uricosurics lose their efficacy as urate-lowering drugs (5,36–38). Benzbromarone seems to be an exception; a number of

studies suggest that at dosages of 25–150 mg/day, the drug retains its uricosuric properties in patients who have mild-to-moderate renal impairment with a creatinine clearance of >25 ml/minute (49–51). The risk of uric acid nephrolithiasis and hepatotoxicity in these patients requires further study (52). The drug is marketed in Europe, but is not available in Canada or the United States.

In summary, results from the present study confirm the long-term efficacy and safety of slow oral desensitization to the minor rashes induced by allopurinol. Although the mechanism underlying "desensitization" to allopurinol has not yet been established, the data presented indicate that this "graded reintroduction strategy" can restore tolerability to the drug in the majority of patients. The procedure can be carried out in an ambulatory setting under close supervision. Careful planning and detailed discussion of the desensitization protocol with each patient prior to initiating therapy are essential. Desensitization to allopurinol poses potential risks (15,19) and is not recommended as first-choice treatment for all patients with pruritic maculopapular eruptions to the drug. The procedure is beneficial in selected patients who cannot be treated with other urate-lowering drugs, particularly those with gout and renal insufficiency (Table 4). Continued monitoring of these patients, both during and following desensitization, is important because sensitivity to the drug may recur.

Given the potential morbidity and mortality from the allopurinol hypersensitivity syndrome, desensitization is not recommended in patients with previous Stevens-Johnson syndrome, toxic epidermal necrolysis, or other life-threatening reactions to the drug (10,53). A slower incremental dosing regimen, with dosage changes every 5–10 days or longer, increases the likelihood of successful desensitization and is recommended for the following high-risk patients: those who are frail and elderly and have multiple medical conditions; those who have had a confluent widespread allopurinol rash, especially when associated with fever, stomatitis, facial or tongue swelling, or eosinophilia (which have been associated with potentially more severe drug-induced cutaneous reactions [54]); and those who have experienced recurrent rashes during the desensitization procedure.

Additional prospective, long-term, dose-ranging studies are required to address the issues of optimal initial dosages and the duration and rate of desensitization to allopurinol. More work remains to be done to define the pathogenesis of allopurinol hypersensitivity events, elucidate the mechanisms underlying desensiti-

zation, and explore new xanthine oxidase inhibitors and other novel therapeutic interventions to treat hyperuricemia in patients who are refractory to both allopurinol and uricosuric drugs.

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