ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: How should hyperuricemia be treated in a patient with allopurinol hypersensitivity?

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A: FIRST, TRY ALTERNATIVE METHODS of lowering uric acid in patients with confirmed recalcitrant gout or other severe hyperuricemia-related condition and previous allopurinol hypersensitivity.

If these fail or are not feasible, desensitization to allopurinol is an option. Since rechallenge with allopurinol poses serious risks, careful risk-benefit assessment is required.

INDICATIONS FOR ALLOPURINOL

Allopurinol inhibits xanthine oxidase and decreases uric acid production. It is used to treat gout and is effective in both urate overproducers and underexcretors. With the growing population of solid-organ transplant recipients, general internists are encountering more patients with progressive debilitating gout. Other indications for allopurinol treatment are Lesch-Nyhan syndrome, recurrent urate kidney stones refractory to other treatments, and prophylaxis of tumor lysis syndrome.

The diagnosis of hyperuricemia-induced disease should be firmly established before allopurinol is started. In cases of gout, crystal confirmation is required. Asymptomatic hyperuricemia should not be treated with allopurinol.

FEATURES OF ALLOPURINOL HYPERSENSITIVITY

The mechanism of allopurinol hypersensitivity is not completely understood. Cell-mediated immune reaction to allopurinol and oxypurinol, the active metabolite of allopurinol, is suspected on the basis of findings of increased in vitro lymphocyte proliferation.[1–3]

Hypersensitivity reactions to allopurinol develop in 2% of patients receiving allopurinol and are severe in 0.4%. Case reports suggest that renal insufficiency and use of thiazide diuretics are risk factors for the development of allopurinol hypersensitivity. The hypersensitivity occurs days to weeks after starting treatment with allopurinol.

Allopurinol hypersensitivity may present with fever, eosinophilia, and rashes that range from maculopapular to toxic epidermal necrolysis. Hepatitis and interstitial nephritis develop less frequently. Elevated serum oxypurinol is often present. Death occurs in up to 26% of hypersensitivity cases, usually caused by sepsis.[4] This high rate probably represents reporting bias, but it underscores the severity of the condition.

Treatment of allopurinol hypersensitivity includes withdrawing allopurinol and giving supportive measures. Corticosteroids are used empirically in severe cases.

FIRST TRY OTHER TREATMENTS

In patients with allopurinol hypersensitivity, one must try other available methods of lowering the serum uric acid level before pursuing desensitization.

Modifying the diet and alcohol intake may reduce uric acid levels modestly.

Limiting the use of low-dose aspirin, diuretics, and other drugs that increase urate levels may also be effective. For patients with coexistent hypertension, the angiotensin-receptor blocker losartan has a mild uric acid-lowering effect and may be preferred to diuretics.

Uricosuric drugs such as probenecid and sulfinpyrazone can be used in patients with creatinine clearance greater than 30 to 40 mL/min. Oxypurinol is available from the manufacturer for compassionate use, but its safety in patients hypersensitive to allopurinol

Before desensitization, try other ways to lower serum uric acid

is not firmly established. Clinically, cross-reactivity between oxypurinol and allopurinol has been described in up to 40% of cases.[1,5] A current multicenter open-label study of oxypurinol is expected to provide further information.

DESENSITIZATION TO ALLOPURINOL

When allopurinol treatment is deemed necessary, desensitization should be considered. Desensitization is generally safe and most patients can tolerate it. However, the patient and the family need to be informed of the risks.

It is prudent to avoid desensitization in patients with a history of severe manifestations of allopurinol hypersensitivity such as toxic epidermal necrolysis, hepatitis, or acute interstitial nephritis, on the basis of the largest series published.[6,7] There is more experience with the oral protocol, which has been successfully used in an outpatient setting.

Allopurinol suspension is prepared by the pharmacy from allopurinol tablets dissolved in 1% methylcellulose solution. The dose is incrementally increased every 3 days from 50 µg to 100 µg, 200 µg, 500 µg, 1 mg, 5 mg, 10 mg, 25 mg, 50 mg, and 100 mg.[6,7]

Do not try desensitization if the patient has severe hypersensitivity

A slower protocol is used in high-risk patients: the elderly and those with multiple concomitant medical conditions, more severe rash, or eosinophilia. For those patients, the dosage starts with 10 µg and 25 µg, and doses increase every 5 to 10 days.[7]

The intravenous protocol was used in one patient in whom oral desensitization had previously failed. It is fast and allows stopping the delivery of the medication immediately after a reaction occurs, but the procedure must be done in a setting of continuous monitoring, such as a telemetry unit.[8]

In the larger series, 28 of 32 patients completed the protocol, achieving a dose of 50 to 100 mg/day, and 25 (78%) remained on allopurinol long-term.[7]

Minor skin reactions require discontinuation and repeated desensitization, taking a longer time for each step. Prednisone or antihistamines or both may be helpful to suppress minor early reactions while continuing allopurinol desensitization.

Follow-up is required after desensitization, since late reactions have been described. The final dose of allopurinol after successful desensitization has to be adjusted to the renal function to avoid accumulation of increased oxypurinol levels. Compliance with daily allopurinol intake is required. If doses are missed, loss of tolerance to allopurinol may ensue and the desensitization protocol may need to be repeated from the beginning.

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