ARTHRITIS & RHEUMATISM Volume 37
Number 5, May 1994, pp 777–778

CONCISE COMMUNICATION

Allopurinol mouthwashes in methotrexate-induced stomatitis

Some preliminary studies have shown that allopurinol mouthwashes are effective treatment for 5-fluorouracil (5-FU)–induced stomatitis (1,2). Since the systemic administration of allopurinol does not improve the therapeutic ratio of 5-FU (3), a local action seems likely (2), possibly related to the anti-oxidant properties of this drug (4,5). If so, topical allopurinol could have a beneficial effect in stomatitis induced by antiproliferative agents other than 5-FU, including methotrexate (MTX).

Oral ulcers are among the commonest side effects of MTX therapy in cancer patients and represent a frequent adverse experience in rheumatoid arthritis (RA) patients when treated with weekly low doses of the drug. Stomatitis, with or without oral ulcers, has been reported in 6–55% of MTX-treated RA patients (6–8). In some patients, oral soreness may become very troublesome, though it usually does not represent a primary reason for discontinuation of the drug (7). No specific treatment has been proposed so far. High-dose (45 mg/week) folinic acid supplementation might be effective, but it proved to worsen RA activity indexes in a prospective study (9). Low-dose folinic acid does not affect the efficacy of MTX (10), but its beneficial effect is still controversial. Favorable results were obtained at our institution in a placebo-controlled study of allopurinol mouthwashes for 5-FU–treated patients with colorectal cancer (11). We therefore decided to give allopurinol mouthwashes to our RA patients who had MTX-induced stomatitis.

Allopurinol is generally well tolerated, with few significant adverse effects. However, a life-threatening toxicity syndrome has been described after its use in patients with renal failure (12). Thus, only patients with normal serum creatinine levels and creatinine clearance values above 70 ml entered this study. All patients were fully informed about potential risks of allopurinol therapy, and the study design was approved by the Department of Internal Medicine and Therapeutics of the University of Pavia.

We thus far have treated 6 patients with RA (according to the 1987 revised criteria of the American College of Rheumatology [13]) and 1 with refractory dermatomyositis; their main clinical features are reported in Table 1. During MTX therapy (10–20 mg/week intramuscularly), all these patients had developed persistent stomatitis. Stomatitis was graded according to the Eastern Cooperative Oncology Group criteria (14): grade 0 = no stomatitis, grade 1 = soreness, grade 2 = ulcers present, but patient can eat, grade 3 = ulcers present and patient cannot eat. The ulcers were painful and failed to respond to mouthwashes with topical anesthetics.

The mouthwash suspension consisted of 5 mg/ml of allopurinol in water. It was prepared by dissolving 300 mg of allopurinol granular dispersion (Zyloric; Wellcome Italia, Pomezia, Italy) in 60 ml of water. The patients were instructed to mix the suspension well before using and not to swallow the mouthwash. Each 60-ml suspension was sufficient for 2–4 mouthwashes. Allopurinol mouthwashes were repeated 2–4 times every day for 3 consecutive days every week, starting from the day of MTX administration. The suggested duration of each mouthwash was 1 minute. The regimen was continued indefinitely.

A very good response was found after the first 2 courses of treatment and was maintained in subsequent courses. Oral ulcers completely healed in all patients, and soreness disappeared in 6 of the 7 patients. One patient had a recurrence of grade 2 stomatitis after withdrawal and had a new, complete response after restarting mouthwashes. No local or systemic side effect related to allopurinol treatment was observed during a followup period of 4–8 months. Two patients had preexisting nausea, which was not affected by allopurinol treatment. No deterioration in clinical and laboratory indexes of RA was found during allopurinol treatment.

The daily absorbed dose through oral mucosa is likely to be consistently lower than that reached when the

Table 1. Characteristics of patients treated with allopurinol mouthwashes for methotrexate (MTX)–induced stomatitis*

Patient/ diagnosis	Age/sex	Duration of disease (years)	MTX weekly dosage (mg)	Duration of MTX therapy (months)	Prednisone daily dosage (mg)	Allopurinol treatment: ESR (mm/hour) Week 0	ESR Week 18	Stomatitis score Week 0	Stomatitis score Week 18
1/DM	59/M	2	20	3	37.5	63	75	2	0
2/RA	64/F	29	10	9	–	22	24	2	0
3/RA	71/M	17	10	14	2.5	23	18	1	0
4/RA	69/F	24	15	8	7.5	78	67	2	0
5/RA	57/F	8	15	45	7.5	85	81	1	0
6/RA	73/F	14	10	11	5	33	37	1	1
7/RA	66/F	5	10	2	5	64	40	2	0

* ESR = erythrocyte sedimentation rate (Westergren); DM = dermatomyositis; RA = rheumatoid arthritis.

same amount of allopurinol is ingested. However, since definite data on this topic are not available, allopurinol mouthwashes should be avoided in patients with reduced creatinine clearance (12).

In conclusion, our pilot study suggests that allopurinol mouthwashes may be effective in reducing oral discomfort in MTX-treated RA patients. It is well tolerated and does not affect the underlying disease. Further controlled studies will be necessary to establish the clinical efficacy and safety of this regimen.

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1. Clark PI, Slevin ML: Allopurinol mouthwash and 5-fluorouracil induced oral toxicity. Eur J Surg Oncol 11:267–268, 1985
2. Elzawawy A: Treatment of 5-fluorouracil-induced stomatitis by allopurinol mouthwashes. Oncology 48:282–284, 1991
3. Schwartz PM, Handschumaker RE: Selective antagonism of 5-fluorouracil cytotoxicity by 4-hydroxypyrozolopyrimidine (allopurinol) in vitro. Cancer Res 39:3095–3101, 1979
4. Granger DN, McCord IM, Parks DA, Hollwarth ME: Xanthine-oxidase inhibitors attenuate ischemia-induced vascular permeability changes in the cat intestine. Gastroenterology 90:80–84, 1986
5. Moorhouse PC, Grootveld M, Halliwell B, Quinzan IJ, Gutteridge IMC: Allopurinol and oxypurinol are hydroxyl radical scavengers. FEBS Lett 213:23–27, 1987
6. Tugwell P, Bennett K, Gent M: Methotrexate in rheumatoid arthritis. Ann Intern Med 107:358–366, 1987
7. McKendry RJR, Cyr M: Toxicity of methotrexate compared with azathioprine in the treatment of rheumatoid arthritis. Arch Intern Med 149:685–689, 1989
8. Kremer JM, Phelps CT: Long-term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis: update after a mean of 90 months. Arthritis Rheum 35:138–145, 1992
9. Tishler M, Caspi D, Fishel B, Yaron M: The effects of leucovorin (folinic acid) on methotrexate therapy in rheumatoid arthritis patients. Arthritis Rheum 31:906–908, 1988
10. Weinblatt ME, Maier AL, Coblyn JS: Low-dose leucovorin does not interfere with the efficacy of methotrexate in rheumatoid arthritis: an 8 week randomized placebo controlled trial. J Rheumatol 20:950–952, 1993
11. Porta C, Moroni M, Nastasi G: Allopurinol mouthwashes in the treatment of 5-fluorouracil-induced stomatitis. Am J Clin Oncol (in press)
12. Hande KR, Noone RM, Stone WJ: Severe allopurinol toxicity: description and guidelines for prevention in patients with renal insufficiency. Am J Med 76:47–56, 1984
13. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS, Medsger TA Jr, Mitchell DM, Neustadt DH, Pinals RS, Schaller JG, Sharp JT, Wilder RL, Hunder GG: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 25:1271–1277, 1988
14. Skeel RT: Systemic assessment of the patients with cancer, Handbook of Cancer Chemotherapy. Edited by RT Skeel. Boston, Little Brown, 1987