Treatment with allopurinol decreases the number of acute gout attacks despite persistently elevated serum uric acid levels

Sirs,

Hypouricemic therapy in gout can prevent or resorb tophi and prevent attacks of arthritis. The recommended goal of therapy is serum uric acid (SUA) less than 381 mol/L, a saturation level of extracellular fluid with monosodium urate (1, 2). In reality many patients continue to have SUA levels higher than 381 mol/L. In our experience several patients on allopurinol had persistently higher than recommended SUA levels,and at the same time had less acute gout attacks. This observation prompted us to begin to evaluate the influence of allopurinol on the frequency of gout attacks in relation to SUA levels and the presence of tophi.

We reviewed the charts of patients attending the Department of Veterans Affairs Hospital rheumatology clinic in Philadelphia, PA from 1988 to 1996,and selected patients who had crystal proven gout, and a close follow-up for a year before and a year after allopurinol introduction. We recorded the patient's age, sex,type and duration of gout, allopurinol dose, medication other than allopurinol, acute attacks, presence of tophi, and SUA and creatinine levels.

Twenty-three patients were evaluated; all males, mean age 66 years. Thirteen patients had recurrent gouty attacks, and 10 had tophaceous gout The duration of the gout ranged from 1 year to 30 years (mean 12.5 years). Allopurinol had been given at doses from 50 mg to 400 mg/day (mean 211 mg/day). Seventeen out of 23 patients were taking the same or lower daily doses of anti-inflammatory drugs in a year after allopurinol introduction when compared to a year before.

Six out of 23 patients were started on, or given higher doses of anti-inflammatory drugs at the time of allopurinol introduction. There was a significant decrease in the number of acute attacks during a year of allopurinol therapy, with a mean number of 2.69 attacks/year before and 0.30 attacks/year during a year of treatment ($p < 0.000$). This difference persisted after the exclusion of patients placed on an anti-inflammatory regimen at the time of ALP introduction. SUA levels were lower during a year of allopurinol treatment, with a mean 571 mol/ L before and 446 mol/L during the year of treatment ($p < 0.0001$). Only 7 out of 23 patients (30.4%) had SUA below the target level of 381 mol/L. Sixteen patients (69.6%) had SUA above 381 mol/L. Both groups had significantly fewer acute gout attacks while on allopurinol ($p < 0.0001$). The tophi persisted in all patients.

Achieving the recommended SUA level of less than 381 umol/L may be difficult due to several patient and physician related factors. In this pilot study, we found a significant decrease in the number of gout attacks in patients taking allopurinol despite persistently elevated SUA levels and the presence of tophi. The frequency of acute attacks reportedly correlates with SUA (3,4), so less numerous attacks may be an effect of the decreased urate load, even if SUA levels remain higher than optimal. The anti-oxidant and anti-inflammatory properties of allopurinol have resulted in the investigational use of allopurinol in ischemia-reperfusion injury (5, 6), and in experimental inflammatory arthritis (7-9). It is thus possible that in gout allopurinol exerts an anti-inflammatory effect, ameliorating the incidence and severity of attacks.

Physicians caring for patients with gout may expect less acute attacks with allopurinol treatment, even before SUA levels reach the recommended value. Studies comparing the frequency of attacks at various SUA levels with uricosuric versus allopurinol might help to clarify the mechanisms involved.

A.M. BEUTLER, *MD, Staff Rheumatologist*[1]
M. RULL, *MD, Staff Rheumatologist*[2]
N. SCHLESINGER, *MD, Chief, Rheumatology Rheumatology Section*[3]
D.G. BAKER, *MD, Director, Clinical Research*[4]
B.I. HOFFMAN, *MD, Chief, Rheumatology Department*[5]
H.R. SCHUMACHER JR., *MD, Director, Arthritis-Immunology Center*[6]

[1]Riddle Memorial Hospital, Media, PA, USA; [2]Instituto Nacional Nutricion, Mexico City, Mexico; [3]Rheumatology Section, New Jersey Medical School, Department of Allergology, Immunology and Rheumatology, Newark, NJ; [4]Centocor, Inc., 200 Great Valley Parkway, Malvern, PA; [5]Medical College of Pennsylvania and Hahnemann University, Philadelphia, PA; [6]Arthritis-Immunology Center, VAMC, Philadelphia, PA, USA.

Address correspondence to: Anna M. Beutler, MD, Riddle Memorial Hospital, 1068 W. Baltimore Pike, Media, PA 19063, USA.

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Dermatomyositis and Graves' disease

Sirs,

Dermatomyositis and Graves'disease (GD) are well known autoimmune disorders. Graves' disease is rarely associated with inflammatory myopathies, and the association between GD and dermatomyositis has been reported in only one case (1-3). We present the case of a patient with dermatomyositis who did not respond to conventional therapy. Diagnosis and treatment of the concomitant hyperthyroidism was followed by a significant clinical improvement.

A 62-year-old woman was admitted for evaluation of a 3-months history of progressive, symmetrical proximal muscle weakness of the limb girdles and neck, and mild paradoxical dysphagia. Three and a half years before, the patient had been diagnosed with a left infiltrative ductal breast carcinoma. A modified radical mastectomy was performed and she was treated with chemotherapy and radiotherapy. There was no evidence of recurrent malignancy. Physical examination showed pathognomonic Gottron papules on the hands and elbows and a periorbitary edema with heliotrope rash of the eyelids. On admission, myopathic changes were found on electromyography, and muscle biopsy performed on the deltoids showed the characteristic findings of dermatomyositis. Skeletal muscle serum enzymes (CK, aldolase, GOT, GPT and LDH) were normal, perhaps due to an early disease.

The patient was given corticosteroid treat-

ment (1 mg/kg/d) for 3 weeks without improvement. On examination, her heart rate was 120/min, and slight tremor was observed; thus, a determination of thyroid function was requested. Thyroid function tests showed total T4 serum levels of 13.5 g/dl (normal: 8-12 g/dl) and a free thyroxine index of 2.2 g/dl (normal: 0.8-1.4 g/dl) with suppressed TSH (< 0.01 mU/l). High thyroid autoantibody titers were detected, including thyroglobulin (927 UI/l), and microsomal (1,568 UI/ml) and TSH-R antibodies (28.5 UI/l). The patient's HLA status was HLA-DRB1* 0102, HLA-DRB1* 0107 and HLA-DRB4* 0101. The antinuclear antibody titer was 1/160 and myositis-specific antibodies were negative.

Corticosteroid treatment was maintained at the same dose, and methimazole (30 mg/day) and atenolol (100 mg/d) were started. There was a mild progressive improvement of muscle strength. Azathioprine at a dose of 1.5 mg/kg/d was added as a sparing corticosteroid agent. Six months later muscle strength and dysphagia were greatly improved, although a third drug (hydroxychloroquine 200 mg/d) was needed to control the persistent cutaneous manifestations.

Graves'disease is an organ-specific autoimmune disease. Thyrotoxic myopathy is known to cause muscle symptoms, including muscle weakness and periodic paralysis (4). Idiopathic inflammatory myopathies (IIM) are a group of disorders that include dermatomyositis, polymyositis and inclusion body myositis, and are also considered systemic autoimmune diseases (5). Up to 30% of patients with IIM do not respond to steroid treatment (1 mg/kg/day) and other immunosuppressive drugs, such as azathioprine, cyclosporine, methrotexate or intravenous immunoglobulins (6), are required.

The coexistence of these two entities could be fortuitous or be due to a link with a common underlying mechanism. Individuals with HLA-DR3 are at increased risk for developing autoimmune diseases (inflammatory muscle disease and Graves' disease). Some of our patient's HLA antigens (DRB4 *0101) have recently been associated with dermatomyositis (5), (specifically in patients with anti-Mi-2 antibodies), but not to GD (7). Thus, we cannot conclude that the HLA system plays a role in the coexistence of the two disorders in our patient.

In conclusion, we believe that it is important to keep in mind the possible association of two disorders causing myopathy, such as dermatomyositis and GD, to avoid diagnostic pitfalls. The presence of definite dermatomyositis does not exclude GD, and a lack of response to standard treatment could be influenced by the coexistence of thyroid myopathy, making it necessary to treat both disorders to achieve clinical improvement. Study of the HLA system did not support a pathogenetic relation between these two diseases in our patient.

A. SELVA-O'CALLAGHAN, *MD, PhD*
T. MIJARES-BOECKH-BEHRENS, *MD*
R. SOLANS-LAQUE, *MD, PhD*
T. MOLINS-VARA, *MD*
G. OLIVÉ, *MD*
M. VILARDELL-TARRÉS, *MD, PhD*

Internal Medicine Department, Vall D'Hebron General Hospital, Barcelona 08012, Spain.
Please address correspondence to:
Albert Selva-O'Callaghan, C/ Siracusa 12 Bis "A", Barcelona 08012, Spain.
E-mail: aselva@hg.vhebron.es

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