Treatment of Chronic Gout. Can We Determine When Urate Stores Are Depleted Enough to Prevent Attacks of Gout?

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ABSTRACT. ***Objective.*** To determine if lowering of serum uric acid (SUA) concentrations below 6 mg/dl or longer duration of lowered SUA will result in depletion of urate crystals from the knee joints and prevent further attacks of gout.

Methods. A prospective study was initiated 10 years ago at Philadelphia VA Medical Center to attempt to maintain SUA levels of patients with crystal proven gout at < 6.0 mg/dl. We recalled all 57 patients who were available during 1999. Patients were divided into 2 groups: Group A, with SUA still > 6 mg/dl, and Group B, with SUA ≤ 6 mg/dl. A knee joint aspirate was requested from all asymptomatic Group B patients and many in Group A. Aspirates were examined by polarized light microscopy for identification of crystals.

Results. There were no differences between the groups in age, sex, duration of gout, or serum creatinine. Group A (n = 38) had a mean of 6 attacks of gout for the recent year, those with tophi having the most frequent attacks. Among the 16 patients in this group who agreed to knee aspiration, monosodium urate (MSU) crystals were found in 14, although they were asymptomatic at the time. Nineteen patients (Group B) were able to maintain serum urate levels ≤ 6 mg/dl for > 12 months. Nearly half of them had no attack of gout for 2 or more years, with a mean of 1 attack in the last year for the whole group. Three patients in whom tophi were found did not have major flares of gout within the past year. Knee joint aspiration was done on 16 asymptomatic patients. Seven (44%) still had MSU crystals present in their knees. Patients in this group who were taking prophylactic colchicine did not differ with respect to the character of synovial fluid from those who had discontinued it for up to several years, although the frequency of attacks was less in those who continued colchicine.

Conclusion. A majority of patients were able to deplete urate crystal stores in their knee joint fluids when their SUA levels were kept to ≤ 6 mg/dl for several years. The mechanisms for persistence in some patients, and whether such crystals have clinical implications, are not known. Patients with chronic gout need serum urate concentrations to be kept low to prevent further attacks. (J Rheumatol 2001;28:577–80)

Key Indexing Terms:
CHRONIC GOUT URATE CRYSTALS ALLOPURINOL COLCHICINE

Despite our knowledge and available therapies, many people suffer recurrent attacks of gouty arthritis and develop destructive arthropathy with tophi. Longterm treatment of gout in the community is often still unsatisfactory. After a pattern of recurrent attacks is observed and certainly if tophi are identified, urate lowering agents are generally needed. Many questions concerning treatment remain: How long must colchicine be continued to prevent attacks; how long must the urate lowering agents be continued; and how low must the serum uric acid (SUA) level be to deplete crystal stores or to prevent attacks? Maintaining SUA level at < 6 mg/dl (360 mmol/l), and not just within the "normal range," has been proposed to help assure resolution of tophi and eventual cessation of acute gouty attacks[1]. Bomalaski, *et al*[2] showed that monosodium urate (MSU) crystals persisted in 58% of asymptomatic knees of patients with nontophaceous gout despite lowering of SUA levels to < 7.1 mg/dl for varying periods.

We evaluated 57 patients in a prospective study in which we worked with primary care providers and rheumatologists

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to attempt to lower SUA to ≤ 6 mg/dl. To prevent further gout attacks and ensure resorption of tophaceous deposits, we believe it is important to reduce and maintain serum urate levels to < 4–6 mg/dl or 250–350 µmol/l — well below the level at which urate saturates the extracellular fluid (roughly 6.4 mg/dl or 380.8 µmol/l at 37°C)[3]. We used aspiration of knee joints to search for crystals as one way to test if crystals have been depleted from joints in which they had initially been identified.

MATERIALS AND METHODS

Fifty-seven male patients with crystal proven gout who had been advised to use allopurinol were followed at intervals for 2–10 years at the Department of Veterans Affairs Medical Center (VAMC), Philadelphia. All patients had MSU crystals identified by us in an initial knee synovial fluid (SF) investigation. All these patients were initially found to be hyperuricemic under the care of rheumatologists and/or primary care physicians at the VAMC. Repeated uric acid levels were obtained as ordered by their physicians. Patients and physicians were instructed to gradually increase the urate lowering agent, allopurinol, until SUA reached ≤ 6 mg/dl and to attempt to maintain this level. Patients were recalled during 1999 and a thorough history and examination were conducted. All recorded SUA levels were reviewed. All patients who achieved SUA ≤ 6.0 mg/dl and maintained this level for at least 12 months were asked to undergo reaspiration of the knee. A smaller percentage of patients with SUA > 6 mg/dl also had knee aspirations.

For the knee joint aspiration, the skin was first cleansed with 10% povidone-iodine and the area for arthrocentesis was sprayed with ethyl chloride. Aspiration was done using the medial retropatellar approach with a gauge 20 needle and 5 or 10 cc syringe. The SF was promptly evaluated for volume, leukocyte count and differential, and the presence and location (intracellular/extracellular) of any MSU crystals. If no crystals were seen on a wet drop preparation, the fluid was centrifuged and the pellet was further examined for crystals. All SF were examined with a Nikon compensated polarizing light microscope. SUA levels were determined by the standard uricase method on the day of arthrocentesis. A serum creatinine was simultaneously drawn to determine the patient's renal status. The duration of gouty arthritis, frequency and sites of prior attacks, dosage and duration of drug therapies, and the joints in which MSU crystals were found were determined by interview with patients and a review of clinical records.

RESULTS

The 57 patients studied were divided into 2 groups (Table 1) based on SUA levels measured in 1999: Group A was composed of patients with SUA level > 6 mg/dl and Group B with levels ≤ 6 mg/dl. There were no differences between the groups in age, sex (all were men), duration of gout, or serum creatinine. Table 2 outlines the SF findings from all patients who had knee joint aspiration.

Group A. Sixty-seven percent of patients were inadequately treated according to our objectives, serum urate levels were erratic, but these patients never got their SUA levels below 6 mg/dl. These patients had had 4–12 attacks of gout during the most recent year. Those with tophi had the most frequent attacks. Tophi were identified in 37% of patients. Among the patients with chronic tophaceous gout, 9 were admittedly irregular users of allopurinol, while 3 of them were taking fixed doses (mean 100 mg/day) of allopurinol for > 10 years.

Among these inadequately treated patients, 42% agreed to have their knee aspirated although they were asymptomatic at the time of aspiration. Eighty-eight percent of them had MSU crystals present in the SF, virtually all of which were extracellularly located. The mean level of SUA in these patients with persistent crystals was 8.61 mg/dl. Among patients with chronic overtly tophaceous gout, 80% were found to have MSU crystals. A SF bulge sign was present in 8 patients. Though not all of them consented to have their knees aspirated, 3 of the 5 (60%) were crystal positive. The remaining 11 patients, who did not have a bulge sign but were aspirated, were all found to have some fluid and MSU crystals in the knee. The mean SF volume was 5.86 cm^3. Ninety percent of effusions studied had < 2000 leukocytes/mm^3, which is generally considered to be

Table 1. Clinical data on 57 patients in the study.

	Group A, SUA > 6 mg/dl	Group B, SUA ≤ 6 mg/dl
No. of patients	38	19
Mean duration of gouty arthritis, yrs (range)	15.3 (2–40)	14.7 (5–40)
Mean number of attacks for the recent year (range)	6 (4–12)	1 (0–3)
Mean SUA level, mg/dl (range)	8.58 (6.5–10.4)	5.29 (3.4–6.0)
Length of time taking allopurinol	2 mo–13 yrs	5–20 yrs
Prescribed dose of allopurinol, mg/day	100–300	300–600
No. of patients with serum creatinine > normal (0.5—1.2 mg/dl) (%)	4 (11)	2 (11)
Serum creatinine > 2.0 mg/dl (%)	3 (8)	0
SF bulge sign (%)	8 (21)	8 (42)
No. of patients with persistent tophi (%)	14 (37)	3 (16)
No. of patients who had knee joint aspirations (%)	16 (42)	16 (84)

SUA: serum uric acid.

Table 2. Findings in synovial fluids (SF) from patients who had knee joint aspirations.

	Group A, SUA > 6 mg/dl	Group B, SUA ≤ 6 mg/dl
No. of patients (%)	16 (42)	16 (84)
Mean SF volume, cm^3 (range)	5.86 (4–12)	2.18 (drops–8 cm^3)
Mean SF leukocyte count, cells/mm, (range)	950 (50–1800)	400 (50–1100)
No. of patients with MSU crystals (%)	14 (88)	7 (44)
No. of patients with no tophi, but MSU crystals positive (%)	10 (42)	5 (31)
No. of patients with tophi and MSU crystals (%)	4/5 (80)	2/3 (66)
No. of patients with bulge sign and MSU crystals (%)	3/5 (60)	5/8 (63)
No. of patients without bulge sign, but with MSU crystals (%)	11/11 (100)	2/8 (25)

SUA: serum uric acid, MSU: monosodium urate.

noninflammatory. These counts, however, were higher than the normal range of up to 160/mm^3. The mean leukocyte count for this group was 950 cells/mm^3.

Eighteen patients were taking prophylactic doses of colchicine for at least 2 years. MSU crystals were identified in 50% of those who had SF aspirated. Of these, 75% still had reported at least one acute attack of gout within the past 6 months. Among the 12 patients who had completely discontinued colchicine for several years, 50% had MSU crystals identified in the knee, and 67% had had acute attacks of gout within the past 6 months.

Group B. Thirty-three percent of patients were able to gradually decrease their urate levels and to keep their SUA ≤ 6 mg/dl for at least a year. These patients had 0–3 (mean of one) attacks of gout for the recent year. Forty-two percent of them had not had any acute gout for a period of 2–10 years. Three patients were still found to have tophi despite taking allopurinol for > 10 years. However, each of these 3 had noted a gradual decrease in the size of the tophi through the years and had had no major flares of gout within the past year. The mean maintenance dose of allopurinol in this group of 19 patients was 300 mg/day, but 4 of the patients had been maintained on doses as high as 600 mg/day at one point of their disease course. The average duration of therapy for these patients was 12 years.

SF from the knee joint was obtained from 84% of patients, although they all reported that they had no knee symptoms. Three patients did not give consent for the procedure. The average amount of fluid obtained was 2.18 cm^3. All aspirates were viscous and noninflammatory, with a mean leukocyte count of 400 cells/mm^3. Forty-four percent of patients still had extracellularly located MSU crystals.

A knee SF bulge sign was elicited in 50% of patients; 63% of these were found to have crystals in the knee fluids — all had MSU crystals. Weakly positive rod shaped calcium pyrophosphate dihydrate (CPPD) crystals were seen in addition to MSU crystals in 2 cases. Two of the samples had to be centrifuged to obtain pellets from which the crystals were identified. Of the remaining 50% who did not have a bulge sign, 25% had MSU crystals present on aspiration.

Eight patients had continued taking colchicine daily and all were asymptomatic for at least a year. Of those who agreed to have their knee aspirated, 50% taking this drug for at least 5 years were symptom-free and yet were MSU crystal positive (Table 3). Among the 11 patients who had stopped taking colchicine for at least 2 years, 64% reported an attack of gout in some other joint during the recent year, with only 20% of them having persistent MSU crystals in the studied knee.

Table 3. Characteristics of Group B patients (SUA ≤ 6 mg/dl) taking or not taking colchicine therapy.

	Taking Colchicine	Not Taking Colchicine
No. of patients	8	11
Mean duration, yrs (range)	5 (2–7)	3 (1–5)
No. of patients with flare within the year (%)	0	7 (64)
No. of patients who had knee joint aspiration (%)	6 (75)	10 (91)
No. of patients with crystals (%)	3/6 (50)	2/10 (20)
Mean SF leukocyte count, cells/mm^3 (range)	400 (50–1100)	500 (50–600)

SUA: serum uric acid.

DISCUSSION

The majority of the patients in the study clearly did not keep their SUA as low as requested or low enough to prevent frequent recurrences of gouty attacks. Slightly over one-third of our patients had persistent tophi. Difficulties tended to lie with primary care physicians who did not follow SUA levels, as well as with a number of patients who continued excess alcohol use, affecting both compliance and urate handling. Because of the self-limited nature of acute gout, it seems that many of our patients tended to discontinue the prescribed antihyperuricemic agent. A few patients who had tophi were maintained on a fixed dose (mean 100 mg/day) of allopurinol for several years. Whether starting patients on 300 mg/day might have improved results is not known, but this would have increased risks of reactions. Uric acid lowering on treatment with allopurinol is dose related. When serum urate levels are maintained well below the saturation level of sodium urate, crystalline deposits of urate can dissolve and tophi can decrease in size[4]. A small group of patients who had tophi despite keeping their SUA level within our requested range had gradual decreases in the size of their tophi. Although initial and followup radiographs of the symptomatic joints were not performed in this study, serial radiographs might be another means of determining depletion of articular/osseous urate crystal stores.

Among the patients adequately treated according to our plan, 44% still had observable MSU crystals present in the studied knees, with just less than half having no attacks of gout for at least 2 years. The presence of crystals in asymptomatic joints is not a surprise[2,5,6], but we were surprised that crystals still persisted with SUA levels clearly below 6.0 mg/dl and no recent attacks. The 56% of patients who had MSU crystals depleted from their knee joints did seem to do better. A small number of patients did have attacks in some other joints occasionally. This suggests that confirmed depletion of crystals from a readily aspirated joint may still be a reasonable objective, although not a guarantee of freedom from acute attacks of suspected gout. Depletion of all urates from joints may take longer than has been thought. Interestingly, attacks may stop even before all crystals are gone.

Controversy exists on when physicians should stop colchicine that has been initiated to prevent gout attacks during urate lowering therapy. Wortmann[7] stated that colchicine prevents acute gout attacks in 85% of patients initiating treatment with urate lowering drugs, and should be discontinued after the serum urate has been controlled and the patient has not had an acute attack for 1–3 months. The basis for this statement, which is a fairly common recommendation, is not given. Emmerson[8] recommended continuing colchicine intake for at least a year, again without any specific supporting data. It has been reported that colchicine exerts its inhibitory effect on leukocyte chemotaxis and reduces subclinical joint inflammation[9]. Our study showed that leukocyte counts in SF aspirates in asymptomatic joints of patients with SUA levels ≤ 6 mg/dl did not differ between those taking prophylactic colchicine and those who had been off the drug for years. The numbers may have been insufficient to detect small changes.

We observed that MSU crystals persisted longer than we expected, suggesting that continued prophylaxis might be merited as crystals might still cause inflammation. In the small numbers of patients studied, the frequency of attacks was definitely lower in the group of patients who continued colchicine compared to those who stopped. There is still no clear answer on when to stop colchicine. Our group previously showed that attacks diminished once allopurinol was started, even before SUA was normal[10].

An earlier study showed that 83% of asymptomatic patients with a positive bulge sign were crystal positive[2]. Sixty percent of our patients (combining both groups A and B) with clinical evidence of fluid had MSU crystals in their knees. In our study, many patients without a clinically detected bulge also had fluid obtained by arthrocentesis and did have crystals. The positive predictive value of the SF bulge sign for presence of crystals in asymptomatic patients based on our findings remains unclear. We can only comment on the bulge sign present during the hospital visit, as this evidence of joint effusion can come and go. Two patients who had a SF bulge sign although they were MSU crystal negative were found to have CPPD crystals, most likely secondary to associated osteoarthritis.

In general, once a patient is treated with an antihyperuricemic agent, he should continue to take it indefinitely. Unfortunately, it is difficult to determine when the total body urate pool has been sufficiently reduced for antihyperuricemic agents to be discontinued. Three patients in our study still revealed knee MSU crystals despite keeping their SUA level ≤ 6 mg/dl for > 20 years. There may be important variability in levels at which MSU crystals precipitate or are resorbed. This would be an interesting area for future study.

In summary, the majority of patients in this study were able to deplete urate crystal stores in their knee joints when their serum uric acid levels were kept to ≤ 6 mg/dl for several years. However, the clinical implications and mechanisms for the persistence of crystals in some knee joints of asymptomatic patients with serum urate levels < 6 mg/dl remain to be investigated further. On the other hand, most of our patients with chronic (tophaceous) gout clearly need closer followup with rheumatologists and primary care physicians for proper adjustment of urate lowering agents, and instructions need to be given on the importance of keeping SUA levels low enough to have a chance to deplete MSU stores and to prevent further attacks of gout.

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