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LETTERS

Potential side effects of treatment with glucosamine and chondroitin

To the Editor:

In the last 5 years, I have seen more than 200 patients with osteoarthritic pain who have taken combination glucosamine and chondroitin preparations. As is usual with over-the-counter supplements, this use runs the whole gamut of brands, many of which are mixed with vitamins, minerals, and herbal antiinflammatory agents. Since I have been acutely aware of the responsibility foisted upon me by the tacit consent I have given to patients' using these agents, I insist that patients give full informed consent to their use and undergo clinical and laboratory followup (complete blood cell count, chemistry-12 panel, creatine phosphokinase studies, and urinalysis) at 1 month after treatment initiation and every 6 months thereafter. I have found the following:

1. One instance of photosensitization, reproducible with rechallenge.

2. Three cases of reversible systolic hypertension, moderate in degree (20–30 mm Hg), in the absence of previous hypertension and unaccompanied by symptoms or laboratory abnormalities.

3. Four episodes of 1+ to 2+ proteinuria, which I did not quantitate because of the costs involved and because I was going to recommend discontinuation of the supplements anyway.

4. Three patients with elevation of creatine phosphokinase levels (in the range of 250–450 units/liter; normal 24–195 in our laboratory), asymptomatic, reversible, and in 1 instance not recurring with rechallenge.

Although I am unable to identify concurrent medications or conditions that could be blamed for these phenomena, I am not at all certain that they were related to the glucosamine/chondroitin. They may have been due to impurities or to other components in the supplements, or they might have been a natural effect of the fact that if one tests for enough things, one inevitably finds minor and irrelevant abnormalities. These possibilities should be considered in the design of prospective trials on these agents.

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Cystitis, bladder cancer, and myelodysplasia in patients with Wegener's granulomatosis: comment on the article by Reinhold-Keller et al

To the Editor:

Recently, Reinhold-Keller et al reported their observations on a cohort of 155 patients with Wegener's granulomatosis (WG) (1). Their report provides important information regarding the prognosis of patients with WG and demonstrates that prolonged survival is common when the disease is managed at a dedicated vasculitis center. However, several points in the comparison between the cohort described by Reinhold-Keller et al and our National Institutes of Health (NIH) cohort deserve further consideration.

Reinhold-Keller and colleagues define cyclophosphamide (CYC)–induced cystitis by the occurrence of nonglomerular hematuria with confirmation of CYC-induced bladder damage by cystoscopy. In the Discussion section of their article, they state that half of 145 CYC-treated patients in the NIH cohort developed CYC-induced cystitis. This statement is not accurate. In the NIH study to which they refer (2), 73 of 145 CYC-treated patients (50%) developed nonglomerular hematuria. However, only 42 of the patients with nonglomerular hematuria had CYC-induced bladder damage confirmed by cystoscopy. Thus, according to the definition used by Reinhold-Keller et al, only 29% of our 145 CYC-treated patients (not half) developed CYC-induced cystitis. Reinhold-Keller and colleagues do not provide information on how many of their CYC-treated patients had nonglomerular hematuria or what percent of those with nonglomerular hematuria underwent cystoscopy. If cystoscopy was not performed on all patients with nonglomerular hematuria, then the authors may have significantly underestimated the true incidence of CYC-induced cystitis in their patient cohort.

With regard to the development of bladder cancer, the cohort described by Reinhold-Keller et al was followed up for a median of 7 years, and 1 of 142 CYC-treated patients developed bladder cancer (1). In the NIH cohort, the estimated incidence of bladder cancer 7 years after the first CYC dose was 2%, with a 95% confidence interval of 0–4%.

Given these considerations, it is not clear whether there is a significant difference in the rate of CYC-induced cystitis or bladder cancer between these 2 cohorts. Thus, I question whether the data presented by Reinhold-Keller et al convincingly demonstrate that the use of oral mesna reduces the incidence of either CYC-related cystitis or bladder cancer, as they contend.

I was also struck by the high incidence of myelodysplasia syndrome (MDS) reported by Reinhold-Keller et al, which occurred despite a relatively low cumulative CYC dose. In the NIH cohort (3), only 2% of CYC-treated patients developed MDS, in contrast to 8% in the cohort described by Reinhold-Keller and colleagues. The reason for this 4-fold higher incidence of MDS in the German cohort is unclear, but I do not believe it can be explained by any subtle differences in duration of followup between the 2 cohorts. The median cumulative dose of CYC in the NIH cohort described in ref. 3 (not specifically reported in prior publications) was 74.9 gm (Sneller MC et al: unpublished data), which is nearly identical to the 75-gm median cumulative dose in the German cohort. Thus, the higher rate of MDS cannot be explained by differences in the cumulative CYC dose. In contrast to the NIH cohort, it appears that a significant portion of patients in the German cohort received at least some of their CYC treatment in the form of 10–20-mg/kg pulses given every 3 weeks (1). If so, this raises the question as to whether delivery of the same cumulative dose of CYC in the form of high-dose pulses (as

opposed to lower daily dosing) could be associated with a higher incidence of MDS.

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1. Reinhold-Keller E, Beuge N, Latza U, de Groot K, Rudert H, Nölle B, et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. Arthritis Rheum 2000;43:1021–32.
2. Talar-Williams C, Hijazi YM, Walther MM, Linehan WM, Hallahan CW, Lubensky I, et al. Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. Ann Intern Med 1996;124:477–84.
3. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener's granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116:488–98.

Reply

To the Editor:

We thank Dr. Sneller for his comments on our recently published article. He asks for further information on the diagnostic procedure in cases of nonglomerular hematuria, especially in CYC–treated patients. Because the use of mesna reduces the risk of CYC-induced cystitis but does not abolish it completely (1,2), all patients in our center who have nonglomerular hematuria in the absence of signs of glomerulonephritis (i.e., with no erythrocyte casts), including those with a normal urinary protein pattern (3), undergo cystoscopy. Another reason for the broader indication for cystoscopy is that WG is significantly associated with urologic tumors, as we have recently reported (4).

In the NIH cohort of WG patients, CYC-induced cystitis was observed in 68 of 158 patients (43%) and, after extended followup, in 42 of 145 patients (29%), without the use of mesna as uroprotection in either observation period (1,2). In comparison, CYC-induced cystitis with mesna uroprotection occurred in our cohort in only 17 of 142 patients (12%). Thus, based on the data from the NIH studies described in refs. 1 and 2, the relative risk for the occurrence of CYC-induced cystitis with mesna uroprotection as opposed to without mesna uroprotection is only 0.28 (95% confidence interval 0.17–0.45) and 0.41 (95% confidence interval 0.25–0.69), respectively. The incidence of cystitis with CYC combined with mesna treatment is significantly lower than the risk with CYC treatment without uroprotection ($P = 0.00001$ and $P = 0.0004$, respectively, versus the 2 NIH studies).

Mesna may also be protective with respect to bladder carcinoma. In the NIH studies, 4 of 158 patients (3%) (1) and 7 of 145 patients (5%) (2) developed bladder cancer, versus only 1 patient from our cohort (<1%; $P = 0.034$ versus the NIH cohort [2]). The benefit of mesna as uroprotection would probably be shown to be even more pronounced if all 3 cohorts had the same followup period. The followup was longest in our cohort (2,144 patient-years, versus 1,229 in the study by Hoffman et al [1] and 1,333 in the study by Talar-William's et al [2]). This is relevant given that the risk of CYC-induced cystitis and subsequent bladder carcinoma increases continuously with the duration of followup (2). In this context it is noteworthy that an extension of the followup period from a median of 7 years (as reported in our article) by an additional 39 months (up to July 2000) in our cohort did not result in any further occurrence of bladder carcinoma among the 17 patients who had developed CYC-induced cystitis.

The above data thus provide clear evidence in favor of the use of mesna as uroprotection in patients who are being treated daily with oral CYC. It would be useful to conduct a prospective randomized controlled study to more adequately assess the value of mesna as uroprotection with CYC treatment.

Dr. Sneller also asks for an explanation as to why MDS occurred more frequently in our cohort (8%) than in the NIH cohort (3% [1]). Since the cumulative doses of CYC were similar in the 2 cohorts, the difference in the incidence of MDS is most likely due to the longer duration of followup in our cohort. MDS in our patients occurred late in the disease course (median 60 months [range 22–168 months] after the diagnosis of WG). Furthermore, our patients, after successful induction of WG remission, received long-term treatment with a remission maintenance regimen with less potent but also cytotoxic drugs (low-dose methotrexate or azathioprine), which may have added to bone marrow toxicity and thus contributed to the development of MDS. We do not know whether this was also the case in the NIH cohort (1). Dr. Sneller's assumption that pulse CYC treatment may have contributed to the development of MDS certainly does not hold true. Because of the lower efficacy of this regimen compared with daily oral CYC, at least in our experience (5), only 7 of our patients, whose WG has been less serious, have received pulse CYC exclusively. None of those patients has developed MDS.

One hundred-thirty-five of 142 patients in our cohort, including all 11 with MDS, have received daily CYC at some stage during the course of their disease. Therefore, the MDS patients have received a significantly higher cumulative CYC dose than the patients who have not developed MDS. Furthermore, 70 of 135 patients who were treated with daily CYC also received pulse CYC at some stage, mostly for maintenance of remission after daily oral CYC treatment or in cases of severe toxicity from daily oral CYC. Four of 11 patients with MDS (36%) versus 66 of 124 without MDS (53%) received daily oral CYC as well as subsequent pulse CYC. Therefore, Sneller's statement on the contributory role of pulse CYC in the development of MDS does not appear to be correct.

Permanent CYC-associated morbidity (CYC-induced cystitis and MDS) remains a serious problem in the treatment of WG. Since daily oral CYC is still indispensable in the treatment of WG, it should be given over as short a period as possible and in combination with mesna as uroprotection, in order to reduce CYC-related toxicity to the greatest possible extent.

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1. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener's granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116:488–98.
2. Talar-Williams C, Hijazi YM, Walther MM, Linehan WM, Hallahan CW, Lubensky I, et al. Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. Ann Intern Med 1996;124:477–84.
3. Niederstadt C, Happ T, Tatsis E, Schnabel A, Steinhoff J. Glomerular and tubular proteinuria as markers of nephropathy in rheumatoid arthritis. Rheumatology 1999;38:28–33.
4. Tatsis E, Reinhold-Keller E, Steindorf K, Feller AC, Gross WL. Wegener's granulomatosis associated with renal cell carcinoma. Arthritis Rheum 1999;42:751–6.
5. Reinhold-Keller E, Kekow J, Schnabel A, Schmitt WH, Heller M, Beigel A, et al. Influence of disease manifestation and antineutrophil cytoplasmic antibody titer on the response to pulse cyclophosphamide therapy in patients with Wegener's granulomatosis. Arthritis Rheum 1994;37:919–24.

False-positive results obtained using the Mantoux test in Behçet's syndrome: comment on the article by García-Porrúa et al

To the Editor:

We read with interest the report of the excellent and comprehensive study by García-Porrúa and colleagues on predictors of underlying disease in patients with erythema nodosum (1). The authors present data indicating that a Mantoux test is useful in identifying patients with underlying tuberculosis. While we do not dispute the general usefulness of the Mantoux test, we believe that a positive result needs to be interpreted with caution in patients with Behçet's syndrome, in which erythema nodosum occurs commonly (20–50%) (2).

One of our patients, an Egyptian man, presented at the age of 39 with reduced vision in the right eye secondary to a right inferotemporal branch retinal vein occlusion. One year later he developed a branch retinal vein occlusion affecting the left eye. Fluorescein angiography during this episode showed evidence of retinal vasculitis in the left eye. The only significant event in his medical history was that of recurrent oral ulceration. His subsequent progress was complicated by the development of genital ulceration, transient left-sided hemiparesis secondary to brainstem infarction, and multiple episodes of bilateral florid uveitis. Behçet's syndrome was diagnosed based on the 1990 International Study Group classification criteria (3). Tissue typing demonstrated that the patient was HLA–B51 positive.

During the initial evaluation a Mantoux test was performed (intradermal injection of 10 units of tuberculin purified protein derivative), which elicited a marked erythematous inflammatory response (2.5 × 2.75 cm and 4.5 × 5.5 cm at 24 hours and 48 hours, respectively). Despite this, the patient had no personal history of tuberculosis or recent contact with an infected individual. Furthermore, chest radiography results were repeatedly normal, and there remained no further evidence of tuberculosis despite immunosuppressive therapy for the ocular inflammation.

Patients with Behçet's syndrome are known to exhibit abnormal cutaneous inflammatory responses to nonspecific stimuli. For example, in the majority of healthy subjects, intracutaneous injection of monosodium urate crystals leads to an inflammatory response that peaks at 24 hours and has substantially subsided by 48 hours. This response is significantly prolonged in patients with Behçet's syndrome (4,5). In our patient, the duration of erythema following injection of 2.5 mg monosodium urate crystals was clearly abnormal (3 × 3.75 cm at both 24 hours *and* 48 hours).

We agree that the Mantoux test is an important investigative tool in the diagnosis of erythema nodosum, but caution is needed in its interpretation in patients in whom the cause of erythema nodosum may be Behçet's syndrome. Although it is difficult to totally exclude the possibility of underlying tuberculosis, performing the urate crystal test can be useful in patients in whom the Mantoux response is suspected to be false positive.

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1. García-Porrúa C, González-Gay MA, Vázquez-Caruncho M, López-Lazaro L, Lueiro M, Fernández ML, et al. Erythema nodosum: etiologic and predictive factors in a defined population. Arthritis Rheum 2000;43:584–92.
2. Yazici H, Yurdakul S, Hamuryudan V. In: JH Klippel, PA Dieppe, editors. Rheumatology. 2nd ed. London: Mosby; 1998. p. 26.1–6.
3. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet 1990;335:1078–80.
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5. Pickering MC, Haskard DO. Behçet's syndrome. J R Coll Physicians Lond 2000;34:169–77.

Reply

To the Editor:

We very much appreciate Drs. Pickering and Haskard's comment on our work. They raise an important point that warrants further discussion. A positive result on the Mantoux test does not always imply the presence of active tuberculosis. In our series also, some patients with no history of tuberculosis or recent contact with an infected individual had a positive tuberculin test result. Chest radiography findings in these patients were normal, and cultures for *Mycobacterium tuberculosis* were negative. These patients fulfilled classification criteria for erythema nodosum, either idiopathic or secondary to other conditions. Although the tuberculin skin test result was positive in 5 of 5 patients with erythema nodosum secondary to tuberculosis, it was also positive in some cases of either idiopathic erythema nodosum (4 of 39 patients) or nontuberculous secondary erythema nodosum (for example, in 3 cases of erythema nodosum related to drug intake). Although in areas where tuberculosis is relatively common a positive tuberculin test result does not always imply the

presence of active tuberculosis, we believe an intradermal tuberculin test is an important component in the diagnosis of erythema nodosum, since it may provide the first clue of the presence of underlying tuberculosis.

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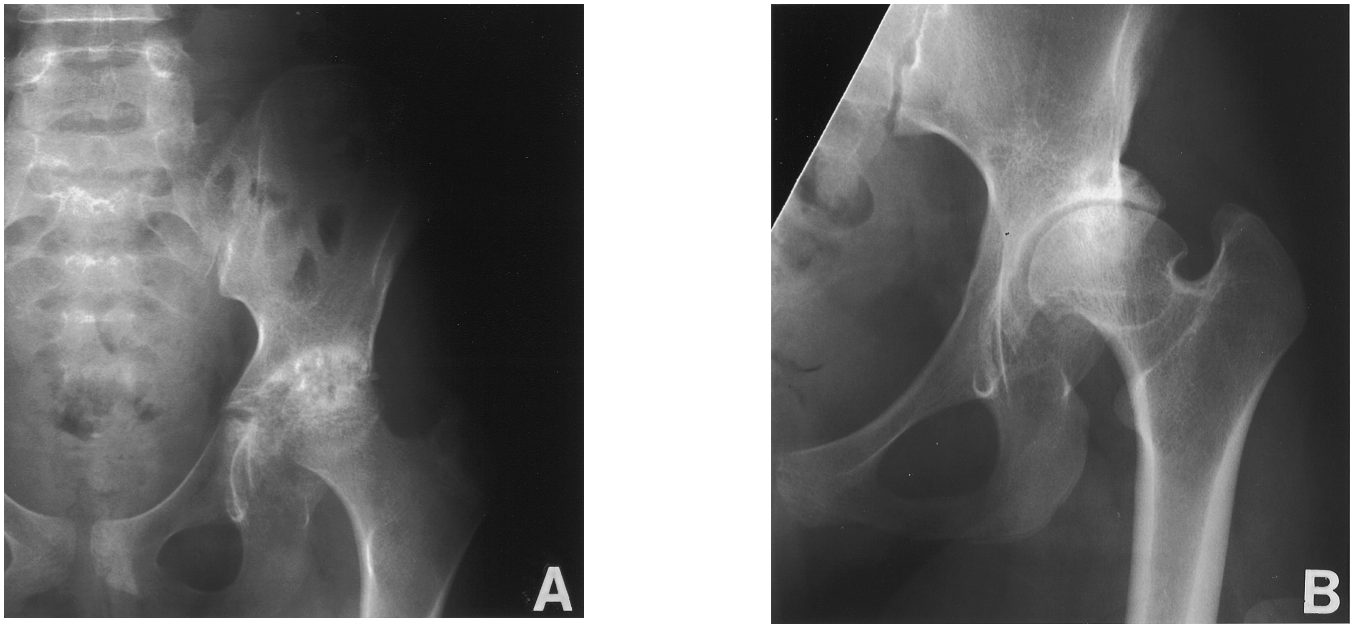
Clinical Images: Hip joint remodeling in systemic-onset juvenile rheumatoid arthritis



The patient is a 20-year-old woman with a history of systemic-onset juvenile rheumatoid arthritis (JRA) diagnosed when she was 2 years old. Her treatment throughout the years consisted of nonsteroidal antiinflammatory drugs (NSAIDs), methotrexate, and every-other-day corticosteroids. Currently, she takes only over-the-counter NSAIDs as needed. Five years ago, she had moderate reduction in left hip abduction and internal and external rotation. Radiographs **(A)** showed severe changes of end-stage JRA of the hip, with joint space obliteration, sclerosis, and cystic changes. Currently, she has only mild reduction of hip motion and no pain. She is an active college student with minimal limitations. Repeat radiographs obtained in February 2000 **(B)** reveal dramatic remodeling of the acetabulum and femoral head and reappearance of the joint space. Obvious flattening of the femoral head and degenerative changes are noted throughout the joint. Severe hip involvement in JRA often leads to significant functional disability and typically necessitates joint replacement in these patients (Blane CE, et al [J Pediatr Orthop 7:677–80] and Maric Z, Haynes RJ [Clin Orthop Rel Res 290:197–9]). Hip joint restoration or remodeling in JRA has been reported rarely (Bernstein B, et al [Arthritis Rheum 20:1099–1104] and García-Morteo O, et al [Arthritis Rheum 24:1570–4]). When this occurs, function may be improved, disability minimized, and the need for surgical intervention delayed by many years.

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