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CONCISE COMMUNICATIONS

The impact of ultrasonography on diagnosis and management of patients with musculoskeletal conditions

There is increasing interest in the use of ultrasonography (US) in rheumatology (1). Ultrasonography is noninvasive, safe (uses no ionizing radiation), and can be used repeatedly in an outpatient setting which provides immediate access for patients. Availability of US varies widely between hospitals, with most of the referrals being for specific conditions such as rotator cuff tears. This usually requires a separate visit to the radiology department and then a return visit to the referring physician. There is accumulating evidence that US is more accurate than clinical examination in the detection of synovitis and tenosynovitis in small joints (2,3), and its use in musculoskeletal conditions is becoming increasingly validated (4). There is, however, a paucity of data assessing its actual impact on patient management. This study evaluated the diagnostic and therapeutic impact of musculoskeletal US in rheumatology outpatient clinics.

Of 520 consecutive rheumatology outpatients seen, 100 were referred for US, and were enrolled in the study following provision of informed consent. All patients underwent a routine assessment, including a detailed history and clinical examination by experienced physicians. The indication for US, the site of interest, and site-specific diagnosis (SSD; e.g., synovitis, tenosynovitis), which was diagnosed clinically by the attending physician, were documented. The overall diagnosis (OD; e.g., rheumatoid arthritis, gout) and management plan were also recorded.

Patients had US performed during the same clinic visit (on the requested sites only) by a rheumatology research fellow experienced in US, using an on-site ATL HDI 3000 machine (Advanced Technology Laboratories, Bothel, Washington). A linear array 10-5 MHz "hockey stick" transducer was used to examine most joints and a curvilinear array 5-3 MHz transducer was used to examine the hip. The referring physician subsequently reviewed the US report for each patient in the same clinic, and any change in the diagnosis or management as a result of US was documented.

Of the 100 patients referred for US, 73 were female and the mean age was 50 years (range 17–87 years). Sixty-four patients were referred to confirm a diagnosis alone, while 36 were referred for diagnosis and local corticosteroid injection. Twenty of these 36 patients (56%) had reported a poor response to a previous "blind" corticosteroid injection. A total of 121 sites were examined by US (Table 1). US was requested to confirm the presence or absence of synovitis in 86 of the 121 sites (71%), enthesitis in 11 of 121 sites (9%), and tenosynovitis in 9 of 121 sites (7%).

Following review of the US findings, the SSD was changed in 53 of 100 patients (53%) and 60 of 121 sites (50%). In order of frequency, the changes in clinical SSD were synovitis in 43 of 60 sites (72%), tenosynovitis in 7 of 60 sites (12%), and enthesitis in 5 of 60 sites (8%). The frequency of SSD change, by site, is listed in Table 1. The OD was changed in 5 of 100 patients (5%). There were a further 8 of 100 patients (8%) in whom US helped confirm a provisional OD. The management plan was altered in 53 of 100 patients (53%) after US, of which 39 were due to a change in SSD and 14 were a result of US confirming a provisional SSD.

Table 1. Sites examined by ultrasonography, with frequency of change in site-specific diagnosis (SSD)

Site of scan	No. (%) of sites examined	Frequency of SSD change, no. (%)
Overall	121 (100)	60/121 (50)
Metacarpophalangeal joints	45 (37)	24/45 (53)
Wrist	17 (14)	8/17 (47)
Proximal interphalangeal joints	15 (12)	5/15 (33)
Hindfoot	12 (10)	7/12 (58)
Knee	10 (8)	5/10 (50)
Forefoot	7 (6)	6/7 (86)
Elbow	5 (4)	1/5 (20)
Other	10 (8)	4/10 (40)

The corticosteroid regimen was affected in 43 patients. Planned intraarticular corticosteroid injections were altered in 22 patients, and in 14 patients, a new injection was given after US. Parenteral corticosteroid therapy was affected in 7 patients. Only 14 (39%) of the 36 intended injections were given at the planned intraarticular site. Disease-modifying antirheumatic drug (DMARD) therapy was affected in 13 patients, of which 10 were due to the detection of extensive subclinical synovitis.

This study suggests that US has a diagnostic and therapeutic impact in the majority of referred patients who attend rheumatology clinics. When these findings are applied in the context of all patients attending clinics during the study period, US has an impact on diagnosis and management in at least 10% (53 of 520) of all cases. Consistent with previous reports, this study demonstrates a poor correlation between US and clinical examination in the detection of synovitis; the changes to DMARD therapy were mainly a result of detection of subclinical synovitis by US. This would suggest patients with clinically stable disease are often undertreated, and may help explain the continued bone damage reported in this group of patients (5).

Response to corticosteroid injections is known to vary considerably, and there is evidence that accurately placed injections result in improved patient outcome (6,7). Interestingly, as a consequence of US, less than half the referred patients received an injection at the preplanned site. The impact of US on corticosteroid injections therefore reflects the limitations of clinical assessment in accurately localizing pathologic sites and may explain, in part, the variation in response to conventionally placed injections. This study also documents the referral pattern when rheumatologists have direct access to US, with most patients referred for assessment of small-joint synovitis and guided injections.

After initial capital expenditure, the only running costs

for US are the service contract and operators' time, in this case, taking 10–15 minutes per patient assessment. In the United Kingdom, charges for an individual small-joint US (which may include the cost of injection) vary from $50 in the public sector to $200 (in United States dollars) in the private sector. The US examinations took place during the outpatient visit, where direct access has the advantage of immediate alteration in the management plan, thereby avoiding additional hospital visits and associated costs.

There are limitations to this study. There was an initial selection bias, since the patients assessed were all referred for US in the first instance, suggesting a degree of uncertainty in the diagnosis or management at the outset. Although a change in the clinical diagnosis or management plan is an important first step, it does not necessarily follow that outcome will be improved. Further work is required to determine whether these changes translate to an improvement in patient outcome. Any benefit will have to be offset with the additional cost of US equipment and training, but should also take into account the direct and indirect cost benefit of a "one-stop" patient service.

In this preliminary, nonrandomized observational study, US has a major impact on the diagnosis and management of musculoskeletal conditions. US is safe, relatively inexpensive, and can be performed effectively by rheumatologists, raising important questions for the future training and practice of rheumatology. A randomized study assessing change in diagnosis and management after US, with specific clinical outcome measures, is warranted.

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Treatment of longstanding active giant cell arteritis with infliximab: report of four cases

Corticosteroids are the drug of choice in the treatment of giant cell arteritis (GCA) (1). An initial dosage of 40–60 mg/day of prednisone or equivalent, in single or divided doses, is adequate in nearly all cases of the disease (2). Once remission of clinical symptoms and normalization of acute-phase reactant levels are achieved, the dosage can be gradually tapered. Long-term corticosteroid treatment, ranging from 1 year to 5 years or more, is required, with frequent serious side effects (3,4). To date, there are no published reports on the efficacy of corticosteroid-sparing drugs or alternative therapeutic approaches to GCA (5).

Vasculitis in GCA is characterized by infiltration of the vessel wall by macrophages, giant cells, and T lymphocytes, with production of many cytokines that are responsible for the acute-phase response (6). Tumor necrosis factor α (TNFα), which is released by macrophages and activated T lymphocytes, plays a major role in the inflammatory response (7). By immunohistochemical techniques, TNFα has been demonstrated in up to 60% of the cells in all areas of inflamed arteries (8); therefore, TNFα could play a primary role in the GCA inflammatory process. In addition, a strong association of GCA with TNFa2 microsatellite polymorphism has been demonstrated (9).

Infliximab, a chimeric monoclonal anti-TNFα antibody, has been demonstrated to have remarkable efficacy and safety in the treatment of rheumatoid arthritis (RA) (10,11) and other rheumatic conditions characterized by a chronic inflammatory response (12,13). No data have been published to date on the use of infliximab in the therapy of GCA. To evaluate the efficacy of TNFα blockade in GCA, we administered infliximab infusions to 4 patients with longstanding GCA that had remained active despite corticosteroid treatment.

All 4 patients met the American College of Rheumatology criteria for the classification of GCA (14). The demographic and clinical characteristics of the patients at the time of diagnosis are summarized in Table 1.

These patients had severe disease and had undergone long courses of corticosteroid treatment without achieving remission. Specifically, each had received prednisone at an initial dosage of 50 mg/day. When symptoms had remitted for 1 month, the dosage was reduced to 40 mg/day. Small monthly decrements of 5 mg to 2.5 mg were successively scheduled until the minimal maintenance dosage was reached. All 4 patients had relapsed every time the corticosteroid dosage was reduced to 7.5–12.5 mg/day, and all had experienced corticosteroid-related serious adverse events such as osteoporosis with fractures, diabetes, and cataracts. The disease duration at the time infliximab was begun was 54 months, 50 months, 45 months, and 42 months, respectively.

After the study was approved by the local ethics

Table 1. Demographic and clinical characteristics at the time of diagnosis in the 4 patients with giant cell arteritis

	Patient 1	Patient 2	Patient 3	Patient 4
Sex	F	F	M	F
Age at disease onset, years	73	75	72	75
Duration of symptoms before diagnosis, months	3	2	2	1
Systemic signs/symptoms (fever, anorexia, weight loss)	Yes	Yes	Yes	Yes
New-onset headache	Yes	Yes	Yes	Yes
Temporal artery abnormality*	Yes	No	Yes	Yes
Erythrocyte sedimentation rate (Westergren), mm/hour	88	76	96	90
C-reactive protein (nephelometry), mg/dl	7.8	6.9	11.2	7.4
Abnormal artery biopsy†	Yes	Yes	Yes	Yes
Jaw or tongue claudication	No	Yes	Yes	No
Visual symptoms	No	No	No	No
Polymyalgia rheumatica	No	Yes	No	Yes

* Temporal artery tenderness, decreased pulsation, or nodules at palpation.
† Inflammatory infiltrate with predominance of mononuclear cells or granulomatous vasculitis with or without multinucleated giant cells.

committee and written informed consent was obtained, the 4 patients were scheduled to receive 3 intravenous infusions of infliximab (3 mg/kg) at weeks 0, 2, and 6, which is the current administration schedule for patients with RA (10,11). The drug was infused over a 2-hour period. During the first 2 weeks, they were also given prednisone 5 mg/day. The steroid was withdrawn if remission was obtained after the second infusion of infliximab. The third infusion was administered only if a patient had achieved clinical remission after the second. Patients whose GCA had not responded after the second infusion of infliximab were withdrawn from the study and prednisone was reinstituted at 15 mg/day. The same steroid regimen was given in case of relapse after the third infusion.

GCA was considered active if at least 1 of the standard clinical variables (systemic signs and symptoms [fever, anorexia, weight loss], proximal musculoskeletal symptoms suggesting polymyalgia rheumatica [PMR], cranial symptoms [headache, jaw claudication, scalp or temporal artery tenderness], or visual symptoms) in association with an elevated erythrocyte sedimentation rate (ESR) (Westergren) and C-reactive protein (CRP) level (nephelometry; normal <0.5 mg/dl) was present. Patients were evaluated for the parameters of disease activity at baseline (T0), after the first infusion (time 1), after the second infusion (time 2), after the third infusion (time 3), and at the end of the followup (time 4, i.e., time of manuscript submission). During the followup period they were evaluated monthly. Monitoring for side effects took place at every visit, with patients being asked to identify any new problems or changes that had occurred since the previous visit. During the infusion and for 1 hour afterward, blood pressure, pulse, and temperature were measured every 30 minutes. Moreover, at every visit, complete blood cell count and liver and kidney function tests were performed.

Patients were considered responders if remission was demonstrated in all parameters of disease activity after the second infusion of infliximab. The same variables were used during the followup period. The goal of therapy was to achieve complete remission of the disease as had been achieved with high-dose prednisone but had not been retained when the prednisone dosage had been reduced.

All 4 patients had active disease before starting infliximab treatment. As shown in Table 2, 3 patients had a complete response to infliximab therapy, with clinical and humoral remission after the second infusion. The remission continued after the third infusion and during the followup

Table 2. Results of infliximab therapy in 4 patients with longstanding GCA*

	Time 0 (baseline)	Time 1 (after first infusion)	Time 2 (after second infusion)	Time 3 (after third infusion)	Time 4 (end of followup period)†
Patient 1					
Systemic symptoms	Yes	No	No	No	No
Cranial symptoms	Yes	No	No	No	No
Visual symptoms	No	No	No	No	No
Articular symptoms	Yes	No	No	No	No
ESR	45	11	12	10	8
CRP	2.6	0.3	0.3	0.4	0.4
Patient 2					
Systemic symptoms	Yes	No	No	No	No
Cranial symptoms	No	No	No	No	No
Visual symptoms	No	No	No	No	No
Articular symptoms	Yes	No	No	No	No
ESR	60	22	12	12	10
CRP	4.6	0.6	0.4	0.3	0.3
Patient 3					
Systemic symptoms	Yes	No	No	No	No
Cranial symptoms	No	No	No	No	No
Visual symptoms	No	No	No	No	No
Articular symptoms	Yes	No	No	No	No
ESR	55	34	11	10	8
CRP	6.4	1.1	0.3	0.3	0.3
Patient 4				Withdrawn	Withdrawn
Systemic symptoms	Yes	No	Yes		
Cranial symptoms	No	No	No		
Visual symptoms	No	No	No		
Articular symptoms	Yes	Yes	Yes		
ESR	73	45	88		
CRP	9.4	6.6	12.2		

* GCA = giant cell arteritis; ESR = erythrocyte sedimentation rate (mm/hour); CRP = C-reactive protein (mg/dl).
† Followup (to the time of manuscript submission) was 6 months in patient 1, 5 months in patient 2, and 5 months in patient 3.

period without any treatment. To date, the disease remains in clinical remission in these 3 patients, without steroid treatment, after 6, 5, and 5 months, respectively, from the third infliximab infusion. Patient 4 did not respond to therapy and she withdrew from the study after the second infusion as dictated by the protocol. After a partial response following the first infusion, at time 2 she had a clinical relapse with increased ESR and CRP values. Fever recurred and proximal musculoskeletal aching typical of PMR persisted. Clinical assessment for any infections yielded negative results. Similar to findings in RA (11), it is possible that this patient's condition might have improved if the dosage of infliximab had been increased.

Infliximab was well tolerated by all patients. No side effects were reported or observed.

The limited number of patients included in this study and the open-label design do not allow us to draw definitive conclusions from our findings. In spite of our encouraging preliminary results, the therapeutic role of infliximab in GCA remains to be more thoroughly evaluated, and controlled studies with a greater number of patients are needed.

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