Baseline Shoulder Ultrasonography Is Not a Predictive Marker of Response to Glucocorticoids in Patients with Polymyalgia Rheumatica: A 12-month Followup Study

Maria Concetta Miceli, Angelo Zoli, Giusy Peluso, Silvia Bosello, Elisa Gremese, and Gianfranco Ferraccioli

ABSTRACT. ***Objective.*** In this study, we evaluated whether ultrasound (US) subdeltoid bursitis (SB) and/or biceps tenosynovitis (BT) presence at baseline could represent a predictive marker of response to standard therapy after 12 months of followup, and whether a positive US examination could highlight the need of higher maintenance dosage of glucocorticoids (GC) at 6 and 12 months in patients with polymyalgia rheumatica (PMR).

Methods. Sixty-six consecutive patients with PMR underwent bilateral shoulder US evaluations before starting therapy and after 12 months of followup. Absence of girdle pain and morning stiffness (clinical remission) and laboratory variables were evaluated. After diagnosis, all patients were treated with prednisone.

Results. At baseline, SB and/or BT were present in 46 patients (70%), of whom 33 (72%) became negative while 13 (28%) remained positive at the 12-month US evaluation. All patients rapidly achieved a clinical remission, and at 6 months 26 (39%) also achieved a laboratory variable normalization. According to US positivity at baseline, no difference was found in remission or relapse rate after 12 months. Thirty patients (46%) at 6 months and 7 (11%) at 12 months were still taking more than 5 mg/day of prednisone. According to the US pattern at baseline, no difference was found in the mean GC dose at 6 and 12 months.

Conclusion. In patients with PMR, the presence of SB and/or BT on US at diagnosis is not a predictive marker of GC response or of a higher GC dosage to maintain remission in a 12-month prospective followup study. (First Release December 15 2016; J Rheumatol 2017;44:241–7; doi:10.3899/jrheum.160090)

Key Indexing Terms:
POLYMYALGIA RHEUMATICA | SUBDELTOID BURSITIS
BICEPS TENDONITIS | STEROID DOSE | SHOULDER ULTRASOUND

Polymyalgia rheumatica (PMR) is a chronic, inflammatory disease characterized by pain and longterm morning stiffness in the neck, shoulders, hips, upper arms, and thighs that affects individuals over the age of 50 years[1,2]. In recent years, because of the increased use of imaging techniques such as musculoskeletal ultrasonography (MSUS) and magnetic resonance imaging (MRI), periarticular and articular inflammatory processes of shoulder and hip joints, such as bursal inflammation and synovitis, have been demonstrated in patients with PMR[2,3,4,5,6].

Imaging studies are not required to establish the diagnosis of PMR, which is based on clinical findings, differential diagnosis, and inflammation laboratory variables, but ultrasound (US) appears to add specificity to the diagnosis. Dasgupta, *et al* proposed to include the MSUS demonstration of bilateral subdeltoid bursitis (SB) and/or long head biceps (LHB) tenosynovitis or glenohumeral synovitis in at least 1 shoulder and synovitis or trochanteric bursitis in at least 1 hip among the provisional classification criteria for the diagnosis of PMR[7]. However, the relevance of MSUS to monitoring the response to standard therapy, or further, to predict PMR behavior in daily clinical practice has not been completely defined.

The initial goal of therapy is to achieve a rapid symptomatic control using glucocorticoids (GC) at low to moderate

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doses, although most patients require long-duration treatment and relapses are common with dosage tapering[3].

The aims of our study were to assess whether MSUS presence of SB and/or LHB tenosynovitis at the diagnosis could represent a predictive marker of response to the standard therapy during a 12-month followup period and whether it could highlight the need for a higher maintenance dosage of GC.

MATERIALS AND METHODS

Sixty-six consecutive outpatients (51 women, aged 72.0 ± 6.9 yrs, range 55–89 yrs) complaining of bilateral shoulder pain and/or morning stiffness > 45 min with an erythrocyte sedimentation rate (ESR) > 50 mm/h and/or a C-reactive protein (CRP) > 5 mg/l were diagnosed with PMR according to the American College of Rheumatology/European League Against Rheumatism 2012 provisional clinical criteria for PMR (without the optional US criteria)[7]. Patients were referred to our tertiary referral hospital outpatient ward by general practitioners, other specialists, the patients themselves, or by the emergency room in an 18-month period. All patients were negative for rheumatoid factor and anticitrullinated protein antibodies and had no other clinical evidence of musculoskeletal diseases. Patients were excluded if they had clinical manifestations of giant cell arteritis or with a positive temporal artery biopsy, or were treated with GC prior to study entry. During the followup period, none of the patients developed rheumatoid arthritis or alternative diagnosis other than PMR.

Each patient underwent a bilateral shoulder MSUS evaluation at the time of diagnosis before starting therapy and after a 12-month period. All US examinations were performed by the same rheumatologist with an expertise in musculoskeletal US (GP) who was unaware of the clinical and laboratory findings of the patients and was not involved in the treatment decisions to reduce operator-dependent variability and to improve the homogeneity of US testing. The equipment used for US was the Esaote Technos machine with a 5–12 MHz linear array transducer. The MSUS evaluation included the B-MODE detection of tenosynovitis and bursitis of the shoulders according to the standardized scanning method and published reference values[8,9] by a dichotomous evaluation (presence/absence). SB was considered if the maximal thickness of hypoechoic signal within the bursa was greater than 2 mm, while LHB tenosynovitis was considered if the thickness of the hypoechoic halo of fluid surrounding the biceps tendon was greater than 2 mm (Figure 1). The Doppler modalities were not considered. The presence of at least monolateral SB or LHB tenosynovitis was considered as a positive pattern.

After diagnosis, all patients were treated with a prednisone dose of 0.2 mg/kg/day for the first month (increased if symptoms were uncontrolled), followed by 15% tapering of the dosage every 4 weeks down to the lesser dosage, allowing the patient to remain asymptomatic while keeping normal laboratory values.

The patients were assessed and treated by fully board-certified rheumatologists (AZ, GFF, SLB, EG) who were blinded to US examination findings.

Clinical remission was defined as the lack of girdle pain and laboratory remission as levels of ESR ≤ 40 mm/h and CRP ≤ 5 mg/l. A low prednisone dose in remission was considered if prednisone was taken at < 5 mg/day.

Data were analyzed using SPSS 15.0 (SPSS). Continuous variables are reported as mean ± SD, while categorical variables are reported as number and percentage. Analysis of categorical variables was performed by the chi-square test or Fisher's exact test when appropriate. Analysis of continuous variables was performed with the Mann-Whitney U test. Statistical significance was defined as a p value < 0.05.

All enrolled subjects provided signed informed consent for clinical information use, and the local Ethical Committee did not request study protocol approval because the patients were followed and treated according to the common daily good clinical practice for PMR.

RESULTS

At baseline, 16 out of the 66 patients with PMR (24.2%) had peripheral arthritis, 15 (22.7%) reported weight loss, and 13 (19.7) complained of persistent low grade fever. At the baseline MSUS evaluation of the shoulders, SB and/or LHB tenosynovitis were observed in 46 patients (69.7%) out of the enrolled cohort. No significant differences in clinical and laboratory inflammatory variables were found between patients with positive and negative MSUS pattern at baseline (Table 1).

After starting prednisone therapy, all patients rapidly presented the improvement of symptoms and achieved clinical remission. Prednisone was gradually tapered until the minimal dose needed to completely control the symptoms and no patients presented recurrence of symptoms such as girdle pain and morning stiffness during the 12-month followup.

After 6 months of followup, among the 46 patients presenting MSUS-positive pattern at the baseline, 17 (37%) showed laboratory remission whereas 29 (63%) still had ESR and/or CRP abnormalities. On the other hand, among the 20 patients with MSUS-negative pattern at baseline, 9 (45%) achieved laboratory remission whereas 11 (55%) still had laboratory activity. No significant association was found between MSUS positivity pattern at the onset of the disease and laboratory remission achievement at the 6-month followup (p = 0.36). Similar results were observed at the 12-month followup, when 23/46 patients (50%) with baseline MSUS positivity were in laboratory remission compared to 9/20 (45%) MSUS-negative patients at baseline, with no correlation between MSUS pattern at the diagnosis and laboratory remission rate at 12 months (p = 0.45).

Considering the 46 patients with MSUS-positive pattern at baseline, 33 (71.7) became negative while 13 (28.2%) remained positive after the 12-month followup. No significant difference in ESR, CRP, and clinical symptoms of presentation (fever, peripheral arthritis) was observed between the 2 groups of patients except for baseline morning stiffness that affected all the 13 patients with persistence of MSUS-positive findings at 12 months compared with 24 (73%) of the patients becoming MSUS-negative (p = 0.03; Table 2). Four (30.8%) of persistently MSUS-positive patients achieved laboratory remission at the 12-month followup while 9 (69.2%) did not, whereas among 33 patients achieving MSUS remission at 12 months, 19 (57.6%) also achieved laboratory remission while 14 (42.4%) did not (p = 0.09).

Considering the US examination at baseline, among the 46 patients with MSUS-positive findings, 35 had SB, 33 had LHB tenosynovitis, and 22 had both SB and LHB sites involved. Thirteen patients presented SB only and 11 LHB tenosynovitis only.

Eight out of 24 patients with SB or LHB tenosynovitis (33.3%) and 7/22 (31.8%) with US positivity of both sites at

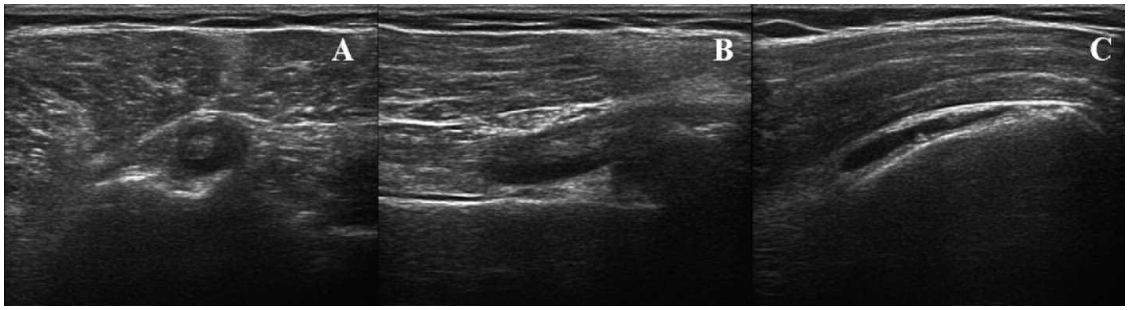

Figure 1. (A) Anterior transverse and (B) longitudinal LHB tendon ultrasound scans showing LHB tenosynovitis, and (C) SB scan showing SB effusion. LHB: long head biceps; SB: subdeltoid bursitis.

Table 1. Baseline clinical and laboratory characteristics of the entire PMR cohort divided in MSUS-positive and -negative patients according to MSUS shoulder examination at baseline. Values are mean ± SD (range) unless otherwise specified.

Characteristics	MSUS-positive Patients, n = 46	MSUS-negative Patients, n = 20	p
Age, yrs	72.1 ± 4.2 (55–89)	72.3 ± 8.2 (57–84)	0.50
Female, n (%)	36 (78.3)	15 (75.0)	0.77
Morning stiffness, n (%)	37 (80.4)	12 (60.0)	0.08
Peripheral arthritis n (%)	10 (21.7)	6 (30.0)	0.47
Fever, n (%)	9 (19.6)	4 (20.0)	0.97
ESR, mm/h	58.2 ± 28.1 (23–120)	60.2 ± 32.3 (24–120)	0.81
CRP, mg/l	41.5 ± 37.7 (1.5–119.0)	43.3 ± 43.6 (2.7–126)	0.53
Ferritin, ng/ml, mean ± SD	233.3 ± 113.6	230.0 ± 122.9	0.47

PMR: polymyalgia rheumatica; MSUS: musculoskeletal ultrasound; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table 2. Baseline clinical and laboratory characteristics of the 46 PMR patients with MSUS-positive findings at baseline ultrasound shoulder examination, divided according to MSUS pattern at the 12-month followup. Values are n (%) or mean ± SD.

Characteristics	MSUS-positive Patients, T12, n = 13	MSUS-negative Patients, T12, n = 33	p
Age, yrs	74.2 ± 4.7	70.2 ± 4.3	NS
Female	10 (76.9)	26 (78.8)	NS
Morning stiffness	13 (100)	24 (72.7)	0.03
Peripheral arthritis	2 (15.4)	8 (24.2)	NS
Fever	3 (23.1)	6 (18.2)	NS
ESR, mm/h	56.3 ± 25.5	59.0 ± 29.3	NS
CRP, mg/l	43 ± 40.7	41 ± 37.1	NS
Ferritin, ng/ml	163.7 ± 147.7	197.6 ± 135.5	NS

PMR: polymyalgia rheumatica; MSUS: musculoskeletal ultrasound; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NS: nonsignificant.

baseline remained US-positive at the 12-month followup (p = nonsignificant). All the 7 patients with both sites positive at baseline had only 1 site positive at 12 months. Regarding GC therapy, 2 out of the 20 baseline US-negative patients (10.0%) were receiving steroid > 5 mg/day at 12 months compared with 3/24 (12.5%) with only 1 US-positive site and 2/22 (9.1%) with both positivity (p = nonsignificant). Laboratory remission at 12 months was obtained by 9/20 (45.0%) US baseline-negative patients, 12/24 (50.0%) with only 1 US-positive site, and 11/22 (50.0%) with both sites (p = nonsignificant).

When we also consider the presence of mono or bilateral positive findings, the numbers are too small to be analyzed separately.

Moreover, among 26 patients in both clinical and laboratory remission at 6 months, 17 (65.3%) presented MSUS positivity at study entry. In the same group of 26 patients, 6 patients (19.2%) experienced a laboratory relapse

at 12 months, while 12 patients (46.2%) maintained laboratory remission (Table 3). No significant correlation was found between MSUS positivity pattern at the diagnosis and laboratory relapse at 12 months (p = 0.53).

With respect to the GC dosage according to MSUS baseline pattern, at the 6-month followup, 24/46 patients (52.1%) with MSUS-positive findings at the onset took prednisone ≤ 5 mg/day (mean dosage 3.7 ± 1.6 mg, range 0–5 mg) and 22 (47.8%) took > 5 mg/day (mean dosage 11.3 ± 3.6 mg, range 6.25–12.5 mg); among patients with baseline MSUS-negative pattern, 12 patients (60.0%) took prednisone ≤ 5 mg/day (mean dosage 3.4 ± 1.4 mg, range 0–5 mg) and 8 (40.0%) took > 5 mg/day (mean dosage 9.0 ± 1.9 mg, range 6.25–10 mg). Between the 2 groups of patients (MSUS-positive and MSUS-negative at baseline), no significant difference was found in the remission rate with low prednisone dose (52% vs 60%, p = nonsignificant).

Similarly, at the 12-month followup, in the group of patients with baseline MSUS-positive pattern, 43 patients (93.4%) took prednisone ≤ 5 mg/day (mean dosage 2.4 ± 2.1 mg, range 0–5 mg) and 3 (6.5%) took > 5 mg/day (mean dosage 12.5 ± 5.0 mg, range 10–20 mg) whereas among MSUS-negative patients, 16 patients (80.0%) took prednisone ≤ 5 mg/day (mean dosage 2.8 ± 1.9 mg, range 0–5 mg) and 4 (20.0%) took > 5 mg/day (mean dosage 8.7 ± 2.1 mg, range 6.25–10 mg). No significant difference was found in the remission rate with low prednisone dose [n = 43 (93.4%) vs 16 (80%), p = nonsignificant; Figure 2].

Further, the number of GC-free patients at the 12-month followup was comparable among patients with or without MSUS inflammatory findings at the baseline [14 (30.4%) in MSUS-positive vs 6 (30.0%) in MSUS-negative, p = 0.6], as well as the mean cumulative dosage of GC (2984.2 ± 1763.8 mg in MSUS-positive and 2550.0 ± 875.4 mg in MSUS-negative, p = 0.45).

DISCUSSION

PMR is a syndrome characterized by aching and prolonged morning stiffness in the neck and in the proximal portions of the extremities. Since there are no specific diagnostic tests or pathologic findings, PMR is defined by its clinical features. The most valuable criteria for differentiation are bilateral shoulder pain or stiffness, ESR > 40 mm/h, duration of morning stiffness exceeding 1 h, age 50 years or older at disease onset, rapid resolution of symptoms with low-dose GC, and exclusion of other diseases mimicking PMR[10,11,12].

Bilateral painful shoulder is a distinctive characteristic in patients with PMR and the typical proximal symptoms are among the hallmarks for the diagnosis of this disease. Shoulders and hips are covered by heavy muscles, and minimal effusions of slight synovitis are not palpable on physical examination, but can be documented by MSUS. Based on US findings, these conditions are reported in patients with PMR: LHB tenosynovitis, subacromial/subdeltoid bursitis, trochanteric bursitis, glenohumeral and hip joint effusions, and synovitis[5,13]. The presence of bursal inflammation and synovitis in PMR has been described by many authors and may be the cause of many of the findings in PMR[2,14]. Moreover, imaging evidence of bilateral subacromial/subdeltoid bursitis can support the diagnosis of PMR in the few patients with normal ESR[15]. In a case-control study of 57 patients with untreated PMR and 114 control individuals with bilateral shoulder aching and stiffness, MSUS detected bilateral subacromial/subdeltoid bursitis in nearly all patients with PMR compared to a small number of controls (96% vs 4%)[5]. MRI showed subacromial/subdeltoid bursitis, confirming MSUS findings in 100% of patients[5].

Few studies have investigated the involvement of shoulder MSUS for the evaluation of the response to treatment in PMR, showing that MSUS could have similar or better sensitivity than clinical and laboratory markers in monitoring disease activity[16,17]. However, whether baseline MSUS findings could predict the clinical or laboratory disease outcomes is not so clear. Several studies have examined the prognostic value of clinical variables such as age[18,19,20,21], sex[18–27,28–37], higher versus lower acute-phase reactants[18,19,20,24,27,34,36,38-46], morning stiffness[38], peripheral

Table 3. Comparison of baseline clinical, laboratory, and ultrasound features between patients reaching clinical remission and patients presenting a laboratory relapse at the 12-month followup, considering the 26 patients in clinical and laboratory remission at 6 months. Values are n (%) or mean ± SD.

Baseline Characteristics	Clinical Remission at 12 Months, n = 20	Laboratory Relapse at 12 Months, n = 6	p
Female	16 (80.0)	6 (100.0)	0.58
Age, yrs	76.4 ± 7.0	71.7 ± 4.6	0.06
ESR, mm/h	55.8 ± 28.7	61.2 ± 29.5	0.43
CRP, mg/l	38.3 ± 34.2	28.9 ± 59.3	0.25
Arthritis	4 (20.0)	2 (33.3)	0.89
Morning stiffness	15 (75.0)	5 (83.3)	0.89
MSUS positivity at baseline	12 (60.0)	5 (83.3)	0.57

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; MSUS: musculoskeletal ultrasound.

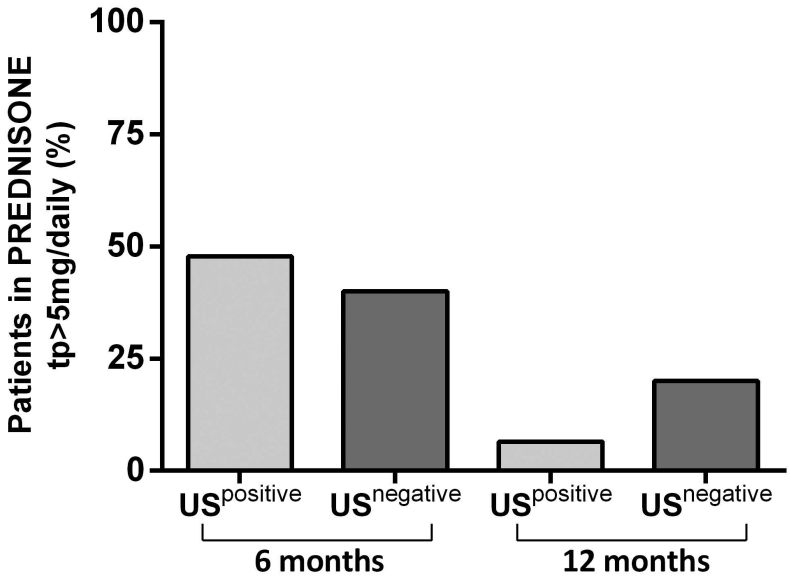

Figure 2. Patients with polymyalgia rheumatica who are still taking a prednisone dose > 5 mg/day at 6 and 12 months according to musculoskeletal ultrasonography positivity at baseline. US: ultrasound; tp: therapy.

arthritis[24,31,36,47,48,49,50], and comorbidities[48,51]. Only 1 longitudinal study by Macchioni, *et al* has analyzed the potential prognostic involvement of MSUS in clinical and laboratory relapse/recurrence[52], reporting that there was no association between the persistence of inflammation at MSUS and clinical and laboratory relapse of the disease.

In our present work, we sought to understand the value of basal shoulders MSUS in predicting remission and response to a standard therapy in a 12-month followup and discriminating between patients who took a lower dosage of prednisone for the maintenance of remission and patients who needed a higher prednisone dose to maintain the remission. In our cohort of patients with PMR, we found that MSUS-positive pattern at the time of diagnosis is not a predictive marker of clinical and laboratory remission at 6 months or after the 1-year followup. Moreover, MSUS SB and/or LHB tenosynovitis persistence at 6 months are/is not predictive of laboratory relapse at 12 months according with a previous study[52]. Further, a positive MSUS pattern at the time of diagnosis is not a predictive marker of a higher corticosteroid maintenance dose in the longterm GC therapy or of a higher mean cumulative dosage of GC in a 12-month followup. The presence of subacromial/subdeltoid bursitis or bicipital tenosynovitis appears, therefore, as bystander manifestations with no clear involvement in therapeutic decision or therapeutic outcomes.

However, the persistence of active laboratory and US disease despite symptoms disappearance at the 1-year followup in patients with PMR raises the issue of the possible existence of a subset of patients requiring a more aggressive therapy in the first months of treatment to avoid the cumulative side effects of persistent corticosteroid therapy. Further studies, in which patients would be randomized according to the MSUS presence of bursitis or tendonitis, could clarify whether a more aggressive therapy[53] in the first 6 months will lead to a steroid-free therapy at 12 months.

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