Polymyalgia rheumatica: observations of disease evolution without corticosteroid treatment

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Objectives: The diagnostic diversity of polymyalgia rheumatica (PMR) can easily be obscured by the widespread use of corticosteroids (CSs) early in the disease course. This study observed the course of PMR without CSs and determined whether alternative medication could be useful.

Methods: Seventy patients with new-onset PMR comprised phase 1. Eight were removed with specific diagnoses (four with giant cell arteritis [GCA]). The remaining 62 were treated with nonsteroidal anti-inflammatory drugs (NSAIDs) alone until enough time had elapsed to ascertain whether their PMR had evolved into another rheumatologic inflammatory condition. Hydroxychloroquine (HCQ) was then added to their regimen. Twenty-five additional patients with PMR comprised phase 2. Twenty-two were immediately treated with HCQ prior to the anticipated disease progression.

Results: In phase 1, 52/62 developed synovitis in multiple other joints 9 months from PMR onset; 48/52 received HCQ, and 42/48 (87.5%) achieved complete remission. In phase 2, during HCQ induction, 21 patients developed similar synovitis; after 6 months of HCQ use, 80% achieved remission. In 73/95 (77%), a definite diagnosis of rheumatoid arthritis (RA) could be made on average 8.5 months from PMR onset. Only 12/95 (13%) stayed true to form with their PMR and did not develop another specific diagnosis.

Conclusion: In this study, true PMR was infrequent in the absence of GCA. PMR in most patients evolved into seronegative RA, which was dramatically responsive to HCQ use. Treatment of acute PMR with HCQ was a rational alternative to CS use even if progressive additive synovitis had not yet occurred.

Keywords: polymyalgia rheumatica, rheumatoid arthritis, corticosteroids

Introduction
Polymyalgia rheumatica (PMR) is a syndrome with initial clinical features of acute inflammatory pain and stiffness in the shoulder girdle and pelvic girdle of older individuals, which have been well described.1–5 Equally well appreciated are the numerous disorders that are capable of presenting with similar symptoms.3–9 Even after excluding infectious, malignant, neurologic, and metabolic illnesses, considerable difficulty remains in differentiating among the various primary rheumatologic inflammatory conditions that can produce PMR phenomena.10 Allowing for the acceptance that PMR can display synovitis does little to clarify this.11,12

Recently, the standards of the criteria used for classification and treatment of PMR have been substantially improved by the efforts of a collaborative initiative.10,13 Nonetheless, the decades-old interventional recommendations remain unchanged, namely, the use of corticosteroids (CSs) followed by reassessment of residual disease activity...
Half of these (26/52) underwent synovial fluid analysis from hands, wrists, knees, and ankles. All 52 fulfilled the 1987 American College of Rheumatology criteria for rheumatoid arthritis (RA). The average 9 months from original disease onset. Typical features included metacarpophalangeal, proximal interphalangeal, and hip joints. Fifty-two of the 62 patients developed observable symptoms, including stiffness, an initial Westergren erythrocyte sedimentation rate (ESR) of 53 (span: 10–118), and an average hemoglobin (Hgb) of 11.3. Fourteen (20%) had weight loss (average: 14 pounds), 13 (19%) had headaches (none with visual changes), seven (10%) experienced night sweats, and three (4%) had fever. Eleven of the 13 with headaches underwent unilateral temporal artery biopsy, and classical giant cell arteritis (GCA) was present pathologically in four. In this study, the diagnosis of GCA required a positive temporal artery biopsy. These four patients with GCA, along with four other patients with specific diagnostic categories (one each with systemic lupus erythematosus [SLE], dermatomyositis, uterine carcinoma, and celiac disease), were removed from the original cohort. Of the remaining 62 patients in phase 1, all were initially treated with nonsteroidal anti-inflammatory drugs (NSAIDs) alone.

**Results**

Fifty-two of the 62 patients developed observable symmetrical synovitis in multiple small and large joints an average 9 months from original disease onset. Typical areas of involvement included the hands, wrists, knees, and ankles. All 52 fulfilled the 1987 American College of Rheumatology (ACR) criteria for rheumatoid arthritis (RA). Half of these (26/52) underwent synovial fluid analysis from a knee (average white blood cell [WBC] count =2,400; span: 100–32,000; no crystals present). Serologically, three of 52 had a positive sheep cell agglutination test (SCAT), and six of 52 had a weakly positive antinuclear antibody test (ANA; titer: 1:80–1:160). Only four of the 52 patients desired to remain on NSAIDs alone. The remaining 48 had no response to NSAIDs and, at this 9-month juncture, were treated with hydroxychloroquine (HCQ; average daily dose: 300 mg). After 6 months of HCQ use (ie, 15 months on average from original disease onset), 42/48 (87.5%) achieved complete resolution of all clinical phenomena and complete resolution (if present initially) of their fever, night sweats, and weight loss. Remission was defined as the complete absence of any musculoskeletal complaints, complete absence of any constitutional symptoms, normalization of ESR and Hgb, and a normal physical examination. Six of the 48 patients required more aggressive treatment with other disease-modifying antirheumatic drugs (DMARDs) and continue to remain free of CS use. Thus, in phase 1, 52/70 patients (74%) with PMR presentation developed RA. Their RA was rarely seropositive, marginally helped by NSAIDs alone, but dramatically responsive to HCQ.

Follow-up for the entire group of 62 patients in phase 1 averaged 4 years. Only ten of the 62 stayed true to form with their original PMR presentation (ie, there were no other add-on symptomatic joints). Five of these responded adequately to NSAIDs alone. The other five showed no response to 6 months of combined NSAID-and-HCQ treatment and eventually required conventional CS treatment. Four years from initial presentation, CS could be discontinued in only three of the five patients.

The four patients with biopsy-proven GCA were also initially treated with HCQ after their diagnosis was confirmed. After 4 months, there was no response in any of the four, and they were all subsequently treated with conventional high-dose CS. True PMR was infrequent in the absence of biopsy-proven GCA because only ten of 70 (14%) cases of PMR did not evolve into another specific diagnostic category. None of these ten patients had any positive serology. The following case history is illustrative.

A 67-year-old white male, previously in excellent health and on no medications, presented with 3 months of aching and stiffness in his shoulders, upper humeral areas, hips, buttocks, and anterior thighs, accompanied by 2 hours of morning stiffness, fatigue (without weakness), night sweats, fever to 102, decreased appetite, a five-pound weight loss, and intermittent headaches. There was no history of jaw claudication, visual disturbances, or tongue pain. ESR was...
81, Hgb was 11.1, and all other laboratory tests and serology results were normal or negative. A left-sided temporal artery biopsy was normal. Four months later, while on NSAIDs alone, he developed pain and swelling in his knees, wrists, and proximal interphalangeal joints of his hands. At that time, HCQ 300 mg daily was begun. At 7 weeks of treatment, there was resolution of fever, night sweats, and headaches, along with slight improvement in morning stiffness; moreover, lost weight was regained. At 10 weeks of treatment, all symptoms of the lower extremity had resolved, shoulder pains were reduced 50% with increased range of motion, morning stiffness was only for 20 minutes, and ESR was 45. At 16 weeks of treatment, morning stiffness lasted 10 minutes, ESR equaled 21, and Hgb was 12.8. At 20 weeks of treatment, the patient was in complete subjective and objective remission and ESR equaled 18. Sequential reductions in HCQ dosage ensued, and HCQ was discontinued after 2 years of usage. Ten years from the time of initial disease onset, he remained in remission.

**Phase 2**

**Patients and methods**

The results of phase 1 suggested that a PMR presentation could be treated with HCQ first and not CSs. Twenty-five additional patients who presented with the same abrupt symptomatology and criteria as noted in phase 1, spanning an average 3.5 months’ duration, were studied. There were eight males and 17 females, aged 50–85 years (mean: 67 years), with an average ESR =58 (span: 10–108) and average Hgb =11.1. Eight patients (32%) had night sweats, seven (28%) weight loss (average: 15 pounds), six (24%) fever, and three (12%) headaches (none with visual changes). Two patients with specific definitive diagnoses (one each with hepatitis C and metastatic carcinoma) were removed from this cohort. Prior to anticipated disease progression (ie, before there was any evidence of disease evolution into another rheumatologic diagnostic category), 22 of the remaining 23 were immediately treated at this 3.5-month stage with HCQ 300 mg average daily dose (one patient desired to be treated only with ibuprofen).

**Results**

On average, during the first 3.5 months of HCQ treatment (ie, an average 7 months from disease onset), 20/22 developed observable symmetrical synovitis in multiple small and large joints. Typical involvement was similar to that seen in phase 1, and all 20 fulfilled the 1987 ACR criteria for RA. Eight of the 20 underwent synovial fluid analysis from a knee (average WBC count: 9,150; span: 200–61,000; no crystals present). Serologically, one of 20 had a positive SCAT, and four of 20 had a weakly positive ANA. After 6 months of HCQ treatment, 16/20 achieved a complete remission of all clinical phenomena, normalization of their ESR and Hgb, and complete resolution (if present initially) of their fever, night sweats, and weight loss. Four of the 20 patients required more aggressive treatment with other DMARDs and continue to remain free of CS use.

Follow-up for the entire group of 23 patients in phase 2 averaged 4 years. Only two of the 23 patients in phase 2 stayed true to form with their original PMR presentation (ie, there were no other symptomatic add-on joints). Neither of these responded to 6 months of NSAIDs and HCQ, and both eventually required CS for adequate treatment. The one patient who desired ibuprofen treatment also eventually developed seronegative RA, but her clinical course was relatively indolent. Thus, the PMR presentation in 21/25 (84%) phase 2 patients evolved into RA, and 80% of those who were treated with HCQ experienced complete resolution of their inflammation. Pooled data from both phases of this study indicate the following:

- In 73/95 patients (77%), a definitive diagnosis of RA could be made on average 8.5 months from PMR disease onset (only four were seropositive by SCAT; anti-CCP was not yet available). Only five of 73 responded adequately to NSAIDs alone.
- Of the 68 RA patients treated with HCQ, 58/68 (85%) were dramatically responsive to this medication. For these 58, an average interval of 13.5 months elapsed from disease onset to remission, which is far shorter than the 24-month expectation for PMR to spontaneously abate. Half of these 58 responders were able to discontinue HCQ use after 2 years without relapse of any inflammatory symptoms; the other half required indefinite use to sustain the response.
- Only 12/95 (13%) stayed true to form, with their PMR presentation not evolving into another specific definitive diagnostic category, and they did not develop progressive additive synovitis. Five of these 12 patients responded to NSAIDs alone. The remaining seven of 12 patients had no response to combined NSAID-and-HCQ use and required conventional CS treatment (and only four could discontinue CS after 4 years).
- Only four of 95 (4%) had biopsy-proven GCA. All four had no response to NSAIDs and HCQ and required conventional high-dose CS. Thus, none of the GCA and true PMR patients who were treated with HCQ had any response to it.
Moreover, six of 95 (6%) had varied other diagnoses (VODs).

Fever, night sweats, and weight loss were not discriminating features and were equally distributed among the RA, PMR, and GCA patients. More specifically, 67% of subjects who exhibited fever developed RA; 67% of those who exhibited weight loss developed RA; and 87% of those who had night sweats developed RA. In addition, eight of 16 patients with headaches developed RA.

**Discussion**

The abrupt onset of proximal arthralgias and myalgias in the elderly, a syndrome known as PMR, is diagnostically heterogeneous. Over the past 35 years, numerous publications have attempted to solve the mystery of the primary diagnosis. However, the widespread use of CS early on in the course of PMR has not adequately allowed for the unfettered observation of disease evolution. This approach has spawned at least one controversial report, whereby the observed progression of some PMR patients into seronegative RA has been conveniently explained as being the “same entity.”

Even though it is now obvious that late-onset seronegative RA and PMR may initially present with overlapping clinical features, the results of this study do not support the “same entity” contention because only the RA patients demonstrated responsiveness to HCQ treatment. The other main findings in this study were as follows: 1) true PMR was infrequent in the absence of biopsy-proven GCA; 2) acute PMR onset in most patients evolved into seronegative RA, which in turn was dramatically responsive to HCQ use; and 3) treatment of acute PMR with HCQ was a rational alternative to CS use even if additive synovitis had not yet occurred. Support for this last statement resides in the entire original cohorts, wherein only 13/95 (14%) had an absolute need for CS treatment (seven true PMR, four GCA, one SLE, and one dermatomyositis). Stated another way, the routine use of CS in PMR was unnecessary in 82/95 (86%): 73 RA, five PMR, and four VOD patients. Thus, by utilizing standard diagnostic exclusions in new-onset PMR, coupled with the subsequent use of NSAIDs and HCQ (and later on, other DMARDs as needed), one could avoid the use of CS in the vast majority of patients in this study. If confirmed by other future prospective protocols, this methodology offers a clear and rational alternative to current published treatment recommendations in PMR.

The adverse functional impact of acute PMR in these 95 patients at initial presentation was, as could be expected, substantial debilitation. Nonetheless, after being provided with a thorough education of traditional concepts of the disease process and its customary treatment (along with a comprehensive discussion of the potential side effects of CS), all patients (excluding the six with VODs) opted for the initial avoidance of CS treatment (89/95). These 89 patients presented consecutively and were not considered for exclusion for any reason. Analyses of their subsequent clinical course, as well as decisions on treatment options, were arrived at by consensus of both the patients and this investigator without the involvement of an ethical committee. Bridge therapy, combining brief CS treatment in combination with HCQ, was rejected by all 89 patients even though it was stated that this regimen could considerably shorten the initial morbidity interval.

This study was clinically oriented and did not use the vast array of currently available investigative tools, some of which may be listed as follows: evaluation of genetic predisposition; assessment of human leukocyte antigen markers, T-cell subsets and surface molecules, serum and tissue cytokines, other circulating biomarkers, synovial antigens, cellular receptors, adhesion molecules, and microRNAs; studies of innate and adaptive immune responses, transcription processes, and intracellular signaling; determination of DNA methylation status, microbiome patterns, and antibody diversity; as well as radiographic studies (eg, ultrasonography). Nonetheless, this is the first published study to prospectively analyze the natural course of PMR in the absence of CS treatment. The results suggest that traditional concepts regarding PMR are in need of reassessment, including the “diagnostic trial” of CSs.

**Disclosure**

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**References**


