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...
6 months later. This methodology can create considerable anxiety in patients and providers when CSs cannot subsequently be tapered or discontinued due to relapses of inflammatory symptoms, which in turn may be superimposed on CS-induced side effects.

No prospective study has ever been published regarding the natural course of PMR in patients who have not received CSs. By withholding CS treatment in 95 consecutive patients with new-onset PMR, the spontaneous clinical course of this syndrome was observed in this study. The results obtained offer a rational alternative to the classification and treatment strategies reported by the collaborative initiative.

Phase 1
Patients and methods
In this part of the study, 70 patients (22 males and 48 females), aged 41–85 years (mean: 66 years), presented with the abrupt onset of symmetrical pain and stiffness in the shoulder girdle and pelvic girdle. PMR criteria were comparable to those in previous reports. All 70 were self-referred, and none requested consultation because of atypia or diagnostic uncertainty. Symptoms averaged 5 months (span: 1–18 months), accompanied by fatigue, an average 2 hours of morning 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 biopsy-proven GCA were also initially 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 remission 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 temporal headaches. There was no history of jaw claudication, visual disturbances, or tongue pain. ESR was
Of the 68 RA patients treated with HCQ, 58/68 (85%)—

In 73/95 patients (77%), a definitive diagnosis of RA

20 underwent synovial fluid analysis from a knee (average

and all 20 fulfilled the 1987 ACR criteria for RA. Eight of the

joints. Typical involvement was similar to that seen in phase 1,

On average, during the first 3.5 months of HCQ treatment

were immediately treated at this 3.5-month stage with HCQ

this cohort. Prior to anticipated disease progression (ie, before

were eight males and 17 females, aged 50–85 years (mean:

age Hgb 67 years), with an average ESR 581

Results

were 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 treat-

ment, 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, span-
ning 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 aver-
age 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).

Sero logically, 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 eventu-
ally 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 dis-
ease onset (only four were seropositive by SCAT; anti-
CCP was not yet available). Only five of 73 responded
deductively 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 inflamma-
tory 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
ture 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. The results suggest that traditional concepts regarding PMR are in need of reassessment, including the “diagnostic trial” of CSs.

Disclosure
The author reports no conflicts of interest in this work. There has been no financial support, grants, or any other benefits from any commercial source for the work reported in this manuscript.

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