Plasma fibrinogen is an accurate marker of disease activity in patients with polymyalgia rheumatica

Eoghan M. McCarthy¹, Paul A. MacMullan¹, Shibe Al-Mudhaffer¹, Anne Madigan¹, Suzanne Donnelly¹, Conor J. McCarthy¹, Eamon S. Molloy², Dermot Kenny³ and Geraldine M. McCarthy¹

Abstract

Objective. The overall aim of this study was to establish whether plasma fibrinogen was a superior biomarker of disease activity in active PMR than the standard biomarkers, ESR and CRP.

Methods. Sixty patients with PMR were divided into active (n = 25) or inactive (n = 35) disease groups based on symptoms, physician assessment and biomarkers ESR and CRP. Plasma fibrinogen was assayed. Groups underwent assessment at baseline and 6 weeks. Disease activity as per the PMR activity score (PMR-AS) was recorded at all visits. Receiver operator curves (ROCs), predictive values and likelihood ratios were calculated for all biomarkers.

Results. Disease activity measures improved significantly in the active group between weeks 1 and 6 (P < 0.001). There was no significant difference between the activity scores at week 6 in the active group and the inactive group. Mean fibrinogen decreased from 5.2 to 3.5 g/l (normal < 4 g/l) between weeks 1 and 6 in the active group. Mean ESR and CRP decreased from 59.6 to 24.3 mm/h (normal < 30 mm/h) and 45.9 to 12.66 mg/l (normal < 5 mg/l), respectively. Receiver operator curve analysis revealed fibrinogen to be more specific than either ESR or CRP for the detection of response to treatment in active PMR, with an overall sensitivity and specificity of 92% and 96%, respectively. Values above the upper limit of normal for fibrinogen, CRP and ESR were associated with likelihood ratios for active disease of 20.53, 2.9 and 2.8, respectively (P < 0.001).

Conclusion. Plasma fibrinogen is at least as useful as CRP and ESR for the diagnosis of active PMR and more specific for confirmation of response to treatment than either ESR or CRP.

Key words: polymyalgia rheumatica, ESR, CRP, fibrinogen, treatment, steroids.

Introduction

PMR, an inflammatory condition of unknown aetiology, is common among older individuals [1]. It occurs more commonly in northern latitudes, with an estimated lifetime occurrence in the USA of 2.4% for females and 1.7% for males [2, 3]. Corticosteroid (CS) therapy is the mainstay of treatment for PMR, with relatively low doses resulting in the prompt resolution of symptoms [4]. The course of PMR is heterogeneous, with a variable CS requirement [5]. Evidence suggests that there are two subsets of patients with PMR: those with a mild, self-limiting disease requiring 1–2 years of treatment, and others with a more chronic, relapsing disease course that may require steroid treatment for several years or indefinitely [6].

Relapses are frequent in both isolated PMR and PMR associated with GCA [7, 8]. In general, they occur when the dose of prednisone is < 7.5 mg/day or it has been discontinued. A quick rate of steroid taper is significantly associated with relapses in patients with isolated PMR [9]. In addition to steroid dose and rate of taper, genetic studies have identified a number of polymorphisms that are associated with the risk of relapse. A polymorphism in the IL-6 promoter gene discerned a subgroup of PMR patients with a higher risk of relapse/recurrence in one study [10]. Although the polymorphism of IL-6 at position...
—174 was not associated with an increased risk of relapse or recurrence in another population-based study [11]. Relapse of isolated PMR was associated with HLA-DRB1*0401 [9]. Moreover, in the same group of patients, although intercellular adhesion molecule 1 (ICAM-1) polymorphism alone was not associated with disease severity, the presence of both HLA-DRB1*0401 and ICAM-1 codon 241 GG homozygosity was significantly associated with increased risk of PMR relapse [12].

PMR is one of the most common indications for long-term steroid use in the community, accounting for 22% of prescriptions [13]. Long-term CS therapy in elderly patients, many of whom have co-morbid conditions, is commonly associated with adverse effects [14].Cumulative steroid dose predicts side-effect occurrence. Of all patients with PMR, 65% have at least one serious CS-related event [14]. Concomitant musculoskeletal complaints such as soft tissue injuries, tendinopathies, OA or FM are common in many patients with PMR, making accurate assessment of disease activity over time a significant challenge [15]. Thus there is a compelling rationale for a biomarker that accurately reflects disease activity and would enable appropriate use of glucocorticoids. The ESR and/or CRP are standard assays used in conjunction with clinical assessment to guide assessment of disease activity and response to steroid treatment [16].

Neither ESR nor CRP is a specific marker of disease activity in PMR, and both can be raised in a wide variety of inflammatory, infectious and neoplastic conditions. ESR in particular increases with age, smoking and renal failure [17]. No consensus exists on whether ESR or CRP is superior in clinical assessment of PMR [18, 19]. PMR patients may have a low ESR at diagnosis [20–22]. Indeed, normal ESR or CRP values have been observed in up to 27% and 14% of relapses, respectively [16, 23–25]. Thus the accuracy of these markers for assessment of disease activity is problematic. In particular, CRP has also been demonstrated to be increased in a significant proportion of patients who have no concomitant morbidity [26]. In patients with underlying inflammatory conditions, studies have demonstrated a discordance between ESR and CRP of 28%, making the accurate assessment of disease activity a diagnostic challenge [27]. Several studies have found a higher prevalence of cardiovascular disease in patients with PMR [28]. The cardiovascular risk may be related to persistent inflammation rather than glucocorticoid therapy [29]. Therefore careful tailoring of the glucocorticoid dosage to the patients needs is crucial to avoid the risk of treatment-related adverse effects and the disability associated with uncontrolled inflammation in an elderly population. Physicians may be reluctant to adjust steroid regimens in otherwise well patients who have a persistent or discordant inflammatory response as judged by the standard biomarkers ESR and CRP.

In the diagnosis and treatment of disease, specific biomarkers provide guidance and treatment. Unlike many other vasculitides, the key cytokine involved in PMR is readily identifiable. Active PMR is characterized by increased serum levels of IL-6 [30]. Several recent case reports have demonstrated that the use of a human mAb against the IL-6 receptor results in significant clinical and laboratory improvement [31]. Furthermore, IL-6 has been identified as a critical factor in the induction of acute-phase responses, placing it pathogenically upstream of other laboratory abnormalities in the inflammatory cascade in PMR and GCA [32]. Plasma fibrinogen has been shown to be exquisitely related to IL-6 production [33]. Standard assays of IL-6 are not widely available, whereas plasma fibrinogen can be routinely assayed in hospital laboratories and is easily available to treating clinicians. We have shown previously in a retrospective study that fibrinogen accurately identifies patients with quiescent PMR [34]. The purpose of this study was to evaluate the utility of fibrinogen as a biomarker of disease activity in patients with active PMR prospectively.

Methods

Study criteria

Ethical approval was received from the Mater Misericordiae University Hospital research ethics committee. All participants provided informed written consent. Patients were screened and prospectively recruited from the rheumatology clinic in the Mater Misericordiae University Hospital, Dublin. Patients with both newly diagnosed and stable/inactive PMR were included. A new diagnosis of PMR was made in patients with typical features of PMR using the Jones and Hazleman criteria [35]. These clinical features included primarily muscular shoulder and/or pelvic girdle pain in the absence of true muscle weakness, morning stiffness >30 min, symptom duration >2 months unless treated, with ESR >30 mm/h or CRP level >6 mg/l, and a prompt and dramatic response to systemic CS therapy. Patients with concurrent PMR/GCA (biopsy proven) were included. Stable or inactive PMR was defined as the absence of typical PMR symptoms on a stable dose of steroid or requiring no steroid treatment for 6 weeks before clinical review. Those with newly diagnosed PMR were commenced on 15 mg prednisolone (GCA starting dose was 60 mg) and maintained on this dose for 6 weeks until their follow-up visit. Patients were excluded if they had either a positive RF and/or anti-CCP, a concomitant diagnosis of another CTD, systemic infection, abnormal levels of serum creatine kinase, or thyroid-stimulating hormone or suspected underlying malignancy.

Clinical and laboratory analysis

Standardized assays for all biomarkers were recorded at all patient visits. In addition, the rheumatologist recorded the following clinical information: age and gender, morning stiffness (in minutes), ability to elevate the upper limbs (EUL on a scale from 0 to 3), physician’s global assessment on a 10-point visual analogue scale (VASph and pain severity on a 10-point VAS (VASp). This information was used to calculate the PMR activity score (PMR-AS) as indicated by Leeb and Bird [36] for all visits: PMR-AS = CRP (mg/dl) + VASph (0–10 scale) + VASph (0–10 scale) + (MST[min] × 0.1) + EUL (0–3 scale).
The four levels of the semi-quantitative EUL scale are as follows: 3 = no upper limb elevation, 2 = elevation (<90°) below the shoulder girdle, 1 = elevation (90°) up to the shoulder girdle and 0 = elevation (>90°) above the shoulder girdle. PMR-AS values <7 indicate low disease activity with a level <1.5 identifying disease remission, values between 7 and 17 indicate moderate disease activity and values greater >17 indicate high disease activity. Blood samples were collected concomitantly with clinical evaluation at the start of therapy and then at week 6. ESR was determined using the Westergren method. As ESR has been demonstrated to increase with age, particularly in females, and because most of our patients were women >50 years, the upper limit of normal considered for ESR in our study was 30 mm/h. CRP was measured by nephelometry with the upper limit for normal CRP being 5 mg/l. Plasma fibrinogen levels were evaluated at diagnosis and at the 6-week visit by a modified Clauss assay with normal values being <4 g/l [37].

Statistical analysis

Results for quantitative variables are reported as the mean (s.d.). Fisher’s exact test was used in the analysis of demographic and categorical data. Between-group disease activity data were assessed using the Wilcoxon signed-rank test. Receiver operator curves (ROCs; a plot of percentage of true-positive results vs percentage of false-positive results), predictive values and likelihood ratios were calculated for all biomarkers measured. Sensitivities and specificities were calculated at different cut-off values. Statistical significance was evaluated at the 0.05 level, two-tailed. Statistical tests were performed using the software programme GraphPad Prism 5.0 (GraphPad Software, La Jolla, CA, USA).

Results

Basic demographics

Sixty patients were prospectively recruited to the study from April 2009 to June 2010. Twenty-five patients had newly diagnosed, active PMR before initiation of steroid treatment, with one patient having concomitant, biopsy-proven GCA. Thirty-five patients had inactive PMR. The basic demographic characteristics of the patients are shown in Table 1. There was no significant difference between the groups with regards to gender and age. There were significant differences in steroid doses between the two groups (P < 0.001).

<table>
<thead>
<tr>
<th>Table 1 Demographic characteristics of patients with PMR</th>
</tr>
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<tbody>
<tr>
<td>Gender, n</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Age, s.d. (range), years</td>
</tr>
<tr>
<td>Median steroid dose, range, mg</td>
</tr>
</tbody>
</table>

DASs

Comparison between groups with active and inactive disease

The mean values for the PMR-AS, ESR, CRP and fibrinogen at the 60 first visits and the 120 overall visits are presented in Table 2. As expected, all parameters reflecting PMR activity were significantly higher in the group with active disease at week 1 compared with week 6 (P < 0.001). Disease activity scores were significantly higher at week 1 in the active group compared with the inactive group at week 1 or 6 (P < 0.001). There was no difference in the scores in the inactive group between weeks 1 and 6. There was no significant difference between the mean PMR-AS in the active group at week 6 and the inactive group at weeks 1 or 6 (Table 2). This indicated that in those patients with initial active disease, disease activity was comparable to that of patients with inactive disease by week 6 of treatment.

Biomarkers of disease activity

Plasma fibrinogen showed the best performance characteristic of the biomarkers assayed in identifying this change in disease activity. Table 3 shows the numbers and percentages of patients with elevated acute-phase reactants at the time of initial assessment and the 6-week follow-up visit. In the active group, fibrinogen, ESR and CRP at baseline were elevated in 92%, 80% and 100% of PMR patients, respectively. After 6 weeks of therapy, the percentages fell to 16, 36 and 60%, respectively. There was no evidence of intercurrent infection or large vessel vasculitis in those patients with a persistent acute-phase response apart from one patient with an initial diagnosis of GCA. Data for the inactive group at weeks 1 and 6 are also included in Table 3.

Diagnostic impact of clinical and laboratory parameters

ROC analysis revealed fibrinogen to be more specific than either ESR or CRP for the detection of response to treatment in patients with active PMR (Fig. 1). Values above the upper limit of normal for fibrinogen, CRP and ESR were associated with likelihood ratios for active disease of 20.53, 2.9 and 2.8, respectively (P < 0.001). Various cut-off values for the disease biomarkers, together with their sensitivities and specificities for disease activity, are reported in Table 4. ESR levels <20 and >40 mm/h, which are accepted levels for disease remission and relapse, respectively, as per ACR Delphi [38], were assessed, as was a CRP of 6 mg/l (the level specified in...
The Jones Hazlemann criteria for diagnosis). The upper limit of the lab normal for fibrinogen (4 g/l) was used, as a fibrinogen level >4 g/l is abnormal and indicative of active inflammation. As a composite end point with a sensitivity and specificity >90%, a fibrinogen level of 4 g/l was significantly superior for the detection of response to treatment in active PMR than both the specified levels of ESR and CRP (P < 0.001).

The role of biomarkers in detecting disease remission

For further analysis, all patients who entered the study were next divided into disease remission (group 1) or persistent disease activity (group 2), based on the PMR-AS. Once more an ESR value of 20 mm/h and CRP of 6 mg/l (lab normal <5 mg/l) were considered the upper limits for detection for remission. The upper limit of the lab normal for fibrinogen (4 g/l) was used. Sensitivity, specificity, positive predictive values (PPVs) and likelihood ratios were calculated for all biomarkers. Overall, 24 patients from 120 assessments were defined as being in remission as per their PMR-AS. All biomarkers were significantly higher in those with disease activity (group 2) compared with those in remission (group 1) (P < 0.0001). Of those in remission, 23 of 24 patients had a normal plasma fibrinogen, with 18 of 24 patients having a normal ESR and 16 of 24 patients a CRP <6 mg/l. The specificity, sensitivity, positive predictive values and likelihood ratios for the different biomarkers are shown in Table 5.

Overall, plasma fibrinogen was more specific than ESR and CRP for the detection of disease remission in this heterogeneous PMR population. Normal fibrinogen demonstrated a superior positive predictive value and likelihood ratio than ESR and CRP for identifying patients in disease remission. In particular, the ESR showed no significant ability to distinguish between disease remission and activity (P = 0.16).

Discussion

The results of the present investigation demonstrate the usefulness of fibrinogen as a biomarker of disease activity

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**TABLE 2** Difference between mean values of the total PMR-AS and biomarkers at the initial and follow-up visits

<table>
<thead>
<tr>
<th>Disease activity scores</th>
<th>Week 1</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>s.o. (range)</td>
</tr>
<tr>
<td>PMR-AS</td>
<td>26.2</td>
<td>10.1 (12.2-51.3)</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>59.6</td>
<td>30.5 (10-109)</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>45.9</td>
<td>29.1 (16.5-116)</td>
</tr>
<tr>
<td>Fibrinogen, g/l</td>
<td>5.2</td>
<td>1.06 (3.7-8.6)</td>
</tr>
</tbody>
</table>

Biomarkers at baseline and 6 weeks in active PMR group

Biomarkers at baseline and 6 weeks in inactive PMR group

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*P = 0.001 compared with baseline values.

**TABLE 3** Patients with elevated level of acute-phase proteins at baseline and 6-week follow-up

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Active group</th>
<th>Inactive group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 1</td>
<td>Week 6</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>23/25 (92)</td>
<td>4/25 (16)*</td>
</tr>
<tr>
<td>ESR</td>
<td>20/25 (80)</td>
<td>9/25 (36)*</td>
</tr>
<tr>
<td>CRP</td>
<td>25/25 (100)</td>
<td>15/25 (60)*</td>
</tr>
</tbody>
</table>

Values are the number of patients with elevated levels/total number of patients tested, with percentage within parentheses. *P=0.001 compared with baseline value.

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**FIG. 1** ROCs for the biomarkers ESR, CRP and fibrinogen.
in patients with PMR. Thus fibrinogen may help rheumatologists and general practitioners to better monitor PMR activity and manage glucocorticoid tapering, particularly as this test is readily accessible in clinical laboratories. To safely guide glucocorticoid taper and detect flares in patients with known PMR, physicians rely on their assessment of a patient’s symptoms and serial measurements of the non-specific inflammatory markers ESR and CRP. Careful tailoring of the glucocorticoid dose to each patient’s needs is crucial to strike the best compromise between the risk of side effects and the risks associated with uncontrolled inflammation. A prompt and safe reduction in steroid dose, while minimizing the occurrence of a disease flare, is the goal of treatment. As 55% of all patients will experience at least one lifetime recurrent flare of symptoms, accurate identification of disease activity is vital. This study has demonstrated that fibrinogen measurement can aid treating physicians more than ESR or CRP. In patients with previously highly active, new-onset PMR, measurement of plasma fibrinogen was more specific for the recognition of response to treatment than either ESR or CRP. In our study, values above the upper limit of lab normal had likelihood ratios for active disease of 20.53, 2.9 and 2.8, respectively, for fibrinogen, CRP and ESR indicating that fibrinogen is a more accurate predictor of disease activity and impending flare than either ESR or CRP. Furthermore, across 120 assessments involving patients at different stages of disease, it demonstrated a superior positive predictive and likelihood ratio for identifying patients in disease remission. The key to the role of fibrinogen as a marker of disease activity lies in its relationship to IL-6. IL-6 is a cytokine with a direct role in vascular inflammation.

Disease activity in both PMR and GCA has been shown to correlate with IL-6 levels [32]. Theoretically IL-6 provides a more accurate measure of tissue pathologic processes because it is one of the pro-inflammatory cytokines released in vascular lesions [39]. Fibrinogen has also been demonstrated to be expressed in arteries of patients with biopsy-proven GCA/PMR [40]. Thus fibrinogen may be thought of as a downstream reflection of the pathologic events that are driven by IL-6 production [39]. As IL-6 is impractical to assay in routine clinical practice, plasma fibrinogen may be its most sensitive surrogate marker in the clinical setting, so aiding physicians’ decisions with regard to disease activity and alteration of steroid dose.

The follow-up period for this pilot study of fibrinogen in PMR was short, and while validation of our results is required in a separate cohort of patients followed for a longer time period, in particular to examine the role of fibrinogen at the time of relapse, this study does support the relevance of plasma fibrinogen in assessing PMR activity in everyday practice. Our data suggest that measurement of fibrinogen as an adjunct to ESR and CRP in patients with suspected active PMR will enhance the accuracy of diagnosis and guide therapeutic decisions. Fibrinogen is inexpensive, readily assayed in all hospital laboratories and the cut-offs associated with disease activity are easily identifiable. Plasma fibrinogen is more specific for the confirmation of both active PMR and response to treatment than either ESR or CRP.

**Rheumatology key messages**

- Plasma fibrinogen is more specific for the confirmation of both active PMR and response to treatment than ESR or CRP.
- Measurement of plasma fibrinogen as an adjunct to ESR and CRP in patients with suspected active PMR will enhance the accuracy of diagnosis.

**Disclosure statement:** The authors have declared no conflicts of interest.

**References**

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