Sixth-month remission as a predictor for twelve-month remission in polymyalgia rheumatica

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Abstract

Objective

To investigate clinical and laboratory prognostic factors of remission after one year of follow-up in patients with polymyalgia rheumatica (PMR) treated with low-dose prednisone.

Methods

In this observational study, in a monocentric Italian Rheumatology Unit, we enrolled eighty-one consecutive PMR patients. Clinical and laboratory tests were performed every 3 months. Clinical remission was defined as the lack of symptoms, while laboratory remission was defined as erythrocyte sedimentation rate ≤40 mm/h and C-reactive protein (CRP) ≤0.5 mg/dl.

Results

Thirty-eight patients reached complete (clinical and laboratory) remission after 12 months of follow-up. A significant lower percentage of complete remission was seen in female gender compared to male (33.9 % vs. 78.2%, p=0.0001) at univariate analysis. No significant differences were found at baseline according to response to therapy during follow-up, while CRP values at the sixth month were significantly lower in patients who reached complete remission after one year (median: 0.4 mg/dl vs. 1 mg/dl, p=0.017). CRP<0.5 mg/dl at 6 months was independently associated with complete remission at 12 months in the multivariate analysis.

Conclusion

The sixth month of therapy is a target for the management of PMR because it can help to identify patients at greater risk of exacerbations, who may benefit from a tighter follow-up and more aggressive therapeutic strategy. Higher CRP values at 6 months appear to be associated with a higher risk of longer steroid therapy.

Key words

polymyalgia rheumatica, remission, C-reactive protein, erythrocyte sedimentation rate

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Introduction

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic condition characterised by aching and morning stiffness in the shoulders, hip girdle, and neck that typically occurs over the age of 50. A rapid resolution of symptoms with low-dose glucocorticoids is a feature of PMR although some patients may experience a disease flare-up during steroid tapering (1-2). Moreover, some patients are refractory to steroid therapy, so a conventional disease-modifying drug (cDMARD) could be added in order to reach remission (3-4).
An accurate differential diagnosis is important: different diseases, at the onset, can mimic polymyalgia rheumatica; among these the most important are the elderly rheumatoid arthritis, giant-cell arteritis and the paraneoplastic polymyalgia, so an accurate reappraisal of non-responsive disease is necessary (5-7).
Nevertheless, sometimes PMR does not respond adequately to therapy. Nowadays, no markers are available to predict disease remission at baseline or during the follow-up (8).
The aim of our study is to evaluate the predicting factors of remission over a twelve-month follow-up period in patients with PMR.

Methods

Study design

A monocentric observational prospective study was performed in our unit.

Patients

Eighty-six consecutive outpatients who fulfilled the ACR/EULAR 2012 provisional criteria for PMR (9) were enrolled in the study; All the patients had never been treated with glucocorticoid (GC) before the diagnosis and all reached a twelve-month follow-up. They all come to our hospital setting referred by GP and have their follow-up in our polymyalgia rheumatica medical clinic.
Exclusion criteria were:

- Age <18 years old;
- Concomitant inflammatory diseases (giant cell arteritis, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease);
- Malignancy;
- Patients previously treated with steroid in the last six months.

During the follow-up 3 patients developed rheumatoid arthritis, 2 patients had a paraneoplastic PMR, so 81 patients concluded the 12 months follow-up and were evaluated.
After the diagnosis was made, the patients started a 0.2 mg/kg/day prednisone dose during the first month, followed by decrease of 1–1.25 mg every 4 weeks after the first period, according to EULAR/ACR recommendations for the management of PMR (10). The prednisone dose was increased to the previous dosage if symptoms relapse or acute phase reactants elevate during the steroid tapering, after exclusion of concomitant infectious disease. In patients refractory to steroid therapy, with persistent girdle pain and persistent elevated acute phase reactants, methotrexate (10–15 mg/week) was added if not contraindicated and well tolerated during the follow-up.
All patients were negative for rheumatoid factor and anticitrullinated protein antibodies and had no other clinical evidence of musculoskeletal diseases. All patients who developed other rheumatological conditions (giant cell arteritis, rheumatoid arthritis, psoriatic arthritis) or cancer during the follow-up were excluded from the study.
All enrolled subjects provided signed informed consent for clinical information use, and the local ethics committee did not request study protocol approval because the patients were followed and treated according to the common daily good clinical practice for PMR.

Data collection

Clinical evaluation and laboratory tests were performed at baseline, after 30 days and then every 3 months. The aim of the study was to evaluate the number of patients reaching remission after twelve months. We define clinical remission as the lack of symptoms and laboratory remission as a normalisation of acute phase reactants. Complete remission was defined as lack of shoulder and hip girdle pain and as levels of erythrocyte sedimentation rate (ESR) ≤40 mm/h and C-reactive protein (CRP) ≤0.5 mg/dl. A steroid dose of

prednisone ≤5 mg/day was allowed for the complete remission.

Statistical analysis

Data were analysed using SPSS 15.0 (SPSS). Continuous variables are reported as mean ± SD, or by median and range of the 10th and 90th percentile, according to data distribution, 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 during the follow-up was performed with the Mann-Whitney U-test. The discriminative power of the Acute Phase Reactants at different time points between remission and persistent disease was calculated by using ROC and expressed by the AUC. The Youden index was applied to determine the optimum sensitivity and specificity and the corresponding cut-off values. Statistical significance was defined as a *p*-value <0.05.

Multivariate linear regression models were created to assess the predictor factors of complete remission. Variables with a p≤0.1 at univariate analysis were entered in backward stepwise regression models, requiring an adjusted *p*-value <0.1 to enter the next step of the analysis. For each variable in the final equation, odds ratio (OR), expressed as exp (B), where B is the coefficient of the variable in the logistic equation, 95% confidence interval (CI) and *p*-value were reported. The Hosmer-Lemeshow test was used to assess the goodness of fit of the model.

Results

Our population had an average age of 71.9±7.1 years and there were 57 women (70.3% of the population in the study). There was an acute phase reactant elevation at baseline, with median ESR values 44 mm/h (IQR: 16.4–95.8), and CRP 2.09 (IQR: 0.6–9.6) mg/dl (Table I).

Twenty-seven (33.0%) reached complete remission at the 6th month, while thirty-eight patients (46.9%) reached complete remission after twelve months of follow-up. Patients achieving complete remission after 6 months, were more prone to maintain it at 12 months, with respect to patients with active disease at 6 months (71% *vs*. 20.4%, *p*<0.001). Despite steroid therapy, 43 patients (53.1%) had persistent symptoms or acute phase reactant elevation at 12 months.

We evaluated all the differences between the two groups that can help us to predict remission after one year of follow-up.

We did not find any significant difference in patients' mean age and in acute phase reactant at disease onset, with comparable value of ESR [median 43 mm/h (IQR: 18–103) *vs*. median 53 mm/h (IQR: 15–83); *p*=ns] and CRP [median 2.1 mg/dl (IQR: 0.6–7) *vs*. median 2 (IQR: 0.4–10.9) (*p*=ns)] between patients that reached complete remission and patients with persistent activity after twelve months of follow-up. The average amount of time patients experienced symptoms prior to diagnosis was 6.5±5 months in patients that reached remission after one year of follow-up, and 6.7±4 months in patients with persistent active disease (*p*=ns).

The steroid initial dose was prednisone 13.6 mg/day (IQR 10–25) in patients that reached remission and prednisone 13 mg/day (IQR 10–25) in patients with persistent active disease, (*p*=ns). No significant difference in steroid therapy at the beginning and after 6 months of follow-up was noted between the two groups of patients, (*p*=ns).

No differences were found between the two groups in the incidence rate of dyslipidaemia, hypertension, obesity, diabetes or exposure to cigarette smoke (Table II).

While at the third month of follow-up the levels of ESR and CRP were com-

Table I. Demographic and clinical characteristics of 81 PMR patients involved in the study.

Age, yy, mean (SD)	**71.9 (7.1)**
Female, n (%)	57 (70.3)
Disease duration, months, mean (SD)	6.5 (4.2)
Smokers, n (%)	6 (7)
Hypercholesterolaemia, n (%)	22 (27.2)
Hypertension, n (%)	44 (54.3)
Diabetes, n (%)	14 (17.3)
ESR, mm/h (median, IQR)	44 (16.4-95.8)
CRP, mg/dl (median, IQR)	2.09 (0.6-9.6)

IQR: interquartile range; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table II. Demographic and clinical characteristics of 81 PMR patients involved in the study according with the remission at 12 months.

	38 pts in complete remission at T12	43 pts with persistent disease activity at T12	*p*-value
Age (yy), (mean±SD)	75.1 ± 6.7	69.7 ± 5.7	ns
Female, n (%)	20 (52.6)	37 (86.0)	<0.001
Disease duration (months), (mean±SD)	6.5 ± 5	6.7 ± 4	ns
ESR T0 (mm/h) (median, IQR)	43 (18-103)	53 (15-83)	ns
CRP T0 (mg/dL) (median, IQR)	2.1 (0.6-7)	2 (0.4-10.9)	ns
ESR T6 (mm/h) (median, IQR)	21 (7.7-45.4)	28 (13.8-58)	.063
CRP T6 (mg/dL) (median, IQR)	0.4 (0.3-2.6)	1 (0.4-3.7)	.017
ESR T12 (mm/h) (median, IQR)	15 (5-37.4)	25 (12-39)	Ns
CRP T12 (mg/dL) (median, IQR)	0.1 (0-0.3)	0.7 (0.2-1.9)	<0.001
Remission T6, n(%)	27	7	<0.001
Prednisone dosage (mg) T0 (median, IQR)	13,6 (10;25)	13 (10;25)	ns
Prednisone dosage (mg) T6 (median, IQR)	5 (2,5;12,25)	6,875 (5;12.5)	ns
Prednisone dosage (mg) T12 (median, IQR)	1,25 (0;5)	5 (2,25-10)	.018
Hypercholesterolaemia, n (%)	9	13	ns
Hypertension, n (%)	22	22	ns
Obesity, n (%)	9	9	ns
Diabetes, n (%)	6	8	ns
Smokers, n (%)	3	3	ns

T12: twelve-month follow-up; SD: standard deviation; IQR: interquartile range; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; T0: baseline; T6: six-month follow-up.

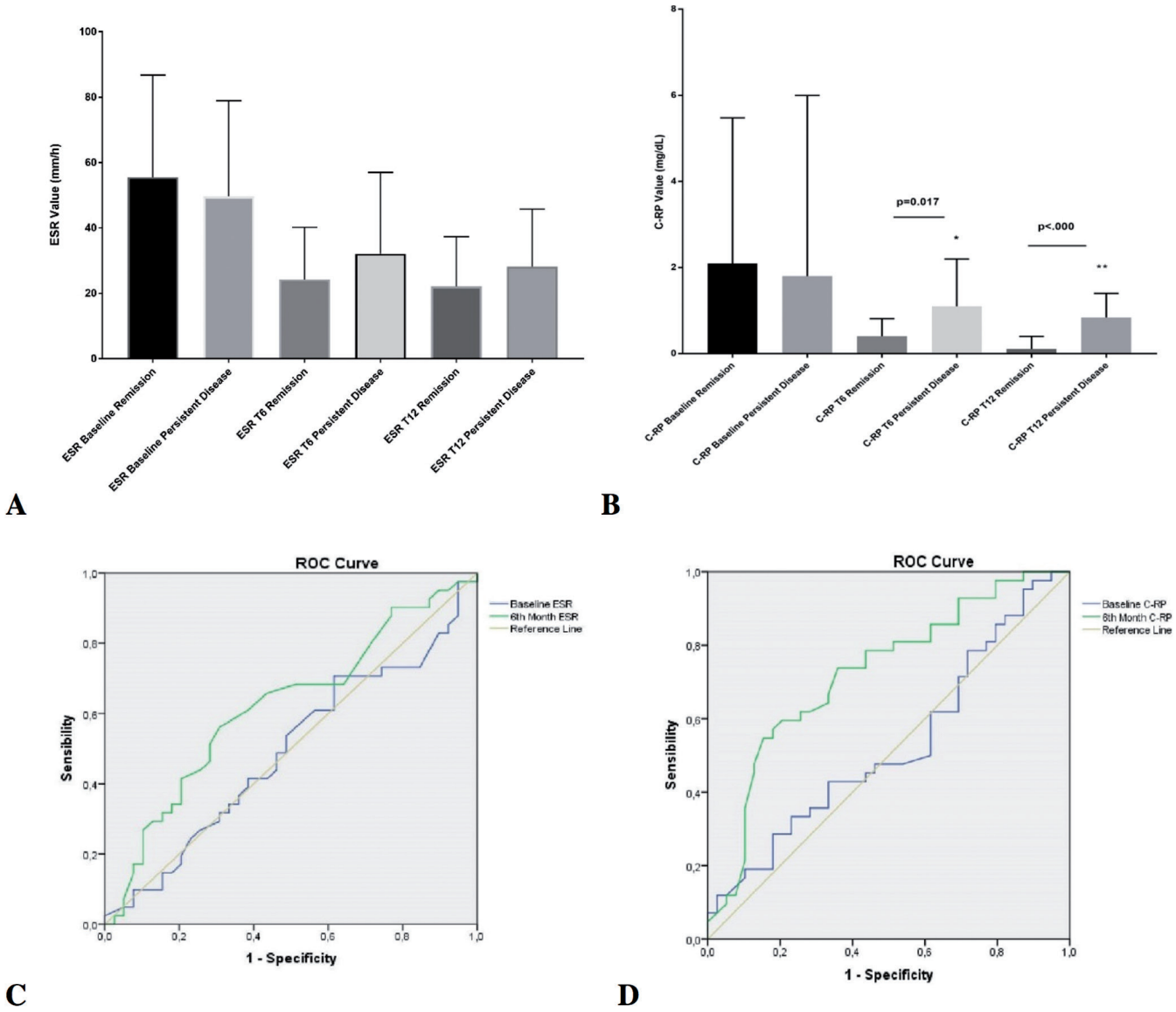

Fig. 1. A: ESR values at different time points in patients that reach remission after one year of follow-up and patients with persistent active disease.
B: CRP values at different time points in patients that reach remission after one year of follow-up and patients with persistent active disease.
C: ROC Curve for CRP values at baseline and after six months of follow-up.
D: ROC Curve for ESR values at baseline and after six months of follow-up.

parable between patients that reached and not reached a complete remission, at the sixth month of follow-up the CRP values of the patients reaching remission at one year were significantly lower compared to patients with persistent disease activity after one year. [median 0.4 mg/dl (IQR: 0.3–2.6) *vs*. 1 mg/dl (IQR: 0.4–3.7), p=0.017]. ESR showed only a trend towards statistical significance, without reaching it [median 21 mm/h (IQR 7.7–45.4) *vs*. 28 mm/g (IQR 13.8-58), p=0.063]. (Fig. 1 A-B)

A ROC curve was constructed to evaluate the predictivity of Acute phase reactant levels at different time poins on the likelihood of achieving remission after a year of follow-up. Only the CPR value at 6 months shows a significant value. The area under the ROC curve was 0.725 (95% CI: 0.61–0.84, p=0.000). We identified the best cut-off for CPR at 6 months of 0.5 mg/dL that yielded a sensitivity of 65.1% and a specificity of 73.8% in identifying patients in remission after one year. CRP values at baseline and ESR values at baseline and at the sixth month of follow-up showed no significance (p=ns). (Fig 1 C-D).

Moreover, a lower percentage of female patients reached complete remission at the end of the 12-month follow-up when compared with male patients (33.9% *vs*. 78.2%, p<0.01).

Thirty-two patients (39.5%) took methotrexate for at least 6 months during the follow-up (12 patients in remission group and 20 in persistent disease group) with no significant differences between the two groups (p=ns). Methotrexate was added in patients with persistent active disease or with disease relapse during the follow-up. If methotrexate was used during the follow-up for less than three months because of intolerance, the patient was considered as if he had never taken this drug. The most common causes of drug discontin-

uation were elevation of liver enzymes and gastorintestinal intolerance)

In the multivariate analysis, only CRP <0.5 mg/dl at 6 months was independently associated with complete remission at 12 month OR of 4.0 (95%CI:1.5–10.6).

Discussion

The aim of our study was to identify the patients that had major chance of remission after 12 months of follow-up between patients with PMR.

PMR is a complex disease as it is hard to manage and there are not prognostic factors that could improve prognosis in difficult cases.

First several comorbidities burden on elderly patient, including diabetes and hypertension, which can be a major limitation to steroid therapy at appropriate doses or for prolonged periods (11-13). In addition, patients often experience disease relapses at the reduction of steroid therapy, which is why we need markers for early identification of patients at higher risk of exacerbation (14).

In this regard, a study by Salvarani *et al*. (15-16) showed that higher ESR values at disease onset characterised patients at higher risk of exacerbations, elevated levels of CRP at the 12th and 24th months were associated with an increased risk of developing at least 1or 2 relapses or recurrences, whereas elevated levels at the 6th and 24th months were associated with an increased risk of developing at least 2 relapses/recurrences. In our study, we did not find the same association between the ESR values at the onset of the disease, however, the 6th CRP showed a better association with a persistent active disease after 12 months of follow-up, although our study has a shorter follow-up (12 months instead of 24).

In another study, Mackie *et al*. (17) identified factors that could help to predict the prognosis at the onset of the disease; in this cohort, female patients with higher ESR values at the onset were characterised by less chance of achieving remission and higher risk for late giant cell arteritis development. Even in our study, the female sex had worst outcome, but none of the disease onset characteristics seems to correlate with the one-year remission.

Moreover, we tried to find an association between disease duration and clinical outcome after a year of follow-up, in order to evaluate if the concept of window of opportunity (18) could be applied also to PMR; unfortunately, we did not find any correlation between disease duration and clinical outcome. All patients demonstrated similar time span between disease onset and diagnosis due to the acute clinical manifestations of PMR that led patients to seek medical attention early (19).

By contrast, at the sixth month after the beginning of therapy, the patients who met both clinical and laboratory response maintained that remission at the end of a one-year follow-up, as opposed to those who did not reach the double response; in particular CPR lower than 0.5 mg/dl is associated with higher chances of remission also in multivariate analysis.

Concerning the therapy, a study of the Systemic Vasculitis Study Group of the Italian Society for Rheumatology (20) demonstrated that patients taking methotrexate had shorter prednisone treatment and steroid sparing effect. However, in our cohort there were no significant differences between the two groups in use of this DMARD in relation to remission achievement.

Moreover, the problem of long-term steroid therapy is increasingly emerging: although in theory we try to stop steroid therapy as soon as possible, in practice several real life studies showed that it is often not possible and that even patients in remission with low doses steroid may not be able to suspend it (21).

Imaging is also not a valuable aid in predicting remission; in a study by Miceli (22), ultrasound evaluation at baseline and during follow-up did not help to evaluate the possibility of therapeutic response, with persistence of ultrasonographic alteration even in patients in remission.

In our cohort we did not identify any prognostic factor at baseline that could help predict the disease course; so it is still important to focus on the follow-up of these patients, personalising therapy and keeping in mind all the comorbidities.

The limits of the study are the fact that it is an observational study, the absence of randomisation in steroid therapy escalation and the short duration of follow-up (twelve months). However, given the small amount of data available in the literature, this could represent an initial step in trying to understand the long-term management of patients with PMR.

In conclusion, the six-month therapy could be an important target for the management of PMR, because it can help identify patients with more aggressive disease, who may benefit from a tighter follow-up and more aggressive therapeutic strategy.

Further efforts must be made to identify risk factors in such patients. Even though no significant feature at baseline was found to predict the outcome, our study managed to find a range of time to optimise the therapy in order to reach remission. In fact, the latter should be the main goal of these patients.

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