Long-term follow-up of polymyalgia rheumatica patients treated with methotrexate and steroids

M.A. Cimmino[1], C, Salvarani[2], P, Macchioni[2], R. Gerli[3], E. Bartoloni Bocci[3], C. Montecucco[4], R. Caporali[4] for the Systemic Vasculitis Study Group of the Italian Society for Rheumatology.

[1]Clinica Reumatologica, Dipartimento di Medicina Interna, Università di Genova; [2]Divisione di Reumatologia, Azienda Ospedaliera di Reggio Emilia; [3]Dipartimento di Medicina Interna e Sperimentale, Università di Perugia; [4]Clinica Reumatologica, IRCCS Policlinico S. Matteo, Università di Pavia, Italy.

Abstract

Objectives

A series of patients with polymyalgia rheumatica (PMR) who received the steroid-sparing combination therapy, prednisone and methotrexate (MTX), underwent a long-term follow-up study at five years to investigate possible reductions of steroid-related side effects. Additional end-points were the number of patients still in need of steroid treatment, the cumulative steroid dose, and the number of flare-ups of PMR.

Patients and methods

Fifty-seven PMR patients who were enrolled in a double-blind placebo-controlled randomised trial on the efficacy of MTX added to standard steroid treatment were reviewed after 5 years. Information was collected on the patients' previous health conditions or causes of death through a standardized questionnaire by direct visit, chart review, or interviews with relatives.

Results

After 6 years from initiation of therapy, MTX-treated patients had lower ESR (17.1±9.7 mm/h vs. 26.8±22.9 mm/h, p=0.08) and CRP (2.7±2.3 mg/L vs. 10.2±16.4 mg/L, p=0.04). 31% MTX-treated patients were still on steroids in comparison with 39.3% controls. The mean cumulative dosage of prednisone in MTX-treated patients was 2.6±3.8 g in comparison with 3.2±4.1 g for controls (p=0.6). PMR flare-ups were seen in 30.8% of MTX-treated patients and in 44.4% of controls (p=0.39). During the follow-up, 58 and 55 side effects were observed in MTX-treated patients and in controls, respectively.

Conclusions

MTX-treated patients showed slightly less residual inflammation than controls, with the same incidence of steroid-related side effects. PMR is not a benign condition, as often reported, since one third of patients need steroid treatment for more than 6 years.

Key words

Polymyalgia, rheumatica, methotrexate, corticosteroid, steroid-related side effect.

Marco A. Cimmino, Associate Professor of Rheumatology; Carlo Salvarani, Consultant Rheumatologist; Pierluigi Macchioni, Assistant Professor; Roberto Gerli, Professor of Rheumatology; Elena Bartoloni Bocci, Fellow in Rheumatology; Carlomaurizio Montecucco, Professor of Rheumatology; Roberto Caporali, Associate Professor of Rheumatology.

Please address correspondence to:
Dr. Marco A. Cimmino, Dipartimento di Medicina Interna e Specialità Mediche, Università di Genova, Viale Benedetto XV no.6, 16132 Genova, Italy.
E-mail: cimmino@unige.it

Received on March 14, 2007; accepted in revised form on July 17, 2007.

Competing interests: none declared.

Introduction

Polymyalgia rheumatica (PMR) is a syndrome characterized by proximal muscular pain and stiffness (1). Its prevalence is 0.37% (95% CI 0.29-0.44) in the Italian general population aged 18 years and older (2). PMR affects elderly people and is often associated with systemic manifestations and elevated concentrations of acute-phase reactants. Therapy relies on oral steroids, with prednisone at initial doses of 15 mg daily with progressive tapering usually suppressing inflammation dramatically (3). However, up to 60% of patients experience exacerbations during steroid tapering, and several studies suggest that only rarely steroid treatment can be discontinued before two years (3). Long-term treatment with steroids is often complicated by side effects, particularly osteoporosis, hypertension, hyperglycemia, and cataract (4). As a result, new therapeutic options are been investigated, especially for the benefit of patients at high risk for steroid-related toxicity. The options that have been considered include different ways of administration of steroids, such as intramuscular (5) or intraarticular metilprednisolone (6), or steroid boli (7), and several disease modifying treatments to be associated with steroids.

We have recently demonstrated that combination therapy with prednisone and methotrexate (MTX) is effective as steroid-sparing treatment for patients with newly diagnosed PMR (8). This schedule reduces the incidence of flare-ups and the amount of prednisone required to maintain remission. However, at short-term follow-up no substantial reduction was found in the incidence of steroid-related side effects in MTX-treated patients despite the lower cumulative dose of prednisone they received. We postulated that, besides the reduced observation period, other possible explanations for this lack of side effect improvement could be the narrow difference in the cumulative dose of prednisone between groups, and the low incidence of side effects in this relatively "healthy" group of PMR patients, a common problem of controlled trials. To test the short-term follow-up hypothesis, we reviewed the charts of the participating patients and visited them again at five years on average after completion of the original study. Besides assessing the incidence of long-term side effects of the combined treatement for PMR, additional end-points of this study included evaluation of the number of patients still in need of steroid treatment, the cumulative steroid dose administered, and the number of recurrences and relapses of PMR. The long-term follow-up permitted to evaluate the natural history of treated PMR and the alternative reasons for articular pain and persisting steroid administration.

Patients and methods

As previously described (8), 72 PMR patients were enrolled by five Italian rheumatology clinics in a multicentric randomised, double-blind, placebo-controlled trial on the efficacy of oral MTX (10 mg weekly) in addition to 25 mg/day prednisone, with the steroid being tapered progressively and discontinued within 24 weeks. Steroid treatement was increased in dosage or restored in case of flare-ups. End points included the proportion of patients who discontinued prednisone treatment, number of flare-ups, and cumulative prednisone dose after 76 weeks. Four of the original five rheumatologic tertiary referral centers participating in the controlled trial, which covered 61 of the original 72 (84.7%) patients, agreed to participate in the subsequent study.

Patients were contacted by phone and asked to visit the clinic. Their history was recorded and they were visited following a standardized protocol. Patients' GPs were asked for previous and ongoing diseases and clinical charts were reviewed, when deemed necessary. If the patient was dead or unavailable for clinical examination, a close relative was interviewed. Information was collected on the patient's previous health and cause of death through a standardized structured questionnaire. The information required included demographic data, duration and dosage of steroid treatment, number of flare-ups, a 100 mm visual analogue scale of pain and physician's evaluation, clinical findings, laboratory examinations, the

health assessment questionnaire (HAQ), and a list of possible adverse events. CRP and ESR were performed on all patients seen in the clinic and results of recent examinations were asked to those contacted by phone. We defined a flare-up of signs and symptoms of PMR (aching and stiffness at shoulder, hip girdle or both) accompanied by an increased ESR (>30 mm/h), CRP concentration (>5 mg/L), or both as a relapse if it was observed during steroid tapering and as a recurrence, if it was observed after steroid withdrawal. However due to the retrospective design of this study, patients could not always remember if flare-ups occurred with or without therapy. As a result, relapses and recurrences were considered together. The clinical referral forms of the original study were retrieved to allow correlation between long-term outcome data and clinical and laboratory information at enrolment. The ethics committees of the participating centres approved the protocol of the original study (8). The informed consent explained to and signed by the patients included the authorization to contact them even after formal completion of the study in order to assess their health conditions.

Statistics included comparison of means by Wilcoxon rank sum test and of percentages by Pearson's chi square test and by Fisher's exact test. Association between variables was tested by Spearman's rank correlation. A logistic regression procedure was used to evaluate variables influencing the main outcomes. A two-sided *p*-value less than 0.05 indicated statistical significance. We used Medcalc software (Belgium), version 8.1.1.0 for all analyses.

Results

Data were obtained from 57/61 (93.4%) of the patients after a mean interval of 58.8±11.1 months after completion of the original study. Forty-two (73.7%) agreed to visit the clinic and underwent clinical examination, five (8.8%) refused to come to the clinic and were interviewed by phone, and 10 (17.5%) were lost to follow-up. For this last cohort, a close relative (7 children, 2 spouses and 1 grandson) was interviewed. Twenty-nine patients (50.9%) belonged to the MTX-treated group and 28 (49.1%) to the placebo-treated group. The two groups were comparable for mean age, sex ratio, and duration of follow-up (Table I). Five patients (10.6%) had died because of congestive heart failure (2 patients), cerebrovascular accident, myocardial infarction, or unknown cause. Two of the 29 MTX-treated patients (6.9%) were dead in comparison with 3/29 (10.3%) for controls.

The differences in the clinical and laboratory features are reported in Table II. Potential side effects of steroid treatment were relatively rare. During follow-up, 58 side effects were observed

Table I. Demographic features of patients and controls.

	MTX-treated patients	Placebo-treated patients	*p*
Number	29	28	
Men/women	10/19	10/18	1
Mean age (years)	78.2 ± 8.7	78.3 ± 6.3	0.9
Duration of follow up (months)	59.1 ± 12.9	58.6 ± 9.3	0.9

Table II. Clinical and laboratory findings in patients treated with methotrexate or placebo in addition to prednisone.

	MTX-treated patients	Placebo-treated patients	*p*
Number on steroids	9/27 (33.3%)	11/28 (39.3%)	0.8
Total steroid dosage (mg)	2628 ± 3836	3188 ± 4068	0.6
Patients with side effects	7/25	5/25	0.7
Mean number of side effects	2 ± 1.8	2.3 ± 1.9	0.6
Patients with flare-ups	8/26 (30.8%)	12/27 (44.4%)	0.39
Patients with pain at the visit	14/26 (53.8%)	15/26 (57.7%)	1
ESR (mm/h)	17.1 ± 9.7	26.8 ± 22.9	0.08
CRP (mg/L)	2.7 ± 2.3	10.2 ± 16.4	0.04
Haemoglobin (g/L)	13.4 ± 1.4	13 ± 1.4	0.4
VAS pain (mm)	19.2 ± 22.7	14.6 ± 15.6	0.4
VAS general health (mm)	16.6 ± 21.8	12.4 ± 14.7	0.4
VAS physician's opinion (mm)	10 ± 12.8	9 ± 14.6	0.8
Patients with arthritis	3/25	3/25	1
Patients with GCA	0/25	3/25	0.2
Patients with girdle pain	5/25	5/25	1
Mean HAQ	0.4 ± 0.5	0.5 ± 0.7	0.5

Table III. Incidence of side effects in patients treated with MTX or placebo during the study period.

Adverse event	MTX-treated pts	Placebo-treated pts	*p*
Hypercorticism	2/25	2/25	1
Dyspepsia	5/25	4/25	1
Peptic ulcer	1/25	1/25	1
Easy bruising	0/25	2/25	0.5
Diabetes mellitus	3/25	5/25	0.7
Vertebral fracture	0/25	2/25	0.5
Other fractures	3/25	1/25	0.6
Hypertension	12/25	13/25	1
Insomnia	6/25	6/25	1
Tachycardia	3/25	1/25	0.6
Anxiety	3/25	3/25	1
Cataract	5/25	6/25	1
Glaucoma	0/25	3/25	0.2
Weight gain	2/25	2/25	1
Infection	3/25	4/25	1

in MTX-treated patients, and 55 in controls. No differences were observed in their incidence, with a mean of 1.9 side effects for MTX-treated patients and 2.6 for controls. The analysis of single steroid-related side effects gave similar results, as shown in Table III. Age, sex, MTX treatment, initial ESR and CRP, total dosage of prednisone, and being still on steroids at the time of the present visit were not associated with experiencing side effects nor with the number of side effects per patient by multiple regression.

Nine out of 29 (31%) MTX-treated patients were still on steroids five years after completion of the study in comparison with 11/28 (39.3%) controls (p=0.8). The mean cumulative dosage of prednisone assumed by MTX-treated patients in the interval between completion of the original study and the present evaluation was 2.6±3.8 g in comparison with 3.2±4.1 g for controls (p=0.6). The mean cumulative dosage of prednisone assumed by MTX-treated patients from initiation of therapy was 5.5±4.2 g in comparison with 6.4±4.4 g for controls (p=0.4). Using logistic regression, continuation of steroid treatment at the present visit was not predicted by sex, age, initial ESR, CRP and HAQ, or by MTX treatment. Flare-ups of PMR were seen in 8/26 (30.8%) MTX-treated patients in comparison with 12/27 (44.4%) controls (p=0.39). The presence of flare-ups was associated only with an increased cumulative steroid dosage (p=0.003). The mean number of flare-ups from initiation of therapy was 1.2±1.2 in patients treated with MTX in comparison with 1.9±1.4 in controls (p=0.05). Three patients developed temporal arteritis during follow-up: they all belonged to the placebo-treated group (p=0.2). Four patients (three belonging to the placebo group) had a cerebrovascular accident. Six patients, equally distributed in the two subgroups, developed peripheral arthritis during follow-up.

Of the MTX-treated patients, 14/26 (53.8%) reported articular or periarticular pain (*vs*. 15/26, 57.7%, for controls) upon re-examination or revision of clinical charts. Twenty-three of the 50 (46%) original patients for which complete data were available, were found affected by a musculoskeletal condition five years after completion of the study. The diagnosis in each patient is given in Figure 1. Conditions included osteoarthritis (9 patients), non-specified arthralgia, carpal tunnel syndrome and fibromyalgia. Three patients had multiple musculoskeletal diseases. Two patients out of 57 (3.5%) had an exacerbation of PMR at the time of the visit. The frequency of girdle pain and stiffness, as well as results of the HAQ were not different in the two groups. Pain intensity, general health and physician's opinion on the patient's conditions by visual analogue scale were not significantly different. ESR (17.1±9.7 mm/h *vs*. 26.8±22.9 mm/h, p=0.08) and CRP (2.7±2.3 mg/L *vs*. 10.2±16.4 mg/L, p=0.04) were lower in MTX-treated patients. Twenty patients (35.1%) were still on steroids after a mean interval of 6.5 years from the beginning of the study. The patients who were still in need of steroid treatment purely for their PMR were 15 (26.3%) (one patient was excluded from this count because the original diagnosis was changed to rheumatoid arthritis, another because he had developed temporal arteritis, and three other patients because they assumed steroids for reasons not related to PMR, such as degenerative pain of the foot, arthralgia, or for customary reason). Fourteen patients (24.6%) were assuming non-steroidal anti-inflammatory drugs and 3 (5.3%) pure analgesics. They were equally distributed in the two subgroups.

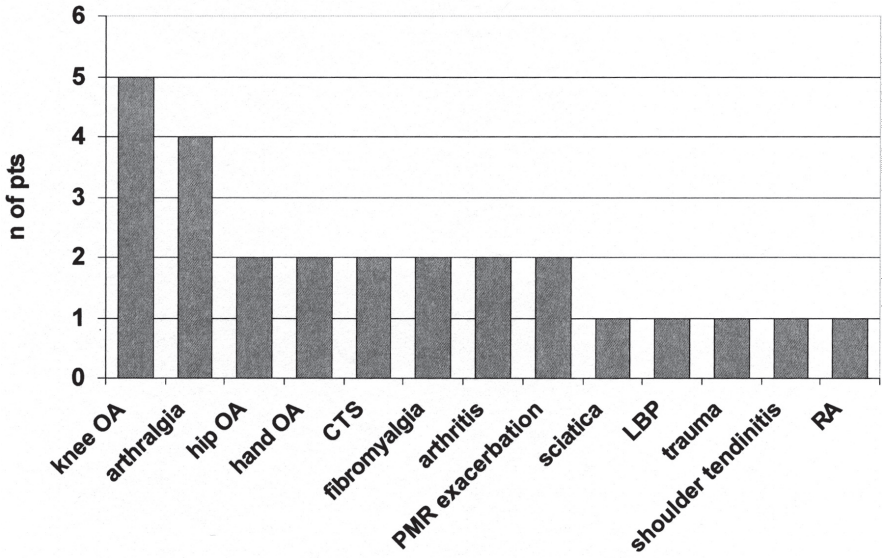

Fig. 1. Causes of musculoskeletal pain at the time of the last visit in a cohort of 50 patients with polymyalgia rheumatica followed over a mean period of five years (CTS: carpal tunnel syndrome; LBP: low back pain; OA: osteoarthritis; RA: rheumatoid arthritis).

Discussion

This is one of the few long-term studies on the outcome of patients treated for PMR in which concomitant rheumatic diseases contributing to symptoms are considered. Although mortality is not increased in PMR in comparison to ethnically matched populations (9, 10), relapses and recurrences are common (11). These events may lead to increased morbidity related to prolonged steroid therapy (12). Relapses have been often attributed to the speed of corticosteroid tapering (9, 10) or to a particular genetic background (13, 14). Different alternative therapies have been proposed to facilitate steroid discontinuation (12). Among them MTX has proved to be effective (8). MTX maintained its efficacy over time because MTX-treated patients had less flare-ups of PMR and lower indexes of inflammation. However, no difference in the incidence of steroid-related side effects was found between MTX-treated patients and controls. Both the number of patients with side-effects and the mean number of side-effects were similar. The reliability of data obtained retrospectively

from elderly patients (80% of cases) or their relatives (20%) could be questioned. In many instances, patients were accompanied to the clinic by relatives or care-givers who also helped to remember the clinical history. In addition, discussion with the patients' GPs and review of clinical charts helped to ascertain the major clinical events. The interviewers were unaware of the treatment choice. Underestimation of the incidence of side-effects and flare-ups, although possible, should not have affected differently the two subgroups of patients.

Serious complications of steroid treatment were rare in either groups. This could be due to the fact that, in general, patients enrolled in clinical trials are in average healthier than the remaining patients. This is true also for our study, where exclusion criteria included most conditions adversely affected by MTX or prednisone treatment, such as chronic hepatitis, liver cirrhosis, or serum aminotransferase levels of more than twice the normal value; chronic lung disease; poorly controlled diabetes mellitus (fasting plasma glucose >120 mg/dL); gastric or duodenal ulcer; osteoporotic fractures; peripheral neuropathy; epilepsy; renal failure; poorly controlled hypertension (blood pressure > 140/90 mm Hg); malabsorption; haemolytic or deficiency anaemia; platelet count $<150x10^9$/L; white blood cell count $<3.5x10^9$/L; neutrophil count $<1.5x10^9$/L; acute or chronic active infection; history of neoplasia; corticosteroid medication in the last month, previous therapy with MTX or with other immunosuppressive agents; or history of chronic alcohol abuse or drug addiction. Patients with many of these disorders, being at increased risk of steroid-related side effects, are those who could benefit more from the addition of a steroid-sparing agent, such as MTX. To assess whether MTX supplementation therapy could spare some side-effects of steroids, a prospective evaluation of unselected patients is probably more appropriate.

There were only few differences between patients treated with MTX and prednisone and those treated with prednisone alone (Table II). In particular, the number of patients still on steroids, the mean cumulative dosage of steroids used, the number of patients with flare-ups, the visual analogue scale evaluation of patient's pain and general health, the physician's opinion, the number of patients with arthritis and the mean HAQ value were not significantly different in the two groups. Giant cell arteritis occurred in 3/57 (5.3%) of patients during the follow-up. It is remarkable to observe that it did not occur in patients who were treated with MTX, although this difference was not statistically significant. By summing up the figures of the controlled trial with those of the present follow-up, the cumulative dosage of steroid was 0.9 g lower in MTX-treated patients, but this difference did not reach statistical significance. On the contrary, the number of flare-ups remained significantly lower in MTX-treated patients. However, due to the retrospective design of the present study, these results should be interpreted with caution.

Almost half of the patients enrolled in the original therapeutic trial still showed musculoskeletal complaints five years after completion. This fact is not surprising considering their mean age of nearly 80 years. As expected, most of them had OA, non-specific arthralgia, or fibromyalgia. Two of them had an undifferentiated form of arthritis which could be interpreted as peripheral manifestation of PMR, two were still affected by PMR and 1 had developed rheumatoid arthritis. In many cases, the differential diagnosis between PMR and associated rheumatic complaint was difficult. Accordingly, a few patients could have been erroneously treated with steroids by their GPs for a condition that was not steroid-sensitive. In addition, 31.6% of patients assumed non-steroidal anti-inflammatory-drugs or analgesics for their joint pain. The possibility of steroid-resistant PMR has been described, but its real occurrence is unknown. In our series of 57 patients enrolled in a clinical trial, 2 (3.5%) had persistent symptoms of PMR despite steroid treatment and 15 (26.3%) had to assume steroid to control symptoms of PMR approximately six years after treatment inception.

The fact that one third of patients with PMR has to assume steroids for over six years is in contrast with the common belief that PMR is a benign, self-limiting condition. The fate of PMR patients not treated with steroids is probably not very different, with 32% still complaining of symptoms after a mean period of 7.1 years (15). The percentage of patients needing long-lasting treatment ranged between 15.8% after a four-year follow-up in the study of Ayoub *et al*. (16) and 50.8% after a 5.5-year follow-up in the study of Delecouriere *et al*. (17). With shorter follow-ups (less than two years), the percentage of patients needing continuous treatment was higher with figures comprised between 50.7 % and 97% (18, 19). A remarkable exception was the result of Weyand *et al*. (20), who showed only 1/27 (3.7%) patients still in need of steroids after a mean follow-up of 1.8 years. There is no convincing explanation for this variability since several characteristics of the different cohorts, such as male to female ratio, or the incidence of giant cell arteritis during follow-up, were similar in the different cohorts of patients. This fact may reflect a higher propensity of European rheumatologists to prolong steroid treatment in order to prevent possible recurrences.

An additional result of this study was the observation that patients who were cured from their PMR still show elevation of laboratory indexes of inflammation. This could be due, at least in part, to the age-related increase of inflammation that has been shown also in the healthy elderly (21). MTX-treated patients had a tendency toward less inflammatory residual disease activity over five years, a fact that emphasizes the potential usefulness of this drug. In fact, they had slightly lower ESR and significantly lower CRP than patients treated with steroids alone, who assumed a higher cumulative dosage of steroids.

In conclusion, we have shown that the addition of MTX to conventional steroid treatment cannot decrease the incidence of steroid-related side effects in PMR patients, even in the long term. This could be surprising in view of the lower cumulative dosage of steroids that MTX-treated patients assumed, at least in the first 76 weeks of treatment (8). We feel that the controlled randomised trial is not the ideal setting to test the

hypothesis that a steroid-sparing treatment is also side-effect-sparing, because a subset of relatively healthy patients is selected. An open randomised study of consecutive unselected patients could represent the best design to answer this question.

References

1. SALVARANI C, CANTINI F, BOIARDI L, HUNDER GG: Polymyalgia rheumatica and giant-cell arteritis. *N Engl J Med* 2002; 347: 261-71.
2. SALAFFI F, DE ANGELIS R, GRASSI W: MArche Pain Prevalence Investigation Group (MAPPING) Study, Prevalence of musculoskeletal conditions in an Italian population sample: results of a regional community-based study. I. The MAPPING study. *Clin Exp Rheumatol* 2005; 23: 819-28.
3. GRAN JT: Current therapy of polymyalgia rheumatica. *Scand J Rheumatol* 1999; 28: 269-72.
4. GABRIEL SE, SUNKU J, SALVARANI C, O'FALLON WM, HUNDER GG: Adverse outcomes of antiinflammatory therapy among patients with polymyalgia rheumatica. *Arthritis Rheum* 1997; 40: 1873-8.
5. DASGUPTA B, DOLAN AL, PANAYI GS, FERNANDES L: An initialy double-blind controlled 96 week trial of depot methylprednisolone against oral prednisolone in the treatment of polylyalgia reumatica. *Br J Rheumatol* 1998; 37: 189-95.
6. SALVARANI C, CANTINI F, OLIVIERI I *et al.*: Corticosteroid injections in polymyalgia reumatica: a double blind, prospective, randomized, placebo controlled study. *J Rheumatol* 2000; 27: 1470-6.
7. CIMMINO MA, MACCHIONI P, BOIARDI L, CANTINI F, PULSATELLI L, SALVARANI C: Pulse steroid treatment of polymyalgia rheumatica. *Clin Exp Rheumatol* 2004; 22: 381-2.
8. CAPORALI R, CIMMINO MA, FERRACCIOLI G *et al.*: Methotrexate plus prednisone combined therapy in polymyalgia rheumatica. *Ann Int Med* 2004; 141: 493-500.
9. GONZALEZ-GAY MA, GARCIA-PORRUA C, VAZQUEZ-CARUNCHO M, DABABNEH A, HAJEER A, OLLIER WE: The spectrum of polymyalgia rheumatica in northwestern Spain: incidence and analysis of variables associated with relapse in a 10-year study. *J Rheumatol* 1999; 26: 1362-32.
10. KREMERS HM, REINALDA MS, CROWSON CS, ZINSMEISTER AR, HUNDER GG, GABRIEL SE: Relapse in a population based cohort of patients with polymyalgia rheumatica. *J Rheumatol* 2005; 32: 65-73.
11. GONZALEZ-GAY MA, GARCIA-PORRUA C, SALVARANI C, HUNDER GG: Diagnostic approach in a patient presenting with polymyalgia. *Clin Exp Rheumatol* 1999; 17: 276-8.
12. GONZALEZ-GAY MA, GARCIA-PORRUA C, MIRANDA FILLOY JA, MARTIN J: Giant cell arteritis and polymyalgia rheumatica: pathophysiology and management. *Drugs Aging* 2006; 23: 627-49.
13. AMOLI MM, SHELLEY E, MATTEY DL *et al.*: Intercellular adhesion molecole-1 gene polymorphisms in isolated polymyalgia rheumatica. *J Rheumatol* 2002; 29: 502-4.
14. SALVARANI C, CASALI B, BOIARDI I *et al.*: Intercellular adhesion molecole-1 gene polymorphisms in polymyalgia reumatica/giant cell arteritis: association with disease risk and severity. *J Rheumatol* 2000; 27: 1215-21.
15. BAGRATUNI L: Prognosis in the anarthritic rheumatoid syndrome. *Br Med J* 1963; 1: 513-8.
16. AYOUB WT, FRANKLIN CM, TORRETTI D: Polymyalgia rheumatica. Duration of therapy and long-term outcome. *Am J Med* 1985; 79: 309-15.
17. DELECOEUILLERIE G, JOLY P, COHEN DE LARA A, PAOLAGGI JB: Polymyalgia rheumatica and temporal arteritis: a retrospective analysis of prognostic features and different corticosteroid regimens (11 year survey of 210 patients). *Ann Rheum Dis* 1988; 47: 733-9.
18. JONES JG, HAZLEMAN BL: Prognosis and management of polymyalgia rheumatica. *Ann Rheum Dis* 1981; 40: 1-5.
19. NARVÁEZ J, NOLLA-SOLÉ JM, CLAVAGUERA MT, VALVERDE-GARCÍA J, ROIG-ESCOFET D: Longterm therapy in polymyalgia rheumatica: effect of coexistent temporal arteritis. *J Rheumatol* 1999; 26: 1945-52.
20. WEYAND CM, FULBRIGHT JW, EVANS JE, HUNDER GG, GORONZY JJ: Corticosteroid requirements in polymyalgia rheumatica. *Arch Int Med* 1999; 159: 577-84.
21. FERRUCCI L, CORSI A, LAURETANI F *et al.*: The origins of age-related proinflammatory state. *Blood* 2005; 105: 2294-9.