Prognostic factors and long term evolution in a cohort of 133 patients with giant cell arteritis

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Abstract

Objective

Survival in patients with giant cell arteritis (GCA) has generally been found to be similar to that of the general population The aim of our study was to assess outcome and survival of different subgroups of patients with GCA in relation to clinical, biological data or treatment modalities.

Methods

From 1977 and 1995, 176 patients were treated in the Department of Internal Medicine for GCA. The patient, family or local practitioner were contacted prior to the study (July-October 1995). Treatment modalities and follow-up were obtained for 133 patients. All patients (except 11) had 3 or more 1990 ACR classification criteria for GCA. The 11 patients with 2 criteria had a positive temporal biopsy and were included in the study.

Results

Relapse during corticosteroid tapering treatment was observed in 83 patients (62.4%) with a mean 1.57 relapses per patient. No correlation was found in age, sex, initial dose or type of steroid used (i.e. prednisone or prednisolone). Only a slight correlation in the initial erythrocyte sedimentation rate (ESR) was observed ($p < 0.01$, $r = 0.23$). In 56 patients free of treatment (mean treatment duration: 40 months), 27 (48%) developed a relapse of the disease 1 to 25 months later. No correlation was found in age, sex, initial dose of steroid, number of relapses during treatment, or initial ESR. Survival analysis was performed using the Kaplan-Meier and Mantel-Menszel methods for comparison of groups. At the time of the study, 41 patients had died (30.7%). A significant reduction of survival was found with the presence of permanent visual loss vs absence ($p = 0.04$), in patients who required more than 10 mg/d of glucocorticoid ($p < 0.001$) at 6 months treatment and in patients treated with prednisone (vs prednisolone) ($p < 0.01$). However, these factors were not independently associated with survival in the multivariate analysis.

Conclusion

Relapse was observed in 62.4% of the patients during corticosteroid tapering (correlated with initial ESR). A relapse of the disease was also observed in 48% of patients 1 to 25 months after the end of the treatment and was associated with prednisolone use. Long term survival was better in patients with no initial ocular manifestations, in patients who took less than 10 mg/day of corticosteroids at 6 months of the treatment and in patients treated with prednisolone.

Key words

Giant cell arteritis, prognosis, survival.

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Introduction

Giant cell arteritis (GCA) is a systemic granulomatous vasculitis that predominantly affects large- and medium-sized blood vessels and often involves the cranial branches of the aorta. This disease is a major preventable cause of blindness and cerebrovascular accidents (1). Cellular immunity has been implicated as a possible pathogenic factor, and elastin derived peptides may act as autoimmune targets for T cells (2). Studies of survival in GCA have generally been reported to be similar to the general population irrespective of the country of origin (3-6). Nevertheless, increased mortality seems to be associated with occurrence of visual loss, high maintenance dose of prednisone or pre-existence of ischemic heart disease (3, 7, 8). The aim of our study was to analyze survivorship among patients with GCA and to compare survival in different subgroups depending on clinical or biological data and treatment regimen.

Patients and methods

The hospital register of names and diagnoses of all patients attending our Internal Medicine Department between 1977 and 1995 were reviewed and patients, with an initial clinical diagnosis GCA, were recorded. The registered variables included demographic characteristics, presenting symptoms, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at the time of presentation and during the evolution, treatment modalities and characteristics. All patients were free of prednisone at the time of the first evaluation. Outcome was assessed by clinical and chart review and the patient, family, or family physician was interviewed by telephone using a structured questionnaire. The registered outcome variables included disease activity status, development of comorbid conditions, current therapy, and cause of death. In 176 patients included in the study during the 1977-1995 period, all data and long term follow-up were obtained for 133 patients (collection from July to October 1995). All patients had received at least 6 months treatment in order to be included in the study except when death occurred during this time. For the 43 other patients, long term evolution could not be evaluated because the patients had changed their address and phone number and their family physician had no information about their health status. All patients had a Doppler ultrasonography examination of external carotid arteries and subclavian arteries. Thirteen patients did not have a temporal artery biopsy because they had a typical clinical history with high ESR and good evolution with corticosteroid treatment.

A relapse was defined as an increase in ESR over 30 mm/h and/or CRP over 15 mg/L for more than 3 weeks, with or without symptoms, without intercurrent etiology (particularly without any kind of infection), that required increasing corticosteroid therapy with a favorable outcome (i.e. normal CRP 8 days after increasing corticosteroids). It is well recognized that CRP and acute phase reactants reveal disease activity in GCA and polymyalgia (9).

Treatment modalities were as follows: all patients were treated with an initial dose of corticosteroid of 0.7 to 1 mg/kg for 3 to 4 weeks. At the outcome corticosteroid doses were gradually tapered if the CRP level return to the normal range (mostly 10 % of the doses every 10 days till 10 mg and then 1 mg every month) if not the attack dose was maintained 3 more weeks. Patients received prednisone or prednisolone as prescribed by the hospital physician of our department. There was an equivalent dose between the two corticosteroids (i.e., 5 mg prednisone was equal to 5 mg prednisolone).

Differences between two continuous variables were compared with the Chi-test. Survival analysis was performed using the Kaplan-Meier and Mantel-Menszel methods for comparison of groups. Multivariate analysis was also performed by logistic regression.

Results

Clinical status

All patients (except 11) had 3 or more 1990 ACR classification criteria for GCA (10). Among the 11 patients with 2 criteria for GCA, all had a positive temporal artery biopsy. In the 120

patients in whom a temporal artery biopsy was performed, only 82 were positive (68.3%) but in the 38 negative biopsies 22 had corticosteroid treatment for more than 8 days before the biopsy was performed. Selected clinical features and demographic data are shown in Table I. In patients with positive temporal artery biopsy (n = 82/120), CRP was significantly higher: 95 mg/l ± 8 (SD) vs 61 mg/l ± 11 (SD), p = 0.017. Transient visual loss was observed in 2 patients (1.5 %), permanent visual loss was observed in 11 patients (8.2 %), 3 of which were bilateral.

Treatment modalities are shown in Table II. All patients received corticosteroid treatment. The choice of prednisone or prednisolone at the onset of therapy depended only on the routine practice of the hospital consulting physician (there is an equivalence in doses between 5 mg prednisone and 5 mg prednisolone). The initial daily dose varied mostly from 0.5 to 1 mg/kg for at least 3 to 4 weeks, more if CRP did not return to normal values during this period.

Relapse

We observed 83/133 relapses during corticosteroid treatment (62.5 %) with a mean of 1.57 relapses per patient. No correlation was found with age, number of ACR criteria, initial corticosteroid dose, duration of initial attack treatment or type of corticosteroid used. A slight correlation was found with initial ESR (p < 0.001, r = 0.29), but not with CRP. At the time of the study, 56 patients reached the end of the treatment and were free of corticosteroid. The total duration of the treatment varied from 7 months to 11.5 years (mean 40 months). However, 27 relapses after the end of the corticosteroid treatment of the disease occurred in 56 patients weaned from corticosteroids (48%) 1 to 25 months after the end of the treatment. No correlation was found between relapse of the disease and age, number of ACR criteria, initial corticosteroid dose, duration of initial attack treatment, number of relapses during the treatment, duration of the treatment and initial ESR. Nevertheless, relapse of the disease after the end of the corticosteroid treatment was more frequently observed in patients treated with prednisolone: 27/47 with prednisolone had one or more relapses, 0/9 with prednisone had one or more relapses (p < 0.001).

Survival

At the time of the study, 41 patients had died (30.7%); 16 deaths were related to cardiovascular disease (sudden death), 4 to cancer, 6 to infection, 4 physiological, 1 step fall, 1 acute renal failure, 1 suicide, 1 massive digestive hemorrhage. The cause of death in the 7 remaining patients was not documented. Out of the 41 deaths, 3 (9.75%) were related to the GCA (1 rupture of aortic aneurysm, 1 stroke, 1 mesenteric infarct) and 4 (9.75%) to the corticosteroid treatment (1 step fall due to steroid cataract, 1 suicide, 1 massive digestive hemorrhage, 1 depression). A significant reduction in survival was found in the men vs women subgroup (p = 0.02) in the presence of initial visual loss vs absence (p = 0.04) (Fig. 1). Survival was better in patients who required less than 10 mg/day of corticosteroids after 6 months (p < 0.001) (Fig. 2) and in patients treated with prednisolone vs prednisone (p = 0.006) (Fig. 3). Nevertheless, initial visual loss, with less than 10 mg/day of corticosteroids after 6 months or prednisone treatment were not considered independent risk factors for survival in the multivariate analysis No difference was observed in either the prednisolone or the prednisone group in terms of age, sex,initial ocular manifestations, mean duration of treatment, mean dose of corticosteroid at 12

Table I. Demographic and clinical characteristics of 133 patients.

Age at diagnosis: mean [range] (yrs)	72 [56 - 89]
Sex: n (%)	
Male	38 (28.57)
Female	95 (71.43)
Presentation*: n (%)	
Age at onset ≥ 50 years	133 (100)
New headache	106 (79.7)
Temporal artery abnormality	73 (54.8)
ESR ≥ 50 mm/h	112 (84.2)
Pos. temporal artery biopsy	82/120 (68.3)
PMR association: n (%)	56 (42.1)
Initial ESR: mean [range] (mm/h) (NV ≤ 25 mm/h after 50 years)	89 [16-140]
Initial CRP: mean [range] (mg/l) (NV ≤ 6 mg/L)	84 [2-294]
Follow-up mean [range] (months)	66.7 [0.5-215]

PMR: polymyalgia rheumatica; ESR: erythrocyte sedimentation rate; NV: normal value for the laboratory; CRP: C-reactive protein.
*1990 ACR classification criteria for GCA (10).

Table II. Corticosteroid treatment modalities in the 133 patients with GCA.

Initial daily dose (mg/kg): n (%)	
< 0.5	4 (3)
0.5	29 (22)
> 0.5 to < 1	39 (29)
≥ 1	61 (46)
Type of corticosteroid: n (%)	
Prednisone	47 (35.5)
Prednisolone	86 (64.5)
Duration of initial dose: weeks [range]	8.3 [1-26]
6 months dose: mean [range] (mg/d)	25 [7-70]
12 months dose: mean [range] (mg/d)	16 [0-60]
Relapse during corticosteroid tapering: n (%)	83 (62.4)
mean number / patient: n [range]	1.57 [0-8]
Patients who had stopped corticosteroid: n (%)	56 (42.1)
Mean duration of the treatment: months [range]	40 [7-138]
Mean follow-up after end of treatment: months [range]	52 [0.5-120]
Relapse after the end of corticosteroid treatment: n (%)	27 (48)

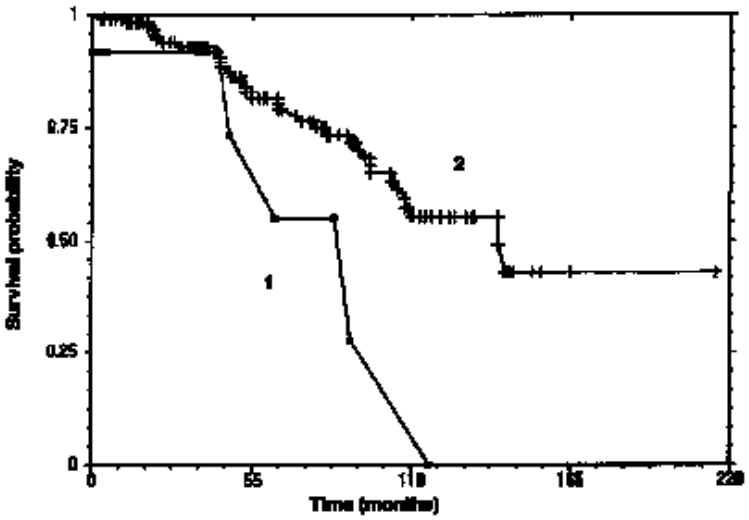

Fig. 1. Survival of patients with (1) or without (2) permanent visual loss (p = 0.04).

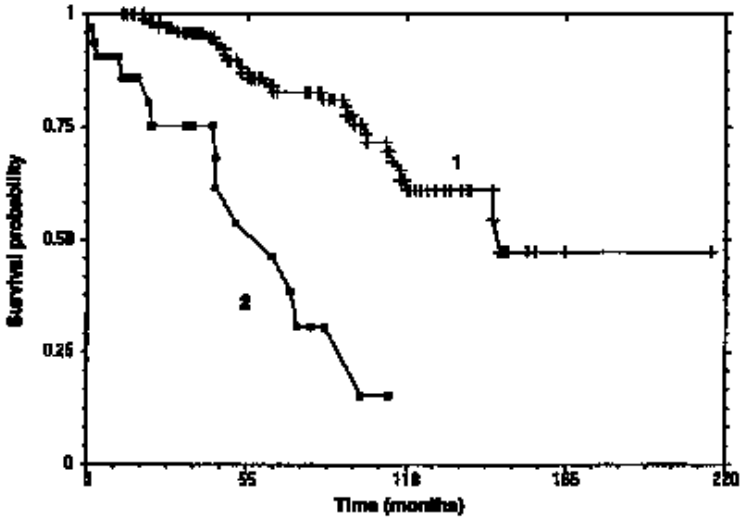

Fig. 2. Survival of patients who need treatment of less (1) or more (2) than 10 mg prednisone or prednisolone /day (p < 0.001) after 6 months.

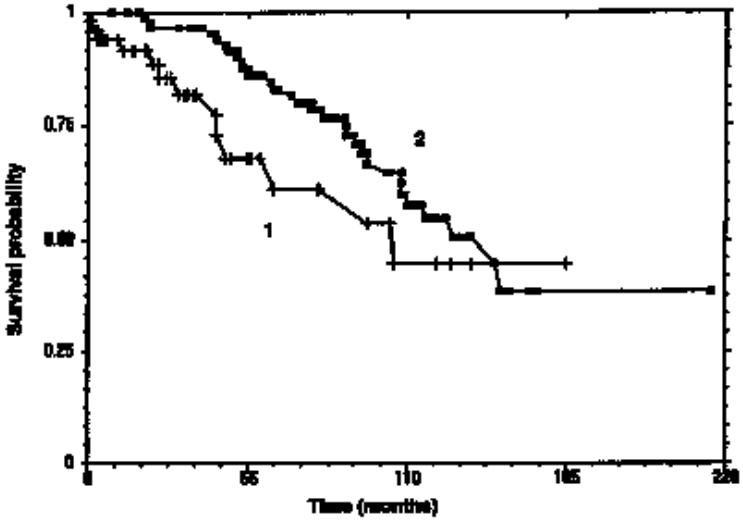

Fig. 3. Survival of patients with prednisone treatment (1) or prednisolone treatment (2) (p = 0.006).

months (15 vs 13 mg/day) but both groups had received more corticosteroids at 6 months (26 vs 19 mg/day, p = 0.005). We found no difference in survival when compared initial daily dose (more versus less than 0.7 mg/day), duration of attack dose (more versus less than 8 weeks), presence versus absence of headache, ESR more versus less than 50 mm/h, relapse versus recurrence of the disease.

Discussion

This was a long term evolution and survival study in patients with GCA with an evaluation of treatment modalities (doses of corticosteroid at 6 and 12 months of treatment, mean duration of the treatment and frequency of relapses). Although some studies have suggested decreased survival, other authors have found survival to be the same as in the general population. This was in accordance with the study of Matteson *et al*. (3) who evaluated 214 patients with GCA and demonstrated that life expectancy in GCA was the same as the general population. However, because of the limited amount of clinical data available in follow-up these authors were not able evaluate survival in their subgroup because of clinical, biological or treatment particularities. To our knowledge this is the first study of survivorship in GCA using these criteria. A total of 133 patients with GCA were evaluated with a mean follow-up of 66.7 months [range 0.5 - 215]. The demographic, clinical and biological features of our patients were similar to those reported in the literature (11). Permanent visual loss was observed in 8.2% in our study although Gonzalez-Gay *et al*. (1) observed 14.2% of their 227 patients with GCA. However, in contrast with these authors (1) we did not find evidence of a relationship between permanent visual loss and stroke, only one patient with permanent visual loss had a stroke 3 months before the treatment initiation.
Patients received treatment (prednisone or prednisolone) as prescribed by the hospital physician of our department according to standard practice (12). Most of the patients had an initial corticosteroid dose between 0.7 to 1 mg/kg.

Mean duration of treatment was 40 months. We observed 62.5% relapses during corticosteroid tapering and 48% relapses 1 to 25 months after the end of treatment. This is generally the rate of relapse during treatment reported in the literature (13), i.e. approximately 1 patient out of 2. Also in agreement with other authors, recurrence was more frequently observed following the end of treatment. It is significant to note that no relapse or recurrence was accompanied with severe symptoms, or visual signs and in most cases an increase of 5 mg/day of corticosteroid was sufficient to normalize the CRP. Bahlas *et al.* (12) observed 25% of relapses at the end of corticosteroid treatment in patients with GCA or PMR using prednisone alone. Nevertheless, in our study relapse after the end of the corticosteroid treatment occurred only in prednisolone treated patients whereas mean duration of treatment did not differ in the two groups (40 months in prednisolone group, 41 months in the prednisone group). The cause of death in the present study is comparable to that described by other authors (3, 8). Cardiovascular disease is the first cause of death (cardiac disease and stroke). These patients required a particularly careful follow-up in order to avoid cardiovascular risk. Therefore, in an attempt to eliminate cardiovascular risk factors, carotid Doppler echography, electrocardiography and thoracic X ray were carried out to evaluate cardiac volume. As previously described by Rao *et al.* (14), these authors suggest that calcium and vitamin D may help to prevent corticosteroid induced osteoporosis, and low dose aspirin could be useful in the prevention of cardiovascular complications. It is of interest to note that corticosteroid treatment induces death as much, or more than the disease itself (4/41 deaths directly related to steroids, 3/41 directly related to GCA). To our knowledge no other study has reported this finding. As regards cardiovascular deaths the authors suggest that some deaths could be linked to corticosteroid treatment (HTA, hyperlipemia and cardiac insufficiency).

Using Kaplan-Meier and the Mantel-Menzel methods for comparison of groups we confirmed, as did Gonzalez-Gay *et al*. (1), that patients with visual loss have a more severe disease and a power prognosis. In these patients we routinely administered 1 mg/kg corticosteroids. It is significant that all of the the deaths were related to cardiovascular causes (myocardial infarction or stroke) or to infection, and none to the disease itself.

Some authors have observed that the therapeutic regimen (doses of corticosteroids,use of IV pulse) did not prevent or influence the outcome (1, 15). It is possible that the negative outcome of patients with visual loss may be related to the high doses of corticosteroids used. Nevertheless, survival did not appear to depend on the initial dose (above or below 0.7 mg/kg) or on the duration of the initial dose (either more or less than 8 weeks) (p = NS in our population). However, survival was found to be directly dependent on the dose of corticosteroid at 6 months (less or more than 10 mg/day). This was also observed by Matteson *et al*. (3).

The intensity of the inflammatory syndrome and a positive temporal biopsy did not modify the survival rate. We were surprised to find a better survival rate in patients treated with prednisolone vs prednisone although the two groups did not differ in age, severity of the disease, mean duration of the treatment and dose of corticosteroid at 12 months. In contrast the mean dose at 6 months was higher in the prednisolone subgroup. Some authors suggest that prednisone bioavailability is better than prednisolone (16). In fact, patients with prednisone developed more diabetes mellitus (6/47 vs 7/86) and more fractures (7/47 vs 10/86). More cardiovascular deaths were observed in the prednisone group (6/12 vs 10/28) but the differences were not considered significant. Nevertheless, initial visual loss, the taking of more than 10 mg/day of corticosteroids after 6 months, and prednisone treatment were not independent risk factors for survival in the multivariate analysis.

In conclusion, the survival rate in GCA was better in patients with an absence of initial visual loss and in patients who received less than 10 mg/day of corticosteroids at 6 months of treatment. No difference in the survival rate was observed either when ESR was higher or lower than 50 mm/h or whether or not the temporal biopsy was positive. Patients treated with prednisolone also had a better survival rate that those treated with prednisone but this may have been the result of a lower bioavailability and less adverse events. This prompted us to reduce the corticosteroid dose regimen in the initial stages of treatment and in the course of GCA as proposed by other authors (15, 17). Cardiovascular events are also the first cause of death, and risk factors should be considered in the management of patients with GCA.

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