Relapses and Recurrences in Giant Cell Arteritis

A Population-Based Study of Patients With Biopsy-Proven Disease From Northwestern Spain

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Abstract: We conducted the present study to determine the incidence of disease flares (relapses and recurrences) in a series of patients with biopsy-proven giant cell arteritis (GCA). We assessed a series of 174 patients who were diagnosed with biopsy-proven GCA, uniformly treated, and followed at the rheumatology division of Hospital Xeral-Calde (Lugo, Spain), the single rheumatology division for a well-defined population. All of them were followed for at least 1 year after the disease diagnosis. Seventy-one (40.8%) experienced relapses or recurrences of the disease. Patients who had relapses or recurrences did not show clinical differences when compared with the remaining biopsy-proven GCA patients. However, the total duration of corticosteroid therapy was significantly longer in those patients who had relapses or recurrences of the disease. The median dose of prednisone and the median duration of corticosteroid treatment at the time of the first relapse were 5 mg/d and 16 months, respectively. Headache (52%) was the most common feature at the time of the first relapse. Polymyalgia rheumatica manifestations occurred in 30% of the patients at that time. However, none of them developed visual loss. Thirty-two patients experienced recurrences of the disease when prednisone dose had been discontinued. The median time from the disease diagnosis to the time of the recurrence was 23 months. The presence of anemia (hemoglobin <12 g/dL) at the time of disease diagnosis was the best predictor of relapses or recurrences of GCA (odds ratio, 2.17; 95% confidence interval, 1.02–4.62; p = 0.04). The results from the present study confirm that relapses and recurrences are frequent in homogenously treated patients with biopsy-proven GCA. A chronic inflammatory response manifested by anemia at the time of disease diagnosis may predict the development of disease flares.

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Abbreviations: CI = confidence interval, ESR = erythrocyte sedimentation rate, GCA = giant cell arteritis, IL = interleukin, IQR = interquartile range, OR = odds ratio, PMR = polymyalgia rheumatica, SD = standard deviation.

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INTRODUCTION

Giant cell arteritis (GCA), also called temporal arteritis, is the most common primary systemic vasculitis in the elderly in Western countries.[20,22] Although patients with GCA have an increased risk of morbidity as the result of visual ischemic complications,[3,14,26,30] stroke,[21,37] or aortic aneurysm or dissection,[15,34] population-based studies have disclosed no increased mortality in these patients compared with a matched population.[11,23,32] However, relapses of this vasculitis occur frequently,[33,36] leading to longer duration of corticosteroid therapy and, in the long run, to increased risk of side effects due to the prolonged use of these drugs.[35] For example, long-term corticosteroid use has been considered responsible for some events, such as bone fractures, diabetes mellitus, or infections, in patients with GCA.

We conducted the present study to determine the incidence and predictors of disease relapses and recurrences in a series of patients with biopsy-proven GCA. We assessed a series of uniformly treated patients who were diagnosed and followed at the single rheumatology division for a well-defined population.[19] We studied the differences between those patients who experienced disease relapses or recurrences and those who did not after at least 1 year's follow-up. We also assessed the best set of predictors for the development of relapses or recurrences in patients with GCA.

PATIENTS AND METHODS

We assessed patients in whom biopsy-proven GCA had been diagnosed at Hospital Xeral-Calde, Lugo, Spain, between 1992 and 2006. This hospital is the reference center for a mixed rural and urban population of almost a quarter million people. Information about the characteristics of this white population has been previously described.[2,7,12]

Temporal artery biopsy procedure in Lugo patients has also been reported elsewhere.[14,17] Biopsies were routinely performed for all patients with clinical manifestations of GCA as previously described.[8,16] Briefly, the side with predominant symptoms and signs was selected for biopsy. In those patients with clinically isolated polymyalgia rheumatica (PMR), without any vascular manifestation of GCA, biopsies were also considered if they had constitutional syndrome (asthenia, anorexia, and weight loss of at least 4 kg) and/or the erythrocyte sedimentation rate (ESR) by Westergren method was greater than 80 mm/1st h.[16,17] Biopsy-proven GCA was diagnosed when the temporal artery biopsy showed a compatible pathology report, describing the characteristic mononuclear cell infiltration of the arterial wall, with or without the presence of granulomas and/or multinucleated giant cells.[13]

Most patients diagnosed with GCA in the Lugo area are seen in the rheumatology division of Hospital Xeral-Calde. For

TABLE 1. Kaplan-Meier Estimates for the Probability of No Disease Flares (Relapses or Recurrences)

Years of Follow-Up*	Probability of No Flare	95% Confidence Interval
1	0.8899	0.8329–0.9283
2	0.7537	0.6806–0.8124
3	0.7202	0.6443–0.7826
4	0.7119	0.6351–0.7755
5	0.7119	0.6351–0.7755
10	0.6862	0.6030–0.7555
15	0.6862	0.6030–0.7555
20	0.6862	0.6030–0.7555

*Follow-up is considered from the onset of corticosteroid therapy to the first flare (failure) or the end of the study (censorship).

the purpose of the present study, we excluded those patients initially diagnosed with GCA and treated in a division other than the rheumatology division. We included only those patients who had full information from the time of disease diagnosis until at least 1 year's follow-up.

Following the inclusion and exclusion criteria discussed above, we reviewed data on 174 from a total of 207 patients with biopsy-proven GCA diagnosed during the period of study. Therefore, although this study is retrospective in design, patients included in the study were uniformly evaluated and treated.

Definitions of GCA manifestations in the Lugo population have been described previously.[10,20] Clinical manifestations were considered within the category of presenting features of the disease if they occurred within the time between the onset of GCA symptoms and 4 weeks after the start of corticosteroid therapy. The initial dose was 40–60 mg/prednisone per day for 3–4 weeks or intravenous methylprednisolone pulse therapy (1 g daily for 3 d) followed by 60 mg/prednisone per day for 3–4 weeks in some patients who had visual manifestations or other severe ischemic manifestations, such as limb claudication or strokes.[10] Subsequently, prednisone dose was reduced by 5 mg every 2–4 weeks. Then, reductions of prednisone dose below 20 mg/d were slower and individualized. In general, a rate of 2.5 mg every 2–3 months was attempted in most patients.

Typical flares (relapses or recurrences) occurred with an important rise of ESR (≥40 mm/1st h) and were associated with disease-related manifestations such as headache or other cranial manifestations, PMR, fever, or constitutional symptoms. However, sometimes disease flares were observed with only mild elevation of ESR. Therefore, we defined the presence of disease flares to be when clear and worsening symptoms occurred with an ESR ≥20 mm/1st h. An isolated rise of ESR without typical symptoms of this vasculitis was not considered a flare. In cases of isolated rise of ESR, the prednisone dose was maintained unchanged until the ESR went back to normal or a disease flare could be defined. Flares that occurred when patients were still taking prednisone or within the first month after prednisone discontinuation were defined as *relapses*. Flares that occurred at least 1 month after the prednisone dose had been discontinued were defined as *recurrences*. In the event of a relapse or recurrence, depending on the current dose of prednisone at the time of the relapse or recurrence, the prednisone dose was increased or reinitiated. In general, prednisone dose was increased to 10 mg/d above the previous effective dose if the patient was taking 15 mg/d or more, and to 5–10 mg/d above the previous effective dose if the patient was taking less than 15 mg/d. In all cases the presence of relapse or recurrence had to be confirmed following remission or improvement of symptoms.

We also analyzed clinical and laboratory data at the time of disease diagnosis for patients included in the study.

Statistical Analysis

Continuous data were described as mean and standard deviation (mean ± SD) or median and interquartile range (IQR), and categorical variables as percentage. The Fisher exact test was used to analyze categorical data. For continuous variables, a statistical comparison was performed with the Student t test.

To obtain a predictive model for disease flares, we performed a forward stepwise logistic regression with an entry p value of 0.20; final models were validated via bootstrap with 1000 replications. Results were shown as odds ratios (OR) and 95% confidence intervals (CI).

Probabilities of no flares (relapses or recurrences) of the disease were estimated via Kaplan-Meier method considering time at first flare as time of failure, and time at end of study as time at censorship (if the patient had not suffered any relapse or recurrence of the disease).

Statistical significance was defined as $p \leq 0.05$. Calculations were performed with the statistical package Stata 10/SE (Stata Corp., College Station, TX).

RESULTS

We studied 174 patients with biopsy-proven GCA diagnosed who fulfilled the inclusion criteria. All of them met the 1990 American College of Rheumatology criteria for the classification of GCA.[29] The median follow-up duration (IQR) of the patients from the onset of corticosteroid therapy until the end of follow-up, regardless of the presence of flares, was 104 (58–155) months.

Relapses or Recurrences of the Disease

The median follow-up duration (IQR) from the onset of corticosteroid therapy to the first disease flare or to the end of follow-up in this series was 43 (18–106) months. Seventy-one of the 174 (40.8%) patients with biopsy-proven GCA experienced relapses or recurrences of the disease. Fifty of them (28.7%) had at least 1 relapse. Nineteen of the 174 (10.9%) patients suffered a relapse within the first year after the disease diagnosis; 14 (8.1%) had at least 2 relapses of the disease. Moreover, 32 (18.4%) patients experienced a recurrence after the prednisone dose had been discontinued.

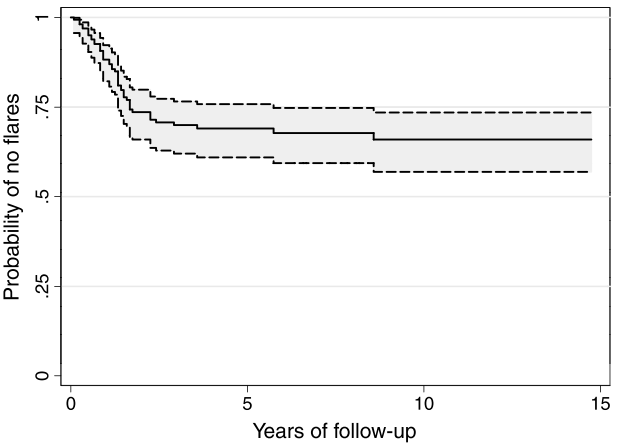

FIGURE 1. Kaplan-Meier estimate of the probability of no flare (relapse or recurrence) as a function of years from diagnosis. Gray area represents 95% confidence band.

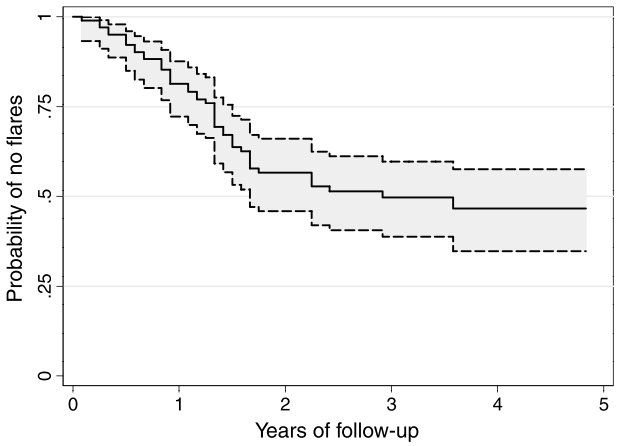

FIGURE 2. Figure represents the same data shown in Figure 1 (Kaplan-Meier estimate of the probability of no flare [relapse or recurrence] as a function of years from diagnosis), but truncating the follow-up at 5 years.

Most flares (relapses and/or recurrences) of the disease occurred within the first 5 years after the disease diagnosis. Table 1 shows Kaplan-Meier estimates for the probability of no flare. Figure 1 shows the probability of no flare as a function of years from diagnosis. Figure 2 represents the same data shown in Figure 1, but truncating the follow-up at 5 years.

Epidemiologic Differences Between GCA Patients Who Did or Did Not Experience Relapses or Recurrences

No differences in age at time of GCA diagnosis, sex, or in delay to disease diagnosis were observed between patients who experienced disease flares and those who did not (Table 2). Moreover, no statistically significant differences in the development of relapses or recurrences were observed according to the season of the year at time of GCA diagnosis; this was also the case for other epidemiologic data. Also, as shown in Table 2, antiaggregation use after disease diagnosis did not influence the rate of disease flares. Antiaggregation treatment was given to 22.5% of patients who experienced flares and to 28.2% of patients who did not experience flares (p = 0.48).

Clinical Differences at Time of Diagnosis Between GCA Patients Who Did or Did Not Experience Relapses or Recurrences

We studied clinical differences at the time of disease diagnosis between patients with GCA who experienced disease flares and those who did not. As shown in Table 3, patients who had relapses or recurrences did not show clinical differences in the clinical spectrum of the vasculitis when compared with the remaining biopsy-proven GCA patients who did not suffer disease flares.

Laboratory Differences at Time of Diagnosis Between GCA Patients Who Did or Did Not Experience Relapses or Recurrences

At the time of disease diagnosis, patients who experienced disease flares over the extended follow-up period had similar ESR values compared with those who did not experience flares (92.7 ± 26.5 mm/1st h vs. 87.3 ± 24.4 mm/1st h; p = 0.17). This was also the case for most of the laboratory parameters found at the time of disease diagnosis. Although patients who had flares during the follow-up more commonly had anemia at time of disease diagnosis (21 [29.6%] vs. 18 [17.5%]), the difference did not achieve statistical significance (p = 0.07) (Table 4).

Differences in Adverse Events Between GCA Patients Who Did or Did Not Experience Relapses or Recurrences

Patients with disease flares (relapses or recurrences) had a higher number of adverse events (mean ± SD, 0.66 ± 1.03) than those without flares (0.46 ± 0.70), but the difference was not statistically significant (p = 0.14). Typical complications that may be influenced by prolonged corticosteroid therapy, such as Cushing syndrome, diabetes mellitus, vertebral or hip fractures,

TABLE 2. Epidemiologic Differences at Time of Disease Diagnosis Between Patients With Biopsy-Proven GCA Who Experienced Relapses or Recurrences (With) or Not (Without) in Lugo (Northwestern Spain)

	With Relapse or Recurrence (n = 71/174; 40.8%)	Without Relapse or Recurrence (n = 103/174; 59.2%)	
Characteristic	**No. (%)**	**No. (%)**	**P**
Delay to diagnosis, wk*	9.9 ± 9.1	10.4 ± 10.2	0.77
Age, yr*	74.2 ± 6.2	75.5 ± 7.0	0.23
Women	38 (53.5)	56 (54.4)	1.00
Rural/urban	49/22	56/47	0.06
Season of GCA diagnosis			0.07
Spring	17 (23.9)	29 (28.2)	
Summer	24 (33.8)	28 (27.2)	
Autumn	5 (7.0)	20 (19.4)	
Winter	25 (35.2)	26 (25.2)	
Hypertension	41 (57.8)	51 (49.5)	0.35
Hypercholesterolemia	14 (19.7)	22 (21.4)	0.85
Diabetes mellitus	13 (18.3)	8 (7.7)	0.07
Antiaggregation or anticoagulation before GCA diagnosis	7 (9.9)	9 (8.7)	0.80
Antiaggregation after GCA diagnosis	16 (22.5)	29 (28.2)	0.48

*Mean ± SD.

TABLE 3. Clinical Differences at Time of Disease Diagnosis Between Patients Who Experienced Relapses or Recurrences (With) or Not (Without)

	With Relapse or Recurrence (n = 71/174; 40.8%)	Without Relapse or Recurrence (n = 103/174; 59.2%)	
Characteristic	**No. (%)**	**No. (%)**	**P**
Constitutional syndrome	49 (69.0)	69 (67.0)	0.87
Fever (temperature ≥38°C)	10 (14.1)	15 (14.6)	1.00
Headache	58 (81.7)	85 (82.5)	1.00
Abnormal temporal artery on physical examination	45 (63.4)	73 (70.9)	0.33
Scalp tenderness	28 (39.4)	30 (29.1)	0.19
Dysphagia	3 (4.2)	5 (4.9)	1.00
Jaw claudication	20 (28.2)	36 (35.0)	0.41
Polymyalgia rheumatica	27 (38.0)	30 (29.1)	0.25
Visual ischemic manifestations	18 (25.4)	20 (19.4)	0.36
Transient visual loss (including amaurosis fugax)	12 (16.9)	15 (14.6)	0.68
Irreversible visual loss	6 (8.5)	9 (8.7)	1.00
Stroke	4 (5.6)	2 (1.9)	0.23
Peripheral arteriopathy*	5 (7.0)	8 (7.8)	1.00

*Diagnosed before or at the time of GCA diagnosis.

were more commonly observed in the subgroup of patients with disease relapses or recurrences, but the difference did not reach statistical significance (p for each comparison > 0.20). In this regard, Cushing syndrome occurred in 7 (9.9%) patients with flares and in 7 (6.8%) patients without flares, diabetes mellitus was observed in 5 (7.0%) patients with flares and in 3 (2.9%) patients without flares, vertebral fractures in 8 (11.3%) patients with flares and in 9 (8.7%) patients without flares, and hip fractures were seen in 6 (8.5%) patients with flares and in 5 (4.9%) patients without flares.

Main Clinical and Laboratory Data at Time of Relapse

The main data at the time of the first relapse in 50 patients with biopsy-proven GCA are summarized in Table 5. The median dose of prednisone and the median duration of corticosteroid treatment at the time of the first relapse were 5 mg/d and 16 months, respectively. Headache (52%) was the most common feature at the time of relapse. PMR manifestations occurred in 15 of the 50 patients (30%) at time of relapse. However, none of them developed visual loss (Table 5).

As expected, the ESR at time of first relapse was >40 mm/1st h in most cases (mean ± SD, 60.6 ± 26.5 mm/1st h; median, 61 mm/1st h; IQR, 42–83 mm/1st h). Also, 11 (22%) and 9 (18%) of the 50 patients had anemia or thrombocytosis, respectively, at time of first relapse. Other laboratory data are shown in Table 5.

Fourteen patients had a second relapse. The median prednisone dose at time of second relapse was 5 mg/d (mean ± SD, 5.5 ± 3.8 mg/d; IQR, 2.5–7.5 mg/d). Seven of the 14 patients (50%)

TABLE 4. Laboratory Differences at Time of Disease Diagnosis Between Patients Who Experienced Relapses or Recurrences (With) or Not (Without)

	With Relapse or Recurrence (n = 71/174; 40.8%)	Without Relapse or Recurrence (n = 103/174; 59.2%)	
Characteristic	**No. (%)**	**No. (%)**	**P**
ESR, mm/1st h*	92.7 ± 26.5	87.3 ± 24.4	0.17
ESR level, mm/1st h			0.60
ESR <70	13 (18.3)	21 (20.4)	
ESR 70–100	32 (45.1)	52 (50.5)	
ESR >100	26 (36.6)	30 (29.1)	
Hemoglobin, g/dL*	11.7 ± 1.7	11.8 ± 1.6	0.82
Anemia (hemoglobin <12 g/dL)	21 (29.6)	18 (17.5)	0.07
Platelet count, 10^3 cells/mm^3*	392 ± 140	392 ± 148	0.99
Thrombocytosis (>400,000/mm^3)	24 (34.8)	33 (33.0)	0.87
WBC count/mm^3*	11007 ± 8357	10199 ± 9440	0.56
Leukocytosis (WBC > 11000/mm^3)	23 (32.4)	23 (22.3)	0.16
Albumin, g/dL	3.63 ± 0.64	3.54 ± 0.50	0.38
Raised alkaline phosphatase	6 (8.5)	17 (16.5)	0.17

*Mean ± SD.

TABLE 5. Main Data at Time of First Relapse* in 50 Patients With Biopsy-Proven GCA

Finding	Result
Time from diagnosis to first relapse, mo	
Mean ± SD	17.9 ± 16.7
Median	16
IQR	10–20
Prednisone dose (mg/d) at time of first relapse	
Mean ± SD	7.4 ± 6.4
Median	5
IQR	2.5–10
Main symptoms at time of first relapse	
Headache	26 (52%)
PMR	15 (30%)
Constitutional syndrome	14 (28%)
Amaurosis	0 (0%)
Main routine laboratory findings at time of first relapse	
ESR mm/1st hour	
Mean ± SD	60.6 ± 26.5
Median	61
IQR	42–83
Hemoglobin g/dL	
Mean ± SD	12.5 ± 1.5
Median	12.9
IQR	11.8–13.4
Anemia (hemoglobin <12 g/dL)	11 (22%)
WBC count (mean ± SD)/mm^3	
Mean ± SD	11,981 ± 11,980
Median	9500
IQR	7900–10,800
Leukocytosis (WBC >11,000/mm^3)	8 (16%)
Platelet count × 10^3 cells/mm^3	
Mean ± SD	323 ± 129
Median	298
IQR	259–387
Thrombocytosis (platelet count >400 × 10^3 cells/mm^3)	9 (18%)

Abbreviations: WBC = white blood cell count.

*Flares that occurred when patients were still taking prednisone or within the first month after prednisone discontinuation were defined as relapses.

had headache, and another 7 (50%) had PMR manifestations at time of second relapse. However, none of them experienced visual loss. As described for the first relapse, the ESR was elevated in most cases (median, 49 mm/1st h; mean ± SD, 51.6 ± 19.2 mm/1st h; IQR, 46–62 mm/1st h).

Main Clinical and Laboratory Data at Time of Recurrence

Thirty-two patients experienced a disease flare after the prednisone dose had been discontinued. The median time from disease diagnosis to the time of the recurrence was 23 months (IQR, 15.5–31 mo). Seventeen of the 32 patients (53.1%) had PMR as a feature of disease recurrence. However, as observed for relapses, amaurosis did not occur in any patient. Recurrences were also associated with a rise of ESR (median, 50 mm/1st h). Other clinical or laboratory features are summarized in Table 6.

Differences Between Patients With Long-Term Follow-Up With or Without Relapses or Recurrences

To provide accurate estimates of the frequency of relapses and recurrences, we studied a series of patients selected on the basis of a lengthy period of follow-up. We defined follow-up regardless of whether or not they had been able to completely withdraw corticosteroids. We assessed the patients who had completed at least 3 years of follow-up (regardless of whether or not they had been able to completely discontinue corticosteroids).

As shown in Table 7, 165 patients with biopsy-proven GCA were followed for at least 3 years after disease diagnosis: 67 (41%) had relapses or recurrences, and 98 (59%) did not. As expected, the total duration of corticosteroid treatment was longer in the group of patients who had disease flares (44.1 ± 30.5 mo) than in those without flares (28.1 ± 20.6 mo) ($p < 0.001$). Also, as shown in Table 7, the cumulative prednisone at the end of follow-up was significantly greater in the patients who experienced disease flares ($p < 0.001$).

TABLE 6. Main Data at Time of Recurrence* in 32 Patients With Biopsy-Proven GCA

Finding	Result
Time from diagnosis to recurrence, mo	
Mean ± SD	30.1 ± 26.9
Median	23
IQR	15.5–31
Main symptoms at time of recurrence	
PMR	17 (53.1%)
Headache	12 (37.5%)
Constitutional syndrome	8 (25%)
Amaurosis	0 (0%)
Main routine laboratory findings at time of recurrence	
ESR, mm/1st h	
Mean ± SD	59.0 ± 36.7
Median	50
IQR	30–80
Hemoglobin, g/dL	
Mean ± SD	12.3 ± 1.9
Median	12.3
IQR	11.4–13.5
Anemia (hemoglobin <12 g/dL)	9 (28.1%)
WBC count (mean ± SD)/mm^3	
Mean ± SD	8733 ± 2805
Median	7900
IQR	7100–9700
Leukocytosis (WBC >11,000/mm^3)	4 (12.5%)
Platelet count × 10^3 cells/mm^3	
Mean ± SD	294 ± 104
Median	272
IQR	219–350
Thrombocytosis (platelet count >400 × 10^3 cells/mm^3)	3 (9.4%)

*Flares that occurred at least 1 month after the prednisone dose had been discontinued were defined as recurrences.

TABLE 7. Differences Between Patients With Long-Term Follow-Up (At Least 3 Years) With or Without Relapses or Recurrences

Feature	With Relapse or Recurrence (n = 67/165; 41%)	Without Relapse or Recurrence (n = 98/165; 59%)	P
Total duration of corticosteroid treatment, mo	44.1 ± 30.5	28.1 ± 20.6	<0.001
Initial dose of prednisone, mg/d			
Mean ± SD	45.9 ± 10.3	45.2 ± 11.5	0.67
Median	45	45	
IQR	40–60	40–60	
Cumulative prednisone dose at 1 yr after diagnosis, mg			
Mean ± SD	7407 ± 4318	7227 ± 7130	0.85
Median	6500	6045	
IQR	5100–8063	5250–7594	
Cumulative prednisone dose at end of follow-up, mg			
Mean ± SD	12,482 ± 4805	9194 ± 5088	<0.001
Median	12,300	8042	
IQR	9050–16,500	5700–10,875	

Predictors of Relapse or Recurrence in Patients With Biopsy-Proven GCA

The presence of anemia (hemoglobin <12 g/dL) at time of disease diagnosis was the best predictor of relapses or recurrences over the extended follow-up (OR, 2.17; 95% CI, 1.02–4.62; p = 0.04) (Table 8). Also, an increased risk of disease flares was observed in patients presenting with leukocytosis (>11,000/mm^3) or scalp tenderness at the time of disease diagnosis. However, as shown in Table 8, in both cases CI encompassed 1.0, limiting the ability to derive strong inference of these results.

DISCUSSION

To our knowledge, the present report constitutes the largest population-based study assessing the frequency of flares in patients with biopsy-proven GCA from southern Europe. The study discloses predictors for the development of flares (relapses or recurrences) in GCA.

Corticosteroid requirements are highly variable in patients with GCA. Relapses or recurrences of the disease are common in these patients.[33,36] As pointed out by Wilke and Hoffman,[38] clinical heterogeneity has contributed to controversy in the analysis of clinical data in patients with GCA. Therefore, population-based studies encompassing homogenously treated patients are of major importance to establish the frequency and the best clinical data that may predict the development of disease flares. In this regard, Proven et al[35] reported the presence of relapses or recurrences in 57 of a series of 120 (48%) individuals with GCA diagnosed in Olmsted County, Minnesota. In the present study, we found relapses or recurrences in 71 of 174 (40.8%) patients with biopsy-proven GCA. As expected, we observed that patients with relapses or recurrences of the disease required longer duration of treatment and had higher cumulative prednisone dose than those who did not suffer disease flares. In the current series, flares occurred more commonly when prednisone dose was lower than 10 mg/d or when it had been discontinued.

TABLE 8. Predictors of Flares (Relapses or Recurrences) in Patients With Biopsy-Proven GCA*

Variable	OR (95% CI)	P
Leukocytosis (WBC >11,000/mm^3)	1.86 (0.92–3.76)	0.08
Anemia (hemoglobin <12 g/dL)	2.17 (1.02–4.62)	0.04
Scalp tenderness	1.73 (0.88–3.39)	0.11

Area under ROC curve: 0.6265, 95% CI: 0.5473–0.7057.

*Adjusted OR obtained by multivariate logistic regression analysis. 95% CI and p values obtained via bootstrap with 1000 replications.

The optimal corticosteroid tapering in patients with GCA has not been defined, but the rate of the initial corticosteroid reduction in the current series (5 mg prednisone every 2–4 wk) seemed to be slower than in some other studies that described an initial corticosteroid reduction of 5–10 mg prednisone/wk. This fact might have influenced the frequency of relapses or corticosteroid side effects in the current series compared to other studies.

A major issue in the management of patients with GCA is predicting the duration of corticosteroid therapy. Proven et al[35] emphasized that even in homogenously treated patients there is great diversity in the duration of treatment. In accordance with previous observations, when we assessed patients in the current series who were followed until complete discontinuation of prednisone, we observed that the mean duration of treatment was longer in the subgroup of patients who discontinued prednisone but experienced disease relapses or recurrences compared with patients who were able to discontinue prednisone without disease relapses or recurrences. Andersson et al[1] reported a longer duration of corticosteroid therapy (median, 5.8 yr) in 90 patients with GCA diagnosed in a medical department in Goteborg compared with that in the current series. Of note, 43% of the patients reported by Andersson et al remained on corticosteroid therapy 5 years after the diagnosis of GCA. Hachulla et al[24] assessed the outcome in a series of patients with GCA treated in a department of internal medicine in France. The mean duration of corticosteroid therapy was 40 months in 56 patients followed until complete drug discontinuation. A shorter duration of corticosteroid therapy was reported by Delecoeuillerie et al[6] in another series of 78 French individuals with GCA (30.9 mo). In contrast to the former Swedish study reported by Andersson et al,[1] Lundberg and Hedfors[31] reported that the average period of GCA therapy in 51 patients with GCA diagnosed in a department of rheumatology in Sweden was 21 months. The reasons for these differences in the length of therapy are difficult to explain. Patient selection related to the centers and lack of uniform treatment protocols might account for these differences. Also, as pointed out by Proven et al,[35] another possible

explanation may be the absence of well-defined tools to establish the presence of mild persistent active disease in GCA patients. This fact may influence physician's decisions regarding corticosteroid use.

An important issue to be addressed is to establish some clinical or laboratory clues that at the time of disease diagnosis may predict the development of relapses or recurrences. In this regard, Proven et al[35] did not find a relationship between the length of corticosteroid therapy and the severity of the disease. However, Nesher et al[33] reported that disease flares were less common among patients with weak initial systemic inflammatory response. In keeping with this observation, Hernández-Rodríguez[27] et al reported that GCA patients with a strong initial systemic inflammatory response had higher and more prolonged corticosteroid requirements and suffered more disease relapses during corticosteroid therapy than patients with a weak inflammatory systemic acute phase response. Also, patients included by Hernández-Rodríguez et al[27] in the group of high inflammatory response (n = 35) had significantly lower mean hemoglobin levels (9.8 g/dL) than those patients (n = 40) with a weak initial inflammatory response (mean hemoglobin, 12.0 g/dL). As reported in the current series, PMR, headache, and constitutional symptoms were the most common features at the time of disease flares in the series by Hernández-Rodríguez et al.[27]

Moderate anemia has frequently been found at the time of diagnosis in patients with GCA.[25] In a former study, we observed that the median hemoglobin value was 11.7 g/dL, and 131 of the 240 (54.6%) patients with biopsy-proven GCA had hemoglobin levels <12 g/dL at time of GCA diagnosis.[18] We also described a negative association between the presence of anemia and the development of severe ischemic complications in individuals with biopsy-proven GCA from northwestern Spain.[18] This finding was in keeping with a previous report[14] on 161 patients with biopsy-proven GCA from Lugo that emphasized the role of anemia as a negative predictive factor for the development of visual ischemic manifestations of GCA. It is noteworthy that a lower hemoglobin value in GCA patients without visual ischemic events or specifically without severe ischemic complications, was also reported by Cid et al[4] in a series of 200 GCA patients from 3 different hospitals of northeast Spain.

Taken with these previous results, the present report highlights the potential value of anemia at the time of GCA diagnosis as a predictor of future flares. In our study a level of hemoglobin <12 g/dL was the best marker associated with a positive predictive value for the development of GCA relapses or recurrences. In keeping with this observation, we previously described that anemia was the best negative predictor for severe ischemic complications in patients with biopsy-proven GCA.[18] Therefore, we face the paradox of protection against severe ischemic complications but at the same time an increased risk of disease flares in those patients presenting with severe inflammation manifested by anemia at the time of disease diagnosis.

The reasons for this effect of anemia, as the result of a chronic inflammatory response, are unknown. Cid et al[4,5] provided data suggesting that inflammation-induced angiogenic activity could counteract the risk of ischemic complications in patients with GCA. These authors studied the clinical relevance of neovascularization in a series of 31 GCA patients and found that those without ischemic complications had significantly higher tissue angiogenesis scores than patients with ischemic events. Angiogenesis was also more severe in GCA patients with a strong acute phase response compared with those with a weak systemic inflammatory response.[5] Based on these results, it is likely to think that an inflammation-induced angiogenic activity may play a compensatory role for ischemia in GCA patients.[5] Moreover, it is known that GCA patients with a strong systemic inflammatory response have elevated tissue expression of proinflammatory cytokines such as interleukin (IL)-1β, tumor necrosis factor-α, and IL-6.[28] Therefore, as pointed out by Hernández-Rodríguez et al,[28] a strong initial inflammatory response mediated by more elevated levels of IL-6 and tumor necrosis factor-α may reduce the risk of severe ischemic events, but it may be associated with prolonged requirements of corticosteroids in patients with GCA.

Genetic factors have been found to influence both disease susceptibility and the risk of severe ischemic complications in GCA.[9,14] It is possible that a genetically mediated increased angiogenic response may also predispose to persistent chronic inflammation, leading to longer corticosteroid requirement and prolonged corticosteroid therapy.

In conclusion, although limitations due to the retrospective nature of the study may exist, the results of the current study confirm that in homogenously treated patients with biopsy-proven GCA, relapses or recurrences are frequent. The data emphasize the potential value of anemia to predict the development of disease flares.

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