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Long-term remission in biopsy proven giant cell arteritis: A retrospective cohort study

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ABSTRACT

Objective: To evaluate the frequency of long-term remission after glucocorticoids (GCs) suspension in an Italian cohort of patients with biopsy-proven GCA and to identify factors that may predict long-term remission.

Methods: We evaluated 131 patients with biopsy-proven transmural GCA diagnosed and followed up at the Rheumatology Unit of Reggio Emilia Hospital (Italy) for whom sufficient information was available from the time of diagnosis until at least 18 months of follow-up. Long-term remission was defined as complete clinical remission without elevation of inflammatory markers for at least one year after the GC withdrawal.

Results: 73 patients (56%) experienced long-term remission. Disease flares were less frequently observed in patients with long-term remission compared to those without ($p = 0.002$). The cumulative doses of prednisone at 1 year and for the entire followup duration were significantly lower ($p < 0.0001$ for both parameters) in patients with long-term remission; similarly, the duration of prednisone treatment was also significantly lower ($p < 0.0001$).

The presence of PMR at diagnosis (HR 0.46) was significantly negatively associated with long-term remission ($p = 0.008$), while hemoglobin levels (HR 1.48) were significantly positively associated ($p < 0.0001$). Patients with long-term remission were able to reach 10 mg/day and 5 mg/day of prednisone sooner than the patients without ($p = 0.02$ and $p < 0.0001$, respectively).

Conclusion: In our cohort of GCA patients around half of the patients were able to attain long-term remission. Recognition of findings which predict disease course may aid decisions regarding therapy.

1. Introduction

Glucocorticoids (GCs) are the cornerstone of treatment of giant cell arteritis (GCA). Adequate doses quickly suppress clinical manifestations of GCA and mostly prevent ischemic complications [1,2]. The duration of GC therapy is highly variable in GCA. Most patients requires 1–2 years of GC treatment. Some patients are able to discontinue GCs within 1–2 years and maintain sustained remission, while other patients have a chronic relapsing course requiring GCs up to several years [3–10]. Identification of predictors of long-term remission without GC treatment can aid to optimize therapeutic strategies, reducing GC exposure and thus minimizing GC-related side effects.

To date, there are limited observations on predictors of disease flares in GCA [11–16], but no study has evaluated clinical and laboratory findings at disease diagnosis that may identify the subgroup of patients able to suspend GC treatment and to achieve a sustained remission. Moreover, it is unknown whether these patients differ in intensity of inflammatory response, clinical presentation, disease course, and GC initial and cumulative dose.

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Therefore, we conducted the present study to evaluate the frequency, timing, and characteristics of patients able to suspend GCs while maintaining disease remission for at least 12 months after GC discontinuation. This study was performed in a large cohort of Italian patients with biopsy-proven GCA diagnosed between 1986 and 2007 with long-term follow-up. In addition, we evaluated the usefulness of clinical, laboratory parameters, and co-morbidities at diagnosis, as well as temporal artery histopathological findings and flares as predictors of sustained remission.

2. Patients and methods

2.1. Patients

We reviewed the computerized pathology laboratory's register, which keeps a record of all temporal artery biopsies (TAB) performed in Reggio Emilia (Italy) at the Arcispedale Santa Maria Nuova Hospital between January 1, 1986 and December 31, 2007. The positive specimens were reviewed by a pathologist (AC) with expertise in vasculitis.

Patients were diagnosed as having biopsy-proven GCA if the histological examination of the TAB showed transmural infiltration of mononuclear cells in the arterial wall with or without giant cells. TAB procedures in Reggio Emilia have been described elsewhere [17,18]. TAB was routinely performed in all patients with clinical manifestations of GCA. The length of TAB after fixation was $\geq$0.5 cm in all cases. We included only those patients diagnosed and followed up for at least 18 months in our Department of Rheumatology for whom sufficient information was available from the time of diagnosis until September 1, 2011 or subject's death. 131 patients satisfied the inclusion criteria and were included in the study. Although this study is retrospective, all patients were uniformly evaluated and treated. The study was approved by the local Ethics Committee.

All medical records of these 131 patients were reviewed. Besides demographic features and comorbidities (hypertension, diabetes mellitus, hypercholesterolemia, hypertriglyceridemia, and smoking status) [17], the following clinical data at the time of diagnosis were assessed: headache, abnormal temporal arteries on physical examination, scalp tenderness, jaw claudication, carotidodynia, visual manifestations (transient visual loss including amaurosis fugax, permanent visual loss, and diplopia), cerebrovascular accidents (CVAs) (stroke and/or transient ischemic attack), systemic signs/symptoms (at least one of the following: fatigue, anorexia, weight loss of at least 4 kg, or fever), fever $\geq$ 38 °C, polymyalgia rheumatica (PMR) (bilateral marked aching and stiffness without other apparent cause in at least 2 of the following regions: neck, shoulder girdle, and hip girdle), and distal musculoskeletal manifestations.

Laboratory parameters were measured prior to the onset of GC therapy and during the follow-up. Erythrocyte sedimentation rate (ESR) was determined using the Westergren method (since most of our patients were women over the age of 50, the upper limit of normal considered for ESR was 30 mm/h). C-reactive protein (CRP) was measured by nephelometry (NA latex CRP kit; Behringwerke, Marburg, Germany; upper limit of the normal reference range 0.5 mg/dl). Hemoglobin levels (anemia if < 12 gm/dl) and platelet count (elevated if > 450,000 mm3) were also considered.

The pathologist (AC) evaluated the following pathological findings in TAB specimens: presence of giant cells, intraluminal acute thrombosis, laminar necrosis, calcifications, and intimal thickening. He also categorized the degree of inflammation present in temporal artery specimens as mild, moderate and severe [19,20]. All patients with visual loss at diagnosis or during the follow-up period were examined by an ophthalmologist (LC). Visual acuity was measured using a Snellen chart, and visual field was tested with a Goldmann perimeter.

All patients with GCA were initially treated with a mean prednisone dose of 47 ± 15 mg/day. Some patients with visual ischemic manifestations also received intravenous pulses of methylprednisolone (1 g/day for 3 consecutive days) followed by prednisone 60 mg/day. The initial dose of prednisone was maintained for the first month, then the dosage was reduced by 5 mg every 2–4 weeks to 20 mg/day. Subsequently, the reduction of prednisone dose below 20 mg/day was slower and individualized. Generally, prednisone was reduced by 2.5 mg every 2–4 weeks to 10 mg and then by 1 mg every 1–2 months until suspension, provided no relapses occurred.

Disease-related signs/symptoms, ESR and CRP levels, and GC dosages were recorded at every follow-up visit (scheduled in most patients every 3 months). Cumulative prednisone dose received after 6 months and 1 year, as well as the total cumulative prednisone dose received during the entire study period were calculated.

We diagnosed disease flares if all the following criteria were satisfied: 1) reappearance of signs/symptoms of GCA/PMR, 2) resolution of signs/symptoms after increasing or restarting GC, 3) ESR $\geq$40 mm/h or CRP $\geq$0.5 mg/d, and 4) exclusion of other causes. Flares occurring during the course of GC treatment were considered relapses, whereas flares occurring at least one month after GC withdrawal were considered recurrences.

In case of asymptomatic increases of ESR and/or CRP the dosage of GC was maintained stable until the next visit, other eventual causes for such increases were investigated and the dosage of GC was increased only if a clinical flare was documented.

Long-term remission was defined as permanent discontinuation of prednisone without recurrence of symptoms and elevation of inflammatory markers for at least 1 year.

2.2. Statistical analysis

Continuous data were described as mean and standard deviation (mean ± SD) or median and interquartile range (IQR), and categorical variables as absolute frequencies and percentages. Continuous variables were compared by using *t*-test or Mann-Whitney test when the distributions were skewed. Comparison of categorical variables was performed by using chi square or Fischer's exact test. Univariate and multivariate Cox proportional hazards models were used to evaluate potential predictors of long-term remission at diagnosis (demographic, clinical, laboratory, pathological findings, comorbidities and initial prednisone dose). The predictors evaluated are listed in Table 1. Disease flares were also added to these predictors. Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed for each predictor in the univariate analysis and in the multivariate model using the backward stepwise approach ($p = 0.10$ for removal, $p = 0.05$ for addition to the model).

The time to achieve maintenance prednisone dose of 10 mg/day and 5 mg/day was estimated with the Kaplan-Meier method, and log-rank test was used to compare time between patients with and without sustained remission, which was especially necessary because the length of follow-up differs between the two study cohorts. All test were two-sided; significance was setat $p < 0.05$. Statistical analysis was performed using SPSS version 22.0 (IBM Statistics, Armonk, NY: IBM Corp, USA).

3. Results

The study population consisted of 131 patients: 103 (79%) females and 28 (21%) males. Mean (±SD) age at diagnosis of GCA was 74 ± 7 years and median follow-up 84 months (IQR 54–127 months). The median follow-up duration was significantly longer in