Steroid Therapy Improves Endothelial Function in Patients with Biopsy-Proven Giant Cell Arteritis

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ABSTRACT. ***Objective.*** Endothelial dysfunction has been found to be present in subjects with both small and medium-size blood vessel vasculitides. We assess whether endothelial dysfunction was also present in patients with biopsy-proven giant cell arteritis (GCA) and whether it might be improved following steroid treatment.

Methods. Endothelial function was determined in cross-sectional and longitudinal studies of 6 patients with biopsy-proven GCA diagnosed between January and May 2002 by measuring flow-mediated endothelial-dependent and independent vasodilatation (EDV and EIV) by brachial ultrasonography. Patients were assessed for endothelial function within 48 hours after the onset of steroid therapy, 4 weeks after the onset of steroid therapy, and 2 years after the disease diagnosis.

Results. EDV was significantly impaired in patients with GCA compared with 12 matched controls [mean 2.9%, median 2.45% (range 2.1% to 4.7%) vs mean 6.5%, median 6.6% (range 3.9% to 9.3%) in matched controls; p = 0.002]. However, no significant difference existed between patients and controls in EIV. Significant improvement of EDV after the suppression of inflammation was achieved. At Week 4 after the onset of steroid therapy all 6 patients showed enhanced responses (p = 0.028). This improvement of EDV was still present when steroid treatment was ended, 2 years after diagnosis.

Conclusion. Endothelial function is significantly impaired in individuals with active biopsy-proven GCA. The results highlight the importance of steroid therapy to improve endothelial function after suppression of the inflammation of GCA. (J Rheumatol 2006;33:74–8)

Key Indexing Terms:
GIANT CELL ARTERITIS TEMPORAL ARTERY BIOPSY ENDOTHELIAL DYSFUNCTION FLOW-MEDIATED ENDOTHELIAL DEPENDENT VASODILATATION

Giant cell arteritis (GCA) is the most common type of vasculitis in the elderly in Western countries[1]. It is characterized by the granulomatous involvement of large and medium-size blood vessels of the aorta with predilection for the extracranial arteries of the carotid artery[2,3].

Vascular endothelial injury is the primary event in atherosclerosis[4] and has been associated with endothelial cell dysfunction[5], which in turn may be linked to short-term cardiovascular events[6]. In this regard, the diffuse endothelial dysfunction observed in patients with rheumatoid arthritis (RA) suggests that vascular inflammation may initiate the accelerated atherosclerotic disease observed in patients with this condition[7].

Endothelial function has been found to be impaired in both children and adults with primary systemic vasculitis[8-10]. Abnormalities of systemic endothelial function are present many years after resolution of acute Kawasaki disease, which may explain the high risk of atherosclerosis and coronary disease observed in these patients[8]. In adults, studies on primary systemic necrotizing vasculitides (Wegener's granulomatosis, polyarteritis nodosa, and Churg-Strauss syndrome) by the Birmingham group have confirmed the presence of endothelial dysfunction in patients with active vasculitis that improved after suppression of inflammation[9]. These investigators demonstrated that endothelial dysfunction was present in both small and medium-size blood vessel vasculitides and excluded any contribution from undetected primary vasculitic inflammation at the site of determination of endothelium function tests (brachial artery)[10]. As recently pointed out by Bacon[11], endothelial dysfunction in patients with primary systemic necrotizing vasculitides predicts enhanced atherosclerosis in these patients.

Although mortality in patients with GCA is increased within the first year after the onset of disease[12], most epidemiological reports on this vasculitis suggest that the

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longterm mortality is similar to that observed in the general population of the same age[12,13]. However, to our knowledge, no information about endothelial function studies in GCA patients has been reported.

We assessed whether endothelial dysfunction is present in patients with biopsy-proven GCA and whether it might be improved after short-term steroid treatment. We also investigated whether endothelial function was abnormal in patients with GCA who ended steroid therapy and were free of symptoms 2 years after the diagnosis of this vasculitis.

MATERIALS AND METHODS

Subjects. This study comprised 6 patients diagnosed with biopsy-proven GCA between January and May 2002 at Hospital Xeral-Calde, Lugo, Spain, that were assessed for endothelial function within 48 h after the onset of steroid therapy. All these patients were required to have a second endothelial function test 4 weeks after the onset of steroid therapy, and a third assessment of endothelial function 2 years after the disease diagnosis. As well, patients were required to have ended steroid therapy and to have no clinical features of GCA and an erythrocyte sedimentation rate (ESR) < 20 mm/h by the time of the last high-frequency ultrasonographic (US) study.

Patients diagnosed with biopsy-proven GCA were treated as described[14,15]. Those without visual manifestations commenced treatment with 40 mg prednisone in 3 doses per day for 3–4 weeks. However, the 2 patients with visual manifestations were initially treated with daily intravenous pulse methylprednisolone (1 g/day for 3 consecutive days) followed by 60 mg prednisone/day for 3 weeks. Then in these 2 cases prednisone dose was reduced 10 mg every 2 weeks to 40 mg/day. Afterwards, prednisone dosage was reduced 5 mg every 2 weeks to 20 mg/day. Prednisone reduction below 20 mg/day was slower and individualized. A rate of 2.5 mg every 2–3 mo to time of complete discontinuation was undertaken.

Age, sex, body mass index, and traditional cardiovascular risk factors (hypertension, diabetes, dyslipidemia, and smoking) were recorded. As well, 2 ethnically matched controls from the Lugo region were studied for each individual patient. Ethical approval for endothelial function studies was given and informed consent was obtained from all cases and controls.

Brachial artery reactivity. Brachial artery diameter and flow were determined by standard techniques with brachial artery US as reported[16-18]. B-mode scan of the right brachial artery, in a longitudinal section 2 to 12 cm proximal to the antecubital fossa, was performed in supine subjects using a 7.5 MHz phased-array transducer on a Hewlett Packard Sonos 5500 system (Hewlett Packard, Palo Alto, CA, USA). The anterior and posterior media-intima interfaces were used to define the baseline artery diameter, calculated as the average of measurements during 4 cardiac cycles at end diastole. The forearm blood pressure cuff was inflated on the ipsilateral wrist to 150 mm Hg above resting systolic blood pressure for 5 min, and then released. Flow-mediated endothelium-dependent vasodilatation (EDV; an increase in brachial artery diameter) was measured 30 to 60 s after release of the cuff.

To assess endothelium-independent vasodilatation (EIV), we used 400 μg of sublingual nitroglycerin, which acts directly on vessel smooth muscle to cause vasodilatation. EIV was measured 4 min after nitroglycerin intake.

In all cases, a cardiologist (CG-J) analyzed all US data offline, blinded to the clinical information. Based on studies of 12 controls the intraobserver variability showed the following coefficients of variation: baseline diameter 1.1%, EDV 1.3%, and EIV 1.9%.

Statistical analysis. Data were expressed as mean, median, and range. Measurements of EDV and EIV represented the maximal increase in brachial diastolic artery diameter and were expressed as percentage of change from baseline. Control and patient groups were compared with the Mann-Whitney test. Paired serial results in individual GCA patients were compared using the Wilcoxon signed-rank test for matched observations. All results were presented as 2 tailed values. Statistical significance was accepted as $p < 0.05$.

RESULTS

Table 1 shows the main clinical features of the 6 patients with biopsy-proven GCA (4 women and 2 men; median age at disease onset 77 yrs, range 72–81 yrs). The 12 ethnically matched controls (8 women, 4 men) were a median age of 78 years (range 72–82) at the time of the study.

Differences between GCA patients and controls. A cross-sectional study was performed to establish differences between patients and controls (Table 2). EDV was significantly impaired in patients with biopsy-proven GCA compared with controls [mean 2.9%, median 2.45% (range 2.1%–4.7%) vs mean 6.5%, median 6.6% (range 3.9%–9.3%) in matched controls; $p = 0.002$]. No significant difference existed between patients and controls in EIV [patients: mean 14.7%, median 15.7% (range 7.9%–19.3%); controls: mean 14.0%, median 13.6% (range 8.7%–22.2%)] or in baseline diameter [patients: mean 0.42 cm, median 0.41 (range 0.36–0.50 cm); controls: mean 0.43 cm, median 0.42 (range 0.38–0.50 cm)]. No correlation existed between EDV in GCA patients and the time delay to diagnosis (data not shown).

Influence of steroid therapy on endothelial function in GCA patients. A longitudinal study of GCA patients disclosed a significant improvement of EDV after the suppression of inflammation (Table 3, Figure 1). In this regard, at Week 4 after the onset of steroid therapy all 6 patients showed enhanced responses [percentage of EDV at Week 4: mean 6.0%, median 5.6% (range 2.9%–9.9%)] compared to percentage of EDV observed at the time of diagnosis ($p = 0.028$). This improvement of EDV was still present when steroid treatment was ended [percentage of EDV 2 years after diagnosis: mean 7.1%, median 6.3% (range 3.6%–11.2%)] compared to percentage of EDV at disease diagnosis ($p = 0.028$). At 2 years after diagnosis, percentages of EDV in GCA patients were similar to those observed

Table 1. Main clinical features in 6 patients with GCA with ultrasonographic evaluation of endothelial function.

Age at disease onset, yrs, median (range)	77 (72–81)
Delay to diagnosis, weeks, median (range)	3 (1–9)
Women/men	4/2
Headache, no. (%)	5 (83.3)
Abnormal temporal artery*, no. (%)	5 (83.3)
Jaw claudication, no. (%)	3 (50.0)
Polymyalgia rheumatica, no. (%)	1 (16.7)
Visual manifestations, no. (%)	2 (33.3)
Amaurosis fugax	1 (16.7)
Unilateral permanent visual loss	1 (16.7)
ESR at disease diagnosis, mm/h, median (range)	92 (81–109)

* On physical examination.

in controls (p = 0.925). However, no significant change occurred in EIV values (Table 3, Figure 2).

DISCUSSION

This study shows for the first time that endothelial function is significantly impaired in individuals with active biopsy-proven GCA. It also emphasizes the potential importance of steroid therapy to improve endothelial function after suppression of the inflammation. In our study the small sample size would be a limitation for negative results, but it does not affect the positive findings observed in all patients. However, since not all GCA patients are in drug-free remission 2 years after the onset of steroid therapy and the inclusion criteria for our study required that patients must have ended steroid therapy and be in clinical remission at the time of 2-year followup, it is possible that this series of 6 GCA patients may constitute a slightly biased group.

For ethical reasons, we did not delay the onset of corticosteroid therapy until endothelial function tests had been performed, and all GCA patients in the study were already using steroids at the time of the first EDV test. Thus, the initial values in the GCA patients might reflect drug effect as well as disease effect. On the other hand, although prolonged corticosteroid therapy seemed to have a beneficial effect in improving EDV in this small series of patients, this is particularly worrisome as corticosteroids may be a risk factor for atherosclerosis. However, no relationship between corticosteroid therapy and atherosclerosis measured by carotid intima-media thickness has been found in patients with RA[19-21]. Also, the association between cortisol and the progression of atherosclerosis determined by studies of carotid intima-media thickness in the general population is not clear[22,23].

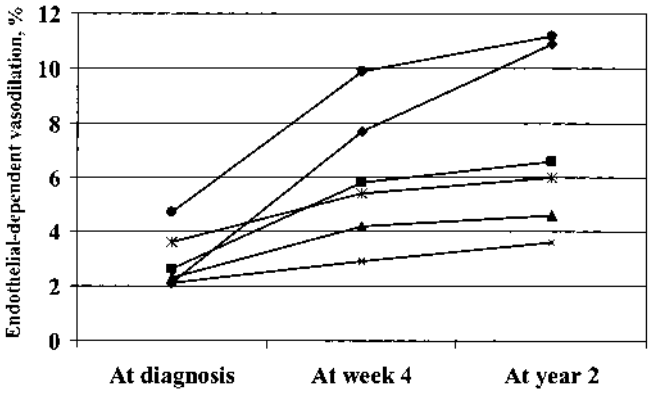

Figure 1. Percentage of endothelial-dependent vasodilatation in 6 patients with GCA at the time of disease diagnosis, and at Week 4 and Year 2 after diagnosis.

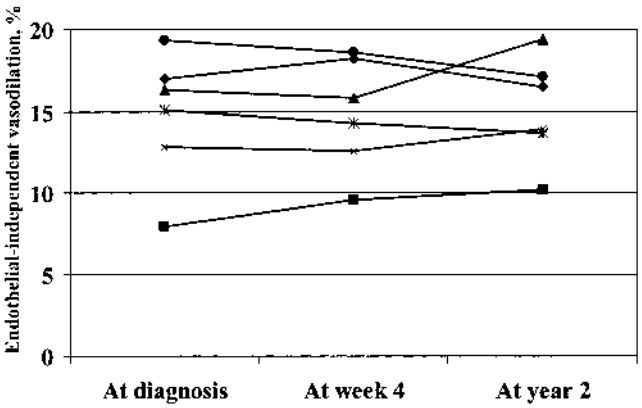

Figure 2. Percentage of endothelial-independent vasodilatation in 6 patients with GCA at the time of disease diagnosis, and at Week 4 and Year 2 after diagnosis.

Table 2. Differences in the percentage of flow-mediated endothelial-dependent vasodilatation (EDV) and endothelial-independent vasodilatation (EIV) between 6 patients with GCA at time of disease diagnosis and 12 matched controls.

Brachial Artery	Controls	Patients	p
EDV, %			0.002
Mean	6.5	2.9	
Median	6.6	2.45	
Range	3.9–9.3	2.1–4.7	
EIV, %			0.779
Mean	14.0	14.7	
Median	13.6	15.7	
Range	8.7–22.2	7.9–19.3	

p = 0.578 for brachial artery basal diameter (patients vs controls).

Table 3. Percentage of flow-medicated endothelial-dependent vasodilatation (EDV) and endothelial-independent vasodilatation (EIV) in 6 patients with GCA at disease diagnosis, and at 4 weeks and 2 years after diagnosis.

	EDV			EIV		
Case	At Diagnosis	At Week 4	At Year 2	At Diagnosis	At Week 4	At Year 2
1	2.1	7.7	10.9	17.0	18.2	16.5
2	2.6	5.8	6.6	7.9	9.6	10.2
3	2.3	4.2	4.6	16.3	15.8	19.4
4	2.1	2.9	3.6	12.8	12.6	13.9
5	3.6	5.4	6.0	15.1	14.3	13.7
6	4.7	9.9	11.2	19.3	18.6	17.1
p*		0.028	0.028		0.917	0.600

* Comparing percentages of EDV or EIV at Week 4 and at Year 2 with those at diagnosis of GCA.

An important result from our study was that after remission induction values of EDV in patients with GCA did not differ significantly from those of healthy controls. This may have potential implications for the outcome of patients with this vasculitis. Dhillon, *et al*[8] assessed endothelial function in the brachial artery of 20 patients 5 to 17 years after acute Kawasaki disease. They found no differences in baseline vessel diameter or percentages of EIV between patients and controls. However, flow-mediated EDV was markedly reduced in patients with Kawasaki disease compared with controls[8]. Persistent endothelial dysfunction in patients with Kawasaki disease several years after disease diagnosis was found to be correlated with abnormal coronary response[8].

Increased mortality due to vascular complications as a consequence of lack of control of inflammation, including myocardial infarction, soon after diagnosis of GCA has been described[24]. Uddhammar, *et al* reported an increased mortality due to cardiovascular complications, including ischemic heart disease (IHD), in patients with GCA from Northern Sweden[25]. However, extensive information on IHD in GCA is not available. To investigate this issue we undertook a study on the incidence of IHD in patients with biopsy-proven GCA from Lugo between 1981 and 2001[26]. In contrast to information generally reported as case reports, we found a low frequency of IHD within the first month after the onset of steroid treatment. Moreover, mortality due to IHD in patients with GCA from Lugo was not much higher than that reported for the Spanish population aged 50 years and older[26].

Since endothelial dysfunction is an early step in the development of atherosclerosis and IHD, and steroid therapy seems to be effective in restoring endothelial function that is impaired in GCA due to the severe inflammation, it is possible that this therapy might be useful in preventing the development of IHD in patients with this vasculitis. This might explain, at least in part, the low incidence of IHD reported in classic followup studies of patients with GCA[27,28].

However, recent population based studies have emphasized that aortic aneurysm disease may occur as a late complication in patients with GCA[29,30]. We observed that patients with high inflammatory response at the time of disease diagnosis, manifested by severely abnormal laboratory findings (ESR > 100 mm/h, hemoglobin < 11 g/dl, or platelet count > 450,000/mm^3), had a higher risk of developing aortic aneurysm disease in the followup results[30]. For that reason, a future study might assess whether this subgroup of GCA patients with severe inflammatory response at the time of disease diagnosis might have persistent impairment of endothelial function. Observation of sustained endothelial dysfunction in periodical studies of flow-mediated vasodilatation in some patients with GCA might be useful in detecting a subgroup of individuals who were more susceptible to the development of accelerated atherosclerosis and aortic aneurysm. Interestingly, none of the 6 GCA patients in the present study exhibited platelet counts > 450,000/mm^3 or hemoglobin values < 11 g/dl at the time of disease diagnosis, and only one of them had ESR > 100 mm/h.

Our study confirmed the presence of endothelial dysfunction in patients with GCA that was improved by steroid therapy. Further studies including larger numbers of patients are needed to confirm these results and to determine whether a subgroup of patients with persistent inflammatory response leading to accelerated atherosclerosis and aortic aneurysm disease can be identified by periodic ultrasonographic studies of the brachial artery.

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