

# Von Willebrand factor in the outcome of temporal arteritis

Maria C Cid, Joan Monteagudo, Joaquim Oristrell, Jaume Vilaseca, Lucio Pallarés, Ricard Cervera, Carme Font, Josep Font, Miguel Ingelmo, Alvaro Urbano-Márquez

## Abstract

**Objective**—To determine fluctuation in circulating von Willebrand factor (vWF) in the outcome of patients with temporal arteritis.

**Methods**—Plasma vWF antigen concentrations were measured in 65 patients with biopsy proven temporal arteritis at different disease activity stages, in 12 with isolated polymyalgia rheumatica, and in 16 controls. Fourteen temporal arteritis patients underwent serial determinations during the course of their disease.

**Results**—vWF concentrations were significantly raised in temporal arteritis (mean 220 [arbitrary units], range 96 to 720) and in polymyalgia rheumatica (mean 196, range 103 to 266) compared with healthy controls (mean 98, range 75 to 137) ( $P < 0.05$ ). Although vWF values tended to be higher in temporal arteritis, no significant differences were found between temporal arteritis and polymyalgia rheumatica patients nor between temporal arteritis patients with ischaemic complications (mean 269, range 130 to 720) and those who presented with polymyalgia rheumatica or constitutional symptoms only (mean 179, range 140 to 220). The highest levels were obtained in patients with associated, mainly infectious, diseases (mean 631, range 240 to 1680). Raised vWF values found in active temporal arteritis patients (mean 220, range 96 to 720) persisted within the first two years after the beginning of treatment (mean 244, range 102 to 510) but tended to normalise in patients in long term remission (mean 143, range 50 to 260).

**Conclusions**—Persistent elevation of vWF during early remission of temporal arteritis might represent an endothelial activation status induced by a remaining inflammatory microenvironment rather than a marker of endothelial cell injury. In long term remission, decreasing vWF concentrations might reflect progression of inflammatory lesions to a healing stage.

(Ann Rheum Dis 1996;55:927-930)

Over the past years circulating von Willebrand factor (vWF) has received a great deal of attention as a potential indicator of endothelial injury in a variety of diseases.<sup>1</sup> vWF is a high molecular weight glycoprotein synthesised by megakaryocytes and endothelial cells. It circulates in plasma in a multimeric form non-covalently linked to factor VIII, and inter-

acts with platelet integrins, mediating their adhesion to the subendothelial matrix of damaged vessels.<sup>2</sup>

Abnormally high plasma vWF concentrations have been observed in several disorders, most of which involve blood vessels through different mechanisms.<sup>1-8</sup> Since vWF is stored in Weibel-Palade bodies of endothelial cells, the hypothesis has been proposed that increased vWF concentrations might reflect the existence of vascular injury.<sup>1,3,4</sup> Furthermore, several investigators have considered the measurement of vWF activity potentially useful for both diagnosis and management of patients with vasculitis.<sup>4</sup>

vWF has been especially studied in temporal arteritis and in its related disorder polymyalgia rheumatica.<sup>5-8</sup> However, doubts about its usefulness in the day to day management of these patients have been raised since the increased concentrations of vWF found in temporal arteritis remain high in spite of clinical and laboratory determined remission induced by corticosteroid treatment.<sup>5-8</sup> Moreover, during early follow up, vWF fluctuations have not been useful in predicting flares.<sup>8</sup> Whether vWF levels remain indefinitely raised or eventually return to normal is not known.

In this study we have determined vWF related antigen (vWFAg) concentrations in a large series of patients with biopsy proven temporal arteritis in order to analyse their variations in different activity stages, including a group of patients with long term follow up.

## Methods

The study group consisted of 65 biopsy proven temporal arteritis patients (20 males and 45 females). Twelve patients (two males and 10 females) fulfilling diagnostic criteria for polymyalgia rheumatica were also included for comparison purposes. All of the later had a negative temporal artery biopsy and never presented cranial manifestations suggestive of temporal arteritis during the period of disease activity or during a three year follow up period.

Data concerning clinical manifestations were obtained prospectively in patients with active disease and in those in recent remission. In individuals in long term remission, clinical information was obtained from their records and completed with an interview with every patient and a general physical examination.

A cross sectional study was performed and patients were classified according to their disease activity. Temporal arteritis or polymyalgia rheumatica were considered active when patients were clinically symptomatic and evaluated previously or within the first week

Hospital Clínic I  
Provincial, Barcelona,  
Spain:  
Department of  
Internal Medicine  
M C Cid  
L Pallarés  
R Cervera  
C Font  
J Font  
M Ingelmo  
A Urbano-Márquez

Department of  
Haemotherapy  
J Monteagudo

Hospital Vall  
d'Hebron, Barcelona,  
Spain:  
Department of  
Internal Medicine  
J Vilaseca

Consorci Hospitalari  
del Parc Taulí,  
Sabadell, Spain:  
Department of  
Internal Medicine.  
J Oristrell

Correspondence to:  
Maria C Cid, Department of  
Internal Medicine, Hospital  
Clínic I Provincial, Villarroel  
170, 08036-Barcelona, Spain

Accepted for publication  
12 August 1996

after starting treatment (prednisone 1 mg kg<sup>-1</sup> d<sup>-1</sup> for temporal arteritis and 15 mg d<sup>-1</sup> for polymyalgia rheumatica). They were considered to be in recent remission when complete recovery of their symptoms occurred, with normalisation of erythrocyte sedimentation rate (ESR), after treatment for at least one month. Patients were considered to be in long term remission when they had been asymptomatic for three or more years after the beginning of treatment. At the time when vWF Ag was determined four of the latter had slightly raised or borderline ESR values which did not result in a clinical flare or require changes in their treatment schedule.

The control group included 16 healthy blood donors (nine males, seven females) aged 63 years (range 60-65). The smoking habits of patients, controls, and pooled plasma donors were not recorded.

Measurements of vWF Ag were performed as described.<sup>9</sup> A pool of plasma samples from normal donors was used as a reference and vWF activity present in this plasma pool was arbitrarily considered to contain 100 U dl<sup>-1</sup> of vWF Ag activity.

For the cross sectional study, 96 determinations were made: 36 in active temporal arteritis patients, 24 in temporal arteritis patients in recent remission (mean seven months, range one to 20 months), 18 in long term remission patients (mean six years, range three to 13 years), 12 in patients with active isolated polymyalgia rheumatica, and six in patients with temporal arteritis and associated diseases: one acute myocardial infarction, four infections (one pneumonia, one acute pyelonephritis with sepsis, one miliary tuberculosis, one oropharyngeal candidiasis), and one dehydration and renal insufficiency secondary to hypercalcaemia caused by coincident primary hyperparathyroidism. In addition, 14 active patients underwent serial determinations at diagnosis and at one to two months, three to six months, and one to three years after the beginning of treatment. None of these patients experienced significant relapses during their follow up. For that reason, months/years after the initiation of treatment are considered equivalent to months/years in clinical remission.

Simultaneously with vWF Ag measurements, other variables were analysed by routine methods: ESR (Westergren), haptoglobin (immunoprecipitation), orosomuroid (immunoprecipitation), C reactive protein (radial immunodiffusion), and platelet count and haemoglobin by usual automated systems.

Analysis of variance (ANOVA) was used for statistical comparison among different groups of patients. Bonferroni's method was applied to correct for multiple comparisons.

### Results

Values resulting from vWF Ag determinations are displayed in figs 1 and 2. vWF Ag levels in active temporal arteritis patients (mean 220 arbitrary units, range 96 to 720) were significantly higher than those obtained from controls (mean 98, range 75 to 137) ( $P < 0.05$ ). Values obtained from patients with

active isolated polymyalgia rheumatica (mean 196, range 103 to 266) were also significantly higher than those from normal donors ( $P < 0.05$ ). Although vWF Ag concentrations tended to be higher in temporal arteritis than in polymyalgia rheumatica the difference was not statistically significant (fig 1).

Among patients with active temporal arteritis, 31 had classical cranial symptoms, 11 with ischaemic complications related to temporal arteritis (seven amaurosis, three amaurosis fugax, one lower limb ischaemia), and five presented with polymyalgia rheumatica or constitutional symptoms only. No significant differences were found in vWF Ag concentrations between patients with active disease and ischaemic manifestations (mean 269, range 130 to 720) and those who suffered from polymyalgia rheumatica or constitutional symptoms only (mean 179, range 140 to 220). There were also no differences between the latter group of temporal arteritis patients and those with isolated polymyalgia rheumatica. The highest vWF Ag concentrations were obtained in patients with temporal arteritis in recent remission suffering from associated conditions (mean 240, range 240 to 1680)—significantly higher than the values obtained in patients with active disease or in those in recent remission but without associated conditions ( $P < 0.05$ ).

Twenty two patients with active temporal arteritis had thrombocytosis (platelet count greater than  $350 \times 10^9$  litre<sup>-1</sup>). No significant differences were found in vWF Ag values between patients with thrombocytosis (mean 229, range 100 to 720) and those without (mean 170, range 96 to 282). While other variables (haemoglobin) or acute phase reactants such as ESR, C reactive protein, haptoglobin, and orosomuroid decreased when patients achieved remission (table), vWF Ag remained elevated. As shown in the table, no significant differences were found between patients with active temporal arteritis (mean 220, range 96 to 720) and those in recent remission (mean 244, range 102 to 510). However, vWF Ag concentrations declined thereafter and were

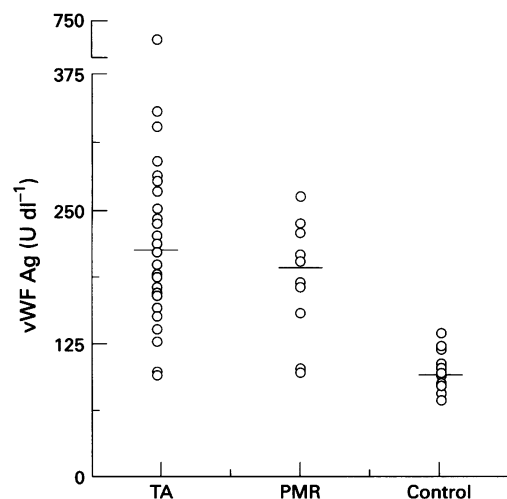


Figure 1 Distribution of plasma vWF antigen concentrations in 36 patients with active temporal arteritis (TA), 12 patients with polymyalgia rheumatica (PMR), and 16 control individuals.

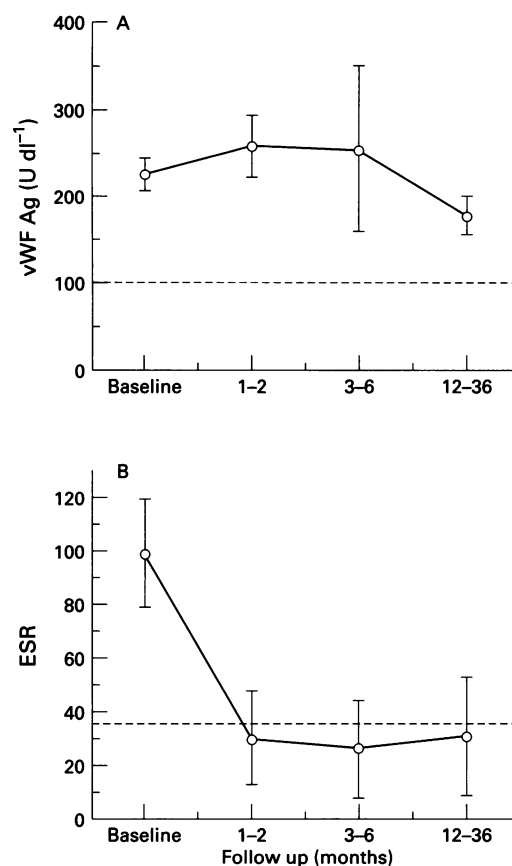


Figure 2 (A) vWF antigen (Ag) concentrations during longitudinal follow up of 14 patients with temporal arteritis. (B) Simultaneously measured ESR values. Values are means, error bars = SD. Dashed line illustrates reference value in pooled plasma from normal individuals (vWF Ag) and upper normal level (ESR).

significantly lower in patients in long term remission (mean 143, range 50 to 260) than in those with active disease or in recent remission ( $P < 0.05$ ) and were similar to those obtained from the control group.

Results from serial determinations performed in 14 patients with temporal arteritis at diagnosis and during follow up are shown in fig 2. In keeping with the data obtained from the cross sectional study, VWF Ag concentrations remained raised during the first three years of follow up.

**Discussion**

vWF Ag plasma concentrations were raised in our series of patients with temporal arteritis, mainly in those with current disease activity or in recent remission. In our study, as well as in other previously published series,<sup>3-8</sup> the smoking habits of the population included

were neglected. Consequently, we cannot rule out the possibility that this variable could have a slight influence on vWF Ag concentrations in both patients and controls. Patients with biopsy proven temporal arteritis tended to have higher vWF Ag concentrations than were found in pure, biopsy negative polymyalgia rheumatica patients but the difference was not significant. Other investigators<sup>6,7</sup> have found a slight but significant increase in vWF Ag values in temporal arteritis compared with isolated polymyalgia rheumatica, and have suggested an interesting role for vWF as a marker of vascular injury in the evaluation of patients with apparently isolated polymyalgia rheumatica. However, in our patients, as well as in other reported series,<sup>6,8</sup> vWF Ag concentrations were highly variable, resulting in a substantial dispersion among individuals whose clinical situations were apparently similar. This finding restricts the potential usefulness of vWF Ag determinations in evaluating systemic vascular involvement in individual patients with suspected vasculitis.

An increase in vWF has been considered to be a result of endothelial injury.<sup>1</sup> However, this hypothesis is barely defensible in temporal arteritis patients. In our series, in agreement with other investigators,<sup>5,6</sup> patients in remission had as high, or even higher, vWF values than patients with active disease. It is difficult to support the view that patients who have been asymptomatic for several months and in very good health have extensive endothelial injury. In fact, we found no significant differences between temporal arteritis patients with severe ischaemic complications, in whom more severe vascular damage is likely, and those who presented with polymyalgia rheumatica or constitutional symptoms only. In addition, raised vWF concentrations have been reported in conditions in which a direct vascular involvement is not a distinctive feature<sup>10</sup> and, indeed, in our patients, the highest vWF Ag concentrations were obtained in those with associated, mainly infectious, diseases. From a clinical point of view, these observations emphasise the lack of specificity of increased vWFAg values and suggest that a very high vWF Ag in the initial follow up of temporal arteritis might indicate the coexistence of an associate disease rather than a relapse of the temporal arteritis per se.

vWF Ag release by endothelial cells can be induced by proinflammatory cytokines in vitro.<sup>11</sup> It is likely that a persistence of raised vWF concentrations in temporal arteritis patients in remission represents continuing low level inflammatory activity in the vessel wall and local endothelial cell activation by cytokines in the vascular microenvironment. Although clinical manifestations and some lymphocyte activation markers in lesions are quickly responsive to steroid treatment,<sup>12</sup> the mechanisms that retain inflammatory cells in the vessel wall do not respond so clearly. Arteritic lesions have been shown to persist for months and even years in some clinically asymptomatic patients with temporal arteritis.<sup>13</sup> Furthermore, neovascularisation within

Table 1 vWF Ag levels, acute phase reactants, and other activity markers in temporal arteritis at different clinical activity stages. Values are means (range)

	Active	Recent remission	Long term remission
vWF Ag (U dl <sup>-1</sup> )	220* (96-720)	244* (102-510)	143 (50-260)
ESR (mm/h)	109** (24-105)	28 (1-66)	24 (2-57)
Haemoglobin (g dl <sup>-1</sup> )	10.9** (8-14)	14.3 (12-16)	13.8 (11-15)
Haptoglobin (g dl <sup>-1</sup> )	422** (187-936)	176 (44-314)	167 (69-237)
CRP (mg dl <sup>-1</sup> )	5.8† (2.4-9)	3.6 (2-5.2)	0.9 (0.7-1)
Orosomucoid (mg dl <sup>-1</sup> )	169** (83-280)	88 (66-128)	75 (49-111)

\* P < 0.05 vs long term remission group only.

\*\* P < 0.05 vs both recent remission and long term remission groups.

† P < 0.05 vs long term remission group only.

vWF Ag, von Willebrand factor related antigen; ESR, erythrocyte sedimentation rate; CRP, C reactive protein.

the inflammatory infiltrates is a prominent but underestimated phenomenon in temporal arteritis lesions<sup>8,14</sup> and vWF Ag production increases during endothelial cell proliferation.<sup>15</sup> Therefore, it is possible that raised vWF concentrations could also be a result of active neovascularisation and vessel repair.

Interestingly, vWF Ag concentrations in patients in long term remission decreased significantly and tended to normalise. A vWF Ag decrease in temporal arteritis patients in long term remission could reflect the outcome of arteritic lesions since over the years the number of patients who reach the healing histological pattern seems to increase.<sup>13</sup>

In summary, our data suggest that vWF Ag concentrations are not useful in the day to day management of patients with temporal arteritis in recent remission, nor in distinguishing between temporal arteritis and polymyalgia rheumatica. However, a decrease in vWF Ag levels can be observed in patients in long lasting remission. Prospective studies must be carried out to discover whether vWF Ag determination in patients in long term remission could be useful in decisions about the withdrawal of corticosteroid treatment.

We wish to thank Mrs Angels Gallés for excellent technical assistance and Dr Josep M Grau for helpful suggestions and comments. This work was supported by a grant from Fondo de Investigación Sanitaria (FIS 93/0603) to MCC and FIS 94/0953 to JO..

- 1 Blann AD. Von Willebrand factor as a marker of injury to the endothelium in inflammatory vascular disease. *J Rheumatol* 1993;20:1469-71.
- 2 Sixma JJ, de Groot PG. Von Willebrand factor and the blood vessel wall. *Mayo Clin Proc* 1991;66:628-33.

- 3 Nusinow SR, Federici AB, Zimmerman TS, Curd JG. Increased von Willebrand factor antigen in the plasma of patients with vasculitis. *Arthritis Rheum* 1984;27:1405-10.
- 4 Woolf AD, Wakerley G, Wallington TB, Scott DGI, Dieppe PA. Factor VIII related antigen in the assessment of vasculitis. *Ann Rheum Dis* 1987;46:441-7.
- 5 Federici AB, Fox RI, Espinoza LR, Zimmerman TS. Elevation of von Willebrand factor is independent of erythrocyte sedimentation rate and persists after glucocorticoid treatment in giant cell arteritis. *Arthritis Rheum* 1984;27:1046-9.
- 6 Persellin ST, Daniels TM, Rings LJ, Kazmier FJ, Bowie EJM, Hunder GG. Factor VIII-von Willebrand factor in giant-cell arteritis and polymyalgia rheumatica. *Mayo Clin Proc* 1985;60:457-62.
- 7 Olsson A, Elling P, Elling H. Serological and immunohistochemical determination of von Willebrand factor antigen in serum and biopsy specimens from patients with arteritis temporalis and polymyalgia rheumatica. *Clin Exp Rheumatol* 1990;8:55-8.
- 8 Nordborg E, Andersson R, Tengborn L, Eden S, Bengtsson BA. von Willebrand factor antigen and plasminogen activator inhibitor in giant cell arteritis. *Ann Rheum Dis* 1991;50:316-20.
- 9 Monteagudo J, Pereira A, Roig S, Reverter JC, Ordinas A, Castillo R. Investigation of plasma von Willebrand factor and circulating platelet aggregating activity in mitomycin C-related hemolytic-uremic syndrome. *Am J Hematol* 1990;33:46-9.
- 10 Mazzone D, Fichera A, Practico G, Sciacia F. Factor VIII activity and factor VIII-related antigen in infants with viral bronchiolitis. *N Engl J Med* 1984;311:1257-8.
- 11 Paleolog EM, Crossman DC, McVey JH, Pearson JD. Differential regulation by cytokines of constitutive and stimulated secretion of von Willebrand factor from endothelial cells. *Blood* 1990;75:688-95.
- 12 Cid MC, Campo E, Ercilla MG, Palacin A, Vilaseca J, Villalta J, et al. Immunohistochemical analysis of lymphoid and macrophage cell subset and their immunological activation markers in temporal arteritis. Influence of corticosteroid treatment. *Arthritis Rheum* 1989;32:884-93.
- 13 Fauchald P, Rygvold O, Oytresse B. Temporal arteritis and polymyalgia rheumatica. Clinical and biopsy findings. *Ann Intern Med* 1972;77:845-52.
- 14 Cid MC, DS Grant, Hoffman GS, Auerbach R, Fauci AS, Kleinman HK. Identification of haptoglobin as an angiogenic factor in sera from patients with systemic vasculitis. *J Clin Invest* 1993;91:977-85.
- 15 Reidy MA, Chopek M, Chao S, McDonald T, Schwartz SM. Injury induces increase of von Willebrand factor in rat endothelial cells. *Am J Pathol* 1989;134:857-64.