Predictors for Treatment Success and Expression of Glucocorticoid Receptor in Giant Cell Arteritis and Polymyalgia Rheumatica

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ABSTRACT. ***Objective.*** Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) generally respond well to treatment with glucocorticoids (GC). We sought to determine the value of clinical, histopathologic, immunohistochemical, and genetic findings and the expression of the glucocorticoid receptor (GR) for discriminating between patients who achieve complete remission, or partial remission, or who do not improve with glucocorticoid treatment.

Methods. We examined biopsies of the temporal artery from 60 patients, of whom 27 had GCA, 13 PMR, and 20 arteriosclerosis.

Results. Of the clinical variables evaluated, jaw claudication was correlated with the histologic classification of the biopsies ($p < 0.0001$). Erythrocyte sedimentation rate was significantly higher in patients with PMR and GCA than in patients with arteriosclerosis ($p < 0.0001$). There were significant differences between patients with GCA versus PMR in the numbers of CD3-, CD8-, and CD4-positive T cells, in CD68-positive monocytes ($p < 0.0001$), and antigen-presenting cells ($p < 0.0001$). CD138-positive and CD20-positive cells were absent in patients with PMR but present in patients with GCA ($p < 0.0001$). In GCA and chronic inflammation most monocytes and lymphocytes expressed GR (88.9%). The number of CD68-positive cells and the extent of GR-staining in chronic inflammation reflected the success of treatment in logistic regression analysis ($p < 0.05$). GR polymorphism showed that more than 90% of patients had the wild-type (homozygote) of the R23K or N363S polymorphism. There was no evidence that this polymorphism influenced response to treatment with GC (Fisher's exact test 1.0).

Conclusion. Expression of GR and the presence of CD20-, CD3-, CD4-, CD8-, CD68-, CD138-positive cells and antigen-presenting cells differ between GCA and PMR. The presence of CD68-positive cells and the extent of GR-staining in chronic inflammation are suitable to predict complete remission in GCA. (First Release August 15 2009; J Rheumatol 2009;36:2269–76; doi:10.3899/jrheum.090075)

Key Indexing Terms:
GIANT CELL ARTERITIS POLYMYALGIA RHEUMATICA TARGET CELL
GLUCOCORTICOID RECEPTOR GLUCOCORTICOIDS COMPLETE REMISSION

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Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are closely related conditions with well defined clinical characteristics but no known etiology[1]. Many authors consider that GCA and PMR are different phases of the same disease. The first clinical description of GCA was by Hutchinson in 1890[2]. Horton, *et al* in 1932 described granulomatous changes of the temporal vessels[3]. The relation of GCA and PMR was first described 20 years later by Paulley and Hughes[4].

PMR and GCA are probably polygenic diseases influenced by multiple environmental and genetic factors[5]. The theory of environmental and genetic causes is supported by data showing the incidence increases at higher latitudes and in US communities with a strong Scandinavian background. Occasionally, the disease clusters in families[6].

The histological findings in PMR are a mild synovitis, which is characterized by a predominance of macrophages and T cells, mostly CD4-positive helper cells. These features are similar to the vasculitic lesions of GCA[7]. Involved

arteries from the aortic arc are affected by focal and segmental inflammatory infiltrates and disruption of the internal elastic lamina. The histological picture in 50% of patients with GCA is granulomatous inflammation with giant cells at the junction between intima and media. Fifty percent of patients lack giant cells but display an infiltrate of mixed inflammatory cells with a predominance of lymphomononuclear cells and occasional eosinophils and neutrophils. In rare cases, the histology shows only small-vessel vasculitis surrounding a normal temporal artery[8,9].

Glucocorticoids (GC) are important therapeutic agents for various inflammatory and autoimmune diseases. There is, however, considerable variability in the sensitivity to GC across individual patients with the same diagnostic entity and across different rheumatologic diagnoses. Normally, GCA and PMR are highly responsive to treatment with GC. Rarely, patients with GCA or PMR are resistant to GC. It is unclear why GC are so effective in GCA and PMR compared with other systemic vasculitides, e.g., Wegener's granulomatosis.

GC treatment is associated with serious side effects like osteoporosis, infections, and diabetes. The mean duration of GC treatment of patients with GCA is 15–17 months and the cumulative prednisone dose about 6–6.5 g[10]. Therefore, we need clear histologic criteria to confirm the diagnosis.

Abnormalities of the number of GC receptors (GR) have been described in primary resistance to GC treatment and have been related to gene mutations[11,12]. Polymorphisms of the GR that seem to be associated with increased sensitivity to GC and a partial form of GC resistance have been identified[13].

The aim of our study was to describe clinical and genetic findings of patients with GCA and patients with PMR in contrast to a control group of patients with arteriosclerosis, and to classify biopsies of the temporal artery on the basis of histopathologic and immunohistochemical findings. We made an attempt to distinguish among patients with GCA, PMR, or arteriosclerosis by immunophenotyping. We also investigated whether there are identifiable characteristics that predict the success of treatment with GC, i.e., which (if any) of the measures (clinical, morphological, immunological, molecular biological) discriminates between patients who are highly responsive to GC, e.g., achieve complete remission (CR), and those who were less responsive, e.g., achieve only a partial remission (PR) or no remission (NC).

MATERIALS AND METHODS

Patients. All biopsies were collected in a tissue bank between 1995 and 2005. The indication for biopsy was suspected GCA in all patients. The clinical data were taken retrospectively from patients' charts. We examined biopsies of 60 patients, of whom 27 had GCA, 13 had PMR without GCA (n = 13), and 20 had arteriosclerosis. Patients with biopsy-negative GCA were excluded.

The following clinical measures were assessed and graded as present or absent: aching shoulder and hip girdles, weight loss, fever, night sweats, diabetes, jaw claudication, visual problems, headache, and hypertension. Erythrocyte sedimentation rate (ESR, mm/h), C-reactive protein (mg/dl), glucose (mg/dl), hemoglobin (g/l), leukocytes/mm^3, and creatinine (mg/ml) were meassured in most of the study patients. Antineutrophil cytoplasmic antibodies (cytoplasmic and perinuclear), antinuclear antibodies, and rheumatoid factor were not systematically assessed.

Morphological diagnosis. The diagnosis was made by an experienced pathologist at the time the biopsy was done. All diagnoses were confirmed by a second pathologist at the time of analysis of the study data. GCA was diagnosed by standard criteria. An arteritis was classified as GCA if giant cells and an inflammatory reaction related to either the elastica externa or interna were found in the vessel wall. An arteritis was classified as consistent with GCA if an inflammatory reaction in the vessel wall was observed, but no giant cells were seen.

Immunohistochemical staining. The antibodies used for immunophenotyping, the source and dilution, the classification of the antibodies, and the pH for antigen-demasking are listed in Table 1. Endogenous peroxidase blocking was done by methanol/H_2O_2. The primary antibodies were diluted in antibody diluent (Dako, Hamburg, Germany). For immunostaining we used a Techmate system and a dextran-coated peroxidase-coupled polymer system (both Dako). The final reaction product was produced by incubation in diaminobenzidine/H_2O_2 for 10 min followed by a counterstain of nuclei in hemalaun.

Assessment of staining results. The morphologic diagnosis was made in conventional H&E staining, using Elastica van Gieson staining for better identification of the elastica externa and interna. For immunophenotyping and analysis we used 400-fold magnification. All immunostained inflammatory cells in the vessel wall were classified as absent, few (1–5 cells/vessel), moderate (6–50/vessel), or heavy (> 50 cells/vessel). S100-positive cells were accepted as antigen-presenting only when small fibers could be observed. Langerhans cells of the skin served as a positive control.

Genotyping of GR polymorphisms. Following histological inspection DNA was extracted from 2 paraffin sections of 10 μm thickness. Sections were immersed in 100 μl of buffer containing 50 mM KCl, 10 mM Tris HCl (pH 8), 0.1 mM EDTA, 0.5% Tween 20, and 5% Chelex 100 (Sigma, Steinheim, Germany) and heated for 5 min at 95°C. Tissue was digested by Proteinase K incubation (0.5 mg/ml) for 2 h followed by heat inactivation of added enzymes (10 min at 97°C). Three microliters of the centrifuged DNA lysates were taken for polymerase chain reaction amplification. Two nonsynonymous polymorphic sites, N363S (rs6195) and R23K (rs6190), of the GR gene *NR3C1* were investigated using primers forward -TGT CAT TCC ACC AAT TCC CG, reverse -CCC AGA GAA GTC AAG TTG TC, and forward -AAG AAA ACC CCA GCA GTG TG, reverse -AAG AAA ACC CCA GCA GTG TG, respectively. Genotyping was carried out using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) as described[14].

Assessment of treatment response to GCC. We discriminated between NC, PR, and CR of symptoms. As only 2 instances of NC were observed we lumped NC and PR together for further analysis.

Assessment of target molecules. A target molecule had to be related to the diagnosis of GCA and observed in most of the specimens, if it would be helpful to eliminate a certain cell type.

Statistical methods. Two-sided t-test, chi-squared test or Fisher's exact test, and analysis of variance were used. $p < 0.05$ was considered to be significant and $p < 0.001$ as highly significant. $p < 0.1$ was considered a trend. A correction was made for multiple comparisons by Bonferroni criterion. A positive predictive value was calculated to determine statistical significance. We applied binary logistic regression to identify variables of interest in predicting treatment success.

RESULTS

Clinical findings. Of the clinical variables studied, ESR and jaw claudication were significantly different in patients with

PMR and GCA ($p < 0.0001$) compared with arteriosclerosis. No other variables described above were related to GCA or PMR (Table 2).

Morphological findings. GCA was characterized by a strong chronic inflammatory reaction located especially near the elastica interna or externa, often, but not always intermin-

Table 1. Antibodies used in the study.

Antibody	Source and Dilution	Classification	pH for Antigen-demasking
CD20	Dako, 1:400	Mouse monoclonal	pH 6
CD3	Dako, 1:50	Mouse monoclonal	pH 9
CD4	Labvision, 1:10	Mouse monoclonal	pH 9
CD8	Dako, 1:50	Mouse monoclonal	pH 9
CD68	Dako, 1:50	Mouse monoclonal	pH 6
CD138	Dako, 1:25	Mouse monoclonal	pH 6
S100	Dako, 1:400	Rabbit polyclonal	pH 6
CD1a	Dako, 1:50	Mouse monoclonal	pH 6
Glucocorticoid receptor	Novocastro, 1:10	Mouse monoclonal	pH 6
Mast cells	Alpha-napthyl-	AS-chloracetate esterase	

Table 2. Clinical data of study patients.

Variable	Polymyalgia Rheumatica without GCA, n = 13	Arteriosclerosis, GCA, n = 20	GCA, n = 27	p
Age, yrs, mean ± SD	69.8 ± 10.0	72.6 ± 10.5	73.4 ± 8.0	NS
Sex, n (%)				
Female	5 (38.5)	7 (35.0)	9 (33.3)	NS
Male	8 (61.5)	13 (65.0)	18 (66.6)	
Erythrocyte sedimentation rate, mm/h, mean ± SD	91.9 ± 9.3	51.6 ± 31.0	88.1 ± 11.9	***
Leukocytes, g/l, mean ± SD	11.1 ± 3.0	9.5 ± 3.1	9.4 ± 2.3	NS
C-reactive protein, mg/dl, mean ± SD	10.3 ± 10.9	3.5 ± 4.8	8.6 ± 5.1	NS
Hemoglobin, g/l, mean ± SD	116 ± 17	121 ± 18	111 ± 19	NS
Glucose, mg/dl, mean ± SD	162.0 ± 99.3	134.9 ± 79.7	116.4 ± 52.3	NS
Diabetes, n (%)	5 (40.7)	6 (35.3)	5 (20.8)	NS
ND	1	3	3	
Creatinine, mg/dl, mean ± SD	1.96 ± 2.9	0.98 ± 0.37	0.84 ± 0.29	NS
Anti-DNA	1 positive case in the arteriosclerosis group			
ANA	All negative			
RF, n (%)	0 (0)	1 (20.0)	8 (72.7)	Too few cases for analysis
ND	9	15	16	
c-ANCA (myeloperoxidase)	All negative			
p-ANCA (proteinase 3)	0	0	2 (13.3)	NS
ND	6	13	12	
Hypertonia, n (%)	3 (25.0)	13 (72.2)	12 (50.0)	NS
ND	1	2	3	
Aching in shoulder girdle, n (%)	9 (75.0)	6 (35.3)	6 (25)	NS
ND	1	3	3	
Aching of hip girdle, n (%)	5 (41.7)	0 (0)	10 (41.7)	NS
ND	1	4	3	
Impaired vision, n (%)	1 (8.3)	3 (18.8)	7 (29.2)	NS
ND	1	4	3	
Fever, n (%)	4 (33.3)	3 (20)	7 (29.2)	NS
ND	1	5	3	
Night sweats, n (%)	5 (41.7)	4 (26.7)	13 (56.5)	NS
ND	1	5	4	
Weight loss, n (%)	5 (41.7)	8 (50)	17 (73.9)	NS
ND	1	4	4	
Jaw claudication, n (%)	0 (0)	0 (0)	11 (91.7)	***
ND	2	4	15	
Headache, n (%)	5 (44.8)	10 (62.5)	17 (77.3)	NS
ND	1	4	7	

ND: not determined; NS: not significant; *** highly significant; ANA: antinuclear antibodies; RF: rheumatoid factor; c-ANCA: cytoplasmic antineutrophil cytoplasmic antibodies; p-ANCA: perinuclear ANCA.

gled with giant cells. Polymorphonuclear leukocytes were observed rarely in H&E staining. Biopsies from patients with PMR showed few lymphocytes or monocytes in temporal arteries, a finding similar to biopsies in arteriosclerosis. In GCA, endothelial cells often were lacking (Table 3).

Immunohistochemical staining of the inflammatory reaction. As shown in Table 4 and Figures 1A and B, there were significant differences between patients with GCA compared with PMR, in the number of T cells, especially the CD8 subset, and CD68-positive monocytes ($p < 0.001$; $p < 0.001$). Antigen-presenting cells were increased in GCA and in PMR. CD20-positive cells were present in 70.4% in the GCA group ($p < 0.0001$), 0% in the PMR group, and 15% in the arteriosclerosis group. CD3-positive cells were present in 96.3% of the GCA group ($p < 0.0002$), 53.8% of the PMR group, and 50% of the arteriosclerosis group. CD4- and CD8-positive cells were present, respectively, in 93.6% and 85.2% in GCA ($p < 0.0001$), 30.8% and 0% in PMR, and 25% and 20% in arteriosclerosis. CD68-positive cells were present in 85.2% of biopsies from patients with GCA ($p < 0.0001$), absent in PMR, and present in 20% of patients with arteriosclerosis. There was no significant difference in the distribution of mast cells between the 3 groups ($p = 0.0957$). CD138-positive cells were present in 70.4% of GCA, absent in PMR, and present in 15% of the arteriosclerosis group ($p < 0.0001$). Antigen-presenting cells (S100-positive) were present in 92.6%, 7.7%, and 25.5%, respectively, of patients with GCA, PMR, and arteriosclerosis ($p < 0.0001$; Figure 1c). But there were no significant differences for the CD1a-positive cells ($p = 0.0968$).

Staining of GR. The results for GR staining are shown in Table 5. GR was found in different amounts in cell nuclei with a diffuse staining pattern (Figure 1D). No immunostaining outside cell nuclei was observed. Cell types positive

Table 3. Morphological findings of the biopsies of the temporal artery.

Variable	Polymyalgia Rheumatica without GCA, n = 13	Arteriosclerosis, GCA, n = 20	GCA, n = 27	PPV	p
Cells/HPF	20.2 ± 7.9	21.3 ± 9.3	32.4 ± 10.3		**
Acute inflammatory reaction, %	0	20	44.4		NS
Chronic inflammatory reaction, %	0	15	81.5	0.88	***
Giant cells, %	0	0	48.1	1	**

HPF: high power field; NS: not significant; ** significant, *** highly significant; PPV: positive predictive value.

Table 4. Immunophenotyping of inflammatory cells.

Variable	Polymyalgia Rheumatica without GCA, n = 13	Arteriosclerosis, GCA, n = 20	GCA, n = 27	PPV	p
CD20 absent	13 (100)	17 (85.0)	8 (29.6)	0.863	**
≤ 5	0 (0)	0 (0)	5 (18.5)		
> 5	0 (0)	3 (15.0)	14 (51.9)		
CD3 absent	6 (46.2)	10 (50.0)	1 (3.7)	0.605	***
≤ 5	6 (46.2)	5 (25.0)	0 (0)		
> 5	1 (7.4)	5 (25.0)	26 (96.3)		
CD4 absent	9 (69.2)	15 (75.0)	1 (3.7)	0.743	***
≤ 5	2 (15.4)	2 (10.0)	1 (3.7)		
> 5	2 (15.4)	3 (15.0)	25 (93.6)		
CD8 absent	13 (100)	16 (80.0)	4 (14.8)	0.852	***
≤ 5	0 (0)	1 (5.0)	0 (0)		
> 5	0 (0)	3 (15.0)	23 (85.2)		
CD68 absent	13 (100)	16 (80.0)	4 (14.8)	0.852	***
≤ 5	0 (0)	1 (5.0)	0 (0)		
> 5	0 (0)	3 (15.0)	23 (85.2)		
Mast cells absent	10 (76.9)	14 (70.0)	12 (44.4)	0.862	***
≤ 5	2 (15.4)	6 (30.0)	11 (40.8)		
> 5	1 (7.7)	0 (0)	4 (14.8)		
CD138 absent	13 (100)	17 (85.0)	8 (29.6)	0.862	***
≤ 5	0 (0)	0 (0)	4 (14.8)		
> 5	0 (0)	3 (15.0)	15 (55.6)		
Antigen-presenting cells (S100)	1 (737)	5 (25.5)	25 (92.6)	0.806	***
Antigen-presenting cells (CD1a)	0 (0)	3 (15.0)	7 (25.9)		NS

NS: not significant; ** significant, *** highly significant; PPV: positive predictive value.

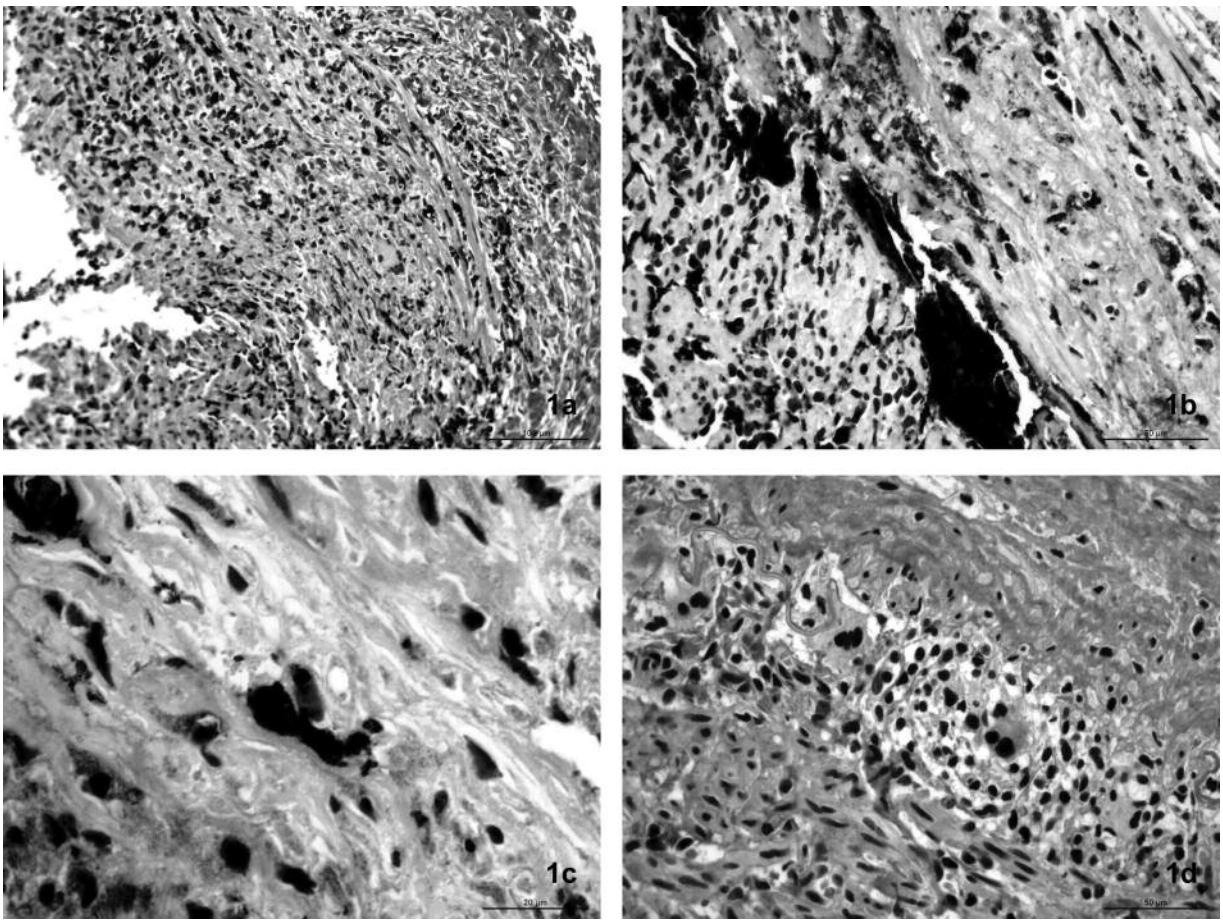

Figure 1. Immunohistochemical analysis of biopsies of the arteria temporalis from patients with giant cell arteritis. A. CD8-positive cells, magnification 200×. B. CD68-positive giant cells, magnification 400×. C. Antigen-presenting cells (S100-positive) and giant cells, magnification 400×. D. Glucocorticoid receptor staining, magnification 400×.

Table 5. Expression of glucocorticoid receptor (GR). Chronic inflammation was characterized by an infiltrate of lymphocytes and monocytes.

Expression of GR	Polymyalgia Rheumatica without GCA, n = 13	Arteriosclerosis, GCA, n = 20	GCA, n = 27	PPV	p
Endothelium	0 (0)	19 (85)	22 (81.5)		NS
Intima	9 (75)	8 (40)	23 (85.2)	0.575	***
Media	6 (46.1)	15 (75)	26 (96.3)	0.553	**
Giant cells			10 (27)		
Chronic	0 (0)	4 (20)	24 (88.9)	0.857	***

NS: not significant; ** significant, *** highly significant; PPV: positive predictive value.

for GR staining were endothelium, lymphocytes, monocytes, giant cells, fibrocytes, and myocytes. Staining intensity differed widely from absent to very strongly labeled nuclei. No immunostaining was observed in neutrophilic leukocytes.

Assessment of the GR polymorphism. More than 90% of our patients displayed the wild-type (homozygote) of the R23K or N363S polymorphism. There was no evidence that this polymorphism influenced the response to treatment with GC (Table 6).

Treatment response. When the treatment responses classified as either complete or noncomplete, including 2 cases of no change, were correlated to the expression of GR as either weakly or strongly positive, we did not find a statistically significant correlation between expression of GR in myocytes (p = 0.509), in fibrocytes of the intima (p = 0.236), endothelial cells (p = 0.4106), and lymphocytes (Table 7). Patients with a CR showed more GR-positive lymphocytes/monocytes (10/18 = 53.6%) compared with those who had a noncomplete treatment response (3/10 = 30%, p = 0.0984). This difference failed to be significant,

Table 6. Polymorphism of glucocorticoid receptor (GR).

Expression of GR	Polymyalgia Rheumatica without GCA, n = 13	Arteriosclerosis, n = 20	GCA, n = 27
Polymorphism 23KGA			
wt/wt, n (%)	13 (100)	14 (87.5)	22 (91.7)
wt/mt, n (%)	0 (0)	2 (12.5)	2 (8.3)
mt/mt, n (%)	0 (0)	0 (0)	0 (0)
Fisher's exact test 1.0			
Polymorphism 363SAG			
wt/wt, n (%)	11 (84.6)	16 (94.1)	22 (91.7)
wt/mt, n (%)	2 (15.4)	1 (5.9)	2 (8.3)
mt/mt, n (%)	0 (0)	0 (0)	0 (0)
Fisher's exact test 1.0			

wt: wild-type; mt: mutant; wt/wt: homozygous wild-type; wt/mt: heterozygous; mt/mt: homozygous mutant.

Table 7. Predictors of complete remission in patients with giant cell arteritis.

Variable	Value	SD	t-value	
CD68	0.858	0.313	2.742	**
CD8+ T lymphocytes	–0.492	0.279	–1.760	*
GR	0.059	0.035	1.697	*
CD138	–0.196	0.139	–1.410	NS
Variables without significance or trend	PMN, round cells, mast cells, CD4+ lymphocytes, CD20+ B lymphocytes, CD1a+ antigen-presenting cells, S100+ antigen-presenting cells, glucocorticoid polymorphism			
Model with morphological data	1.251	0.353	3.537	***
Model with clinical and laboratory data	1.122	1.157	0.740	NS
Variables without significance or trend	Sex, fever, leukocytes, hemoglobin, glucose, creatinine, CRP, hypertonia, diabetes			

NS: not significant; * trend, ** significant, *** highly significant.

however. From other results (numbers of B and T lymphocytes, CD4-positive T lymphocytes, CD8-positive lymphocytes, CD138-positive lymphocytes, CD68-positive lymphocytes, mast cells, neutrophil leukocytes, and round cells) assessed by conventional histologic evaluation, the number of CD68-positive monocytes was decreased in patients with PR or NC ($p = 0.02$). Patients showing more neutrophil leukocytes as compared with those lacking leukoyctes tended to have more complete remission ($p = 0.023$). All patients showing more than 5 neutrophil leukocytes/vessel had a CR. Applying binary logistic regression to our data (historical data, laboratory data, histological data, immunophenotyping, GR polymorphism) and seeking a measure that predicts CR, we found that the number of CD68-positive cells and GR staining in chronic inflammation were related to treatment response ($p < 0.05$ in both cases). We observed a trend ($t = –1.983$) for the number of CD8-positive T lymphocytes. None of the clinical data shown in Table 2 yielded either a significant prediction of a good treatment response or even a trend.

DISCUSSION

We found that CD68-positivity in GCA is a predictor for treatment success with glucocorticoids. CD68-positive cells are a hallmark of the chronic inflammatory reaction in GCA. Macrophages accumulate in the arterial wall and liberate cytokines like interleukin 6 (IL-6), IL-1ß, and transforming growth factor-ß. GC decrease the tissue accumulation of macrophages, reduce the production of eicosanoids and inflammatory cytokines, and inhibit the phagocytic function and bactericidal effects[15-17]. Macrophages are absent in the arterial wall of patients with PMR[18].

GR, the target molecule for GC therapy, is largely expressed in the vessel wall of arteria temporalis and receptor density is increased in GCA compared with arteriosclerosis or PMR. GR was found in different amounts in cell nuclei with a diffuse staining pattern. In GCA, GR was present in the endothelium and media, as compared with PMR, where GR was present only in the media and to a lesser extent than in GCA. GR in GCA was expressed in fibrocytes, fibroblasts, monocytes, giant cells, lymphocytes, and endothelium, but not in neutrophil leukocytes. The inflammatory response in GCA was chronic, not acute. GR staining of the chronic inflammatory cells was also a predictor for treatment success with GC. These findings may be important for treatment decisions. For example, patients

with weak GR and CD68 staining and a poor response to GC might be switched early in the course of treatment to an alternative treatment[19-21].

CD138-positive cells were present in about 70% of the specimens in GCA but not in specimens of PMR. There was a trend that the presence of CD138-positive cells predicts treatment success. Chatelain, *et al* found that presence of plasmocytes was a predictor for permanent visual loss in 391 patients with GCA[22].

The literature reports that B lymphocytes are rare in the vascular lesion in GCA, which is consistent with the lack of autoantibody production, immune complex deposition, or hypergammaglobulinemia, and that numbers of circulating B cells and synthesis of antibodies are affected by the administration of GC[23,24]. Rituximab, an anti-CD20 antibody and a possible target-related therapy, is not a treatment of first choice in systemic vasculitis. In GCA there are only 2 published cases and in both cases it was a rescue therapy[25,26]. In our study, in contrast to the literature, CD20-positive cells were present in about 70% in GCA but not in PMR.

Cell-mediated processes are of primary importance in GCA. The inflammatory infiltrate of affected vessels is predominantly composed of lymphocytes, macrophages, and giant cells[27]. In our study, neutrophil leukocytes were part of the inflammatory reaction of up to 50% of the patients with GCA; CD8-positive cytopathic/suppressor T cells (trend for treatment success), CD4-positive helper cells, and CD3-positive T lymphocytes dominate the inflammatory reaction in GCA. GC therapy produces a depletion of circulating T cells because of emigration, inhibition of cytokines (IL-2, principal T cell growth factor), induction of apoptosis, and decreased release from lymphoid tissue[28,29]. GC have inhibitory effects on specific immune responses mediated by T cells and B cells as well as potent suppressive effects on the effector function of monocytes. This results in reduced trafficking of leukocytes and an attenuated expression of adhesion molecules on the surface of endothelial cells and leukocytes as well. The consequence is accumulation of phagocytic cells at the site of inflammation.

T cell activation in the arterial wall requires activation of specialized antigen-presenting cells[30]. There is little information available regarding the effect of GC in human dentritic cells[31]. They decrease the number of circulating and organ-resident dendritic cells that appear to be mediated in part by GC-induced apoptosis of resident dentritic cells and CD34+ precursor-derived CD14+ dendritic cells[32,33]. In our study, S100-positive cells were an attribute for GCA, which are present in more than 90% of GCA samples and in less than 10% of samples in PMR.

All patients were biopsied because of clinical suspicion for GCA, i.e., they had clinical symptoms of GCA and PMR. This is why the clinical findings in our study are weak as predictors of the course of the disease. Even so, there were significant differences in 2 clinical findings. ESR was much higher in PMR and GCA than in arteriosclerosis; and jaw claudication was associated strongly with GCA.

Can we draw any conclusions from pretreatment clinical or morphological findings about the subsequent treatment success? Logistic regression (Table 7) shows that the number of CD68-positive cells and GR staining in chronic inflammation is a significant predictor of treatment success with GC. The amounts of CD8-positive lymphocytes and CD138-positive cells are candidates for predictors of treatment success but fall short of significance. No clinical measure, however, predicts whether GC treatment will give a complete remission or not.

We looked for clinical and genetic confounders of treatment prediction. We did not find any clinical measures or genetic variables, such as GR polymorphism, that influenced treatment success. This conclusion must be drawn with caution because of the small number of patients in the study, especially for the analysis of the GR polymorphism.

We report about possible target molecules in GCA and their distribution in the vessel wall. We found that CD68-positive monocytes and GR staining in chronic inflammation are suitable indicators to predict a complete remission in GCA, besides 2 other candidate target molecules (cells), namely CD138- and CD8-positive T lymphocytes.

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