Impact of antiplatelet therapy in the development of severe ischemic complications and in the outcome of patients with giant cell arteritis

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ABSTRACT

Objective. *To evaluate whether concomitant treatment with low-dose aspirin or other antiplatelet agents have an impact on the risk of severe ischemic complications and in the outcome of patients with giant cell arteritis (GCA).*

Methods. *A retrospective follow-up study of an unselected population of 121 patients with GCA.*

Results. *Thirty-seven patients (30.5%) received antiplatelet therapy before the onset of GCA symptoms and continued taking it during the corticosteroid treatment (30 received aspirin and 7 other antiplatelet agents). No statistically significant reduction in the incidence of ischemic manifestations (including jaw claudication, visual manifestations, cerebrovascular accidents, ischemic heart disease, and limb claudication due to large artery stenosis) was observed in this group compared with the remaining patients. When we analyzed follow-up data, we found no significant differences between groups in terms of frequency of relapses and percentage of patients recovered from GCA. Corticosteroid requirements among patients in long-lasting remission were lower in those under antiplatelet therapy, but this reduction was fairly modest, statistically non significant and thus of uncertain clinical significance. Similar results were found when only aspirin exposed patients (n=30) were compared to non-exposed patients.*

Logistic regression analysis showed that antiplatelet therapy (p=0.54, OR 1.31; 95% CI: 0.54-3.19) had not an independent protective effect against ischemic events when adjusted for age, sex, and the presence of atherosclerotic risk factors.

Conclusion. *We did not observe a significant benefit derived from the use of antiplatelet therapy in either the incidence of severe ischemic events or the disease outcome. Although our results do not discard a potential therapeutic effect of high-dose aspirin, they do not confirm its suggested protective effect in preventing ischemic complications when used at antiplatelet doses.*

Introduction

Giant cell arteritis (GCA) is the most common vasculitis in elderly people from Western countries (1). Histologic studies have demonstrated that vessel occlusion in GCA is secondary mainly to intimal hyperplasia, which is thought to be induced by a number of inflammatory mediators, particularly platelet-derived growth factor (PDGF) and interferon (IFN)-gamma (2-4). One study has shown that IFN-gamma expression correlates with clinical ischemic complications, underscoring the pivotal role of this cytokine in the pathogenesis of GCA (3). In addition, IFN-gamma microsatellite polymorphisms in patients with biopsy-proven GCA have shown that high IFN-gamma production alleles have been associated with increased incidence of visual ischemic complications (5).

Although ischemic damage in GCA is usually attributed to an occlusive vasculopathy caused by intimal hyperplasia and not by thrombosis, the potential therapeutic benefit of antiplatelet therapy in this disease is being the subject of renewed interest. In 2002, using a mouse chimera model of GCA, Weyand *et al*. demonstrated that aspirin, at doses of 20-100 mg/kg per day (equivalent to 1-2 g/day in humans), inhibits IFN-gamma production in the inflamed arterial wall much more effectively than glucocorticosteroids (6). More recently, two retrospective cohort studies have pointed out that antiplatelet and anticoagulant therapy might reduce ischemic complications

in patients with GCA, including visual loss and cerebrovascular accidents(7, 8). Since then, many clinicians have accepted the addition of low-dose aspirin to standard glucocorticoid therapy as the initial treatment of GCA (9, 10).

However, not all authors have found a protective effect of antiplatelet therapy in preventing ischemic complications (11). In view of these contradictory observations, we have reexamined whether concomitant use of low-dose aspirin or other antiplatelet agents had an impact on the risk of severe ischemic complications and in the outcome of patients with GCA in terms of frequency of relapses, percentage of patients recovered from GCA, and corticosteroid requirements.

Patients and methods

We conducted a retrospective follow-up study in 121 patients with GCA diagnosed by the Department of Rheumatology within the Hospital Universitario de Bellvitge (Barcelona, Spain) from January 1986 until December 2004. The diagnosis of GCA was made according to the 1990 ACR criteria for the classification of GCA (12): 1) age at disease onset ≥50 years, 2) new onset of headache, 3) temporal artery abnormality on examination (decreased pulses unrelated to arteriosclerosis, nodules, thickening, swelling or tenderness to palpation), 4) ESR ≥50 mm/h, and 5) a temporal artery biopsy (TAB) specimen showing vasculitis mainly characterized by mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells. Patients were diagnosed with GCA if they had a positive TAB (73% of cases) or, in cases with a negative biopsy or no biopsy, if they fulfilled the remaining four criteria and had a prompt and persistent response to corticosteroid treatment.

After diagnosis, follow-up of patients was performed by periodic examinations at our outpatient clinic (initially every 2-4 weeks and then every 2-3 months) until either patient's death or long-lasting remission, defined as absence of recurrences for at least 1 year after cessation of treatment. All patients had a sustained follow-up for an average of 3.6 years (range, 1.1 to 15.1 years).

Patients were treated with an initial dose of 40-60 mg/day of prednisone or equivalent, except 5 cases with visual manifestations at presentation who received intravenous methylprednisolone pulse therapy (1 g daily for 3 days) followed by 60 mg prednisone/day. The effective initial dose of prednisone was continued until resolution of reversible symptoms and return of inflammatory markers to normal; this usually took from 2 to 4 weeks. After that, the dose was reduced according to the treating physicians' judgment of the activity of the disease based on laboratory tests and the presence or absence of symptoms considered related to GCA (usually by a maximum of 10% of the total dose every week or every 2 weeks). The median time required to reach a prednisone maintenance dose ≤10 mg/day for the study population was 7.3 months (range, 4 to 24 months).

Inpatients and outpatient charts of patients were reviewed comprehensively to obtain clinical, laboratory, and evolution data according to a specifically designed protocol. These data were usually carefully and adequately described in the medical records. The end-point of patient follow-up was the date of the last clinic visit or the date of death. We determined, from the medical records, whether each patient had been receiving antiplatelet therapy at the time of diagnosis of GCA and grouped the sample size in 2 clinical subsets: *1*. patients who received aspirin or other antiplatelet agents at the time of diagnosis and continued to take them during GCA treatment, and *2*. patients who had not received antiplatelet therapy at all (control group).

Variables recorded included patient's age, sex, symptoms at presentation, presence of traditional risk factors for atherosclerosis (hypercholesterolemia, hypertension, diabetes mellitus, and smoking history), and results of the laboratory tests at baseline evaluation. Followup data included the number of relapses and, in patients recovered from GCA, duration of therapy and the approximate total dose of prednisone received.

Clinical definitions

Patients were considered to have severe ischemic manifestations if they suffered visual manifestations (transient visual loss including amaurosis fugax, permanent visual loss, or diplopia) or cerebrovascular accidents (stroke and/or transient ischemic attacks). In addition, to encompass all of the severe ischemic complications related to GCA, we included in this category patients with large-artery stenosis of the extremities that caused signs of occlusive manifestations (limb claudication) of recent onset, and patients with ischemic heart disease, including only acute coronary syndromes (acute myocardial infarct or unstable angina).

For the purpose of this study, severe ischemic complications were attributed to GCA if they occurred within the time between the onset of GCA symptoms and 4 weeks after the onset of corticosteroid therapy.

Relapse was defined as an increase or recurrence of GCA symptoms with elevated acute phase reactants that occurred during the reduction of the prednisone dosage or during the first month after discontinuation of therapy, as well as regression of these symptoms or signs when the dosage of medication was increased or therapy was resumed. An isolated rise in ESR was not considered sufficient for an increase in GC dose. Long-lasting was recorded as the date of permanent discontinuation of treatment without recurrence of symptoms for at least 1 year.

Statistical analysis

Continuous data were described as mean ± standard deviation (SD) and categorical variables were presented as percentages. Comparisons between groups were made using the Student *t*-test (2-tailed) for continuous variables or the Mann-Whitney U test when the assumption of normality was not achieved. To analyze categorical data, we performed a chi-square test or a Fisher exact test. Multivariate logistic regression analysis was used to identify factors independently associated with the occurrence of an ischemic event. A final model was generated to estimate the odds ratio (OR) with its

95% confidence interval (95% CI) associated with the use of antiplatelet therapy adjusting for age, sex, and the presence of atherosclerotic risk factors. Statistical significance was defined as $p \leq 0.05$.

Power analysis

According to the literature, ischemic events such as vision loss and cerebrovascular accidents occur in up to 20-50% of patients with GCA (13, 14). In our series, 28.1% (34/121) of patients presented one or more severe ischemic complications including visual manifestations, cerebrovascular accidents, ischemic heart disease, and limb claudication due to large artery stenosis; this percetange raised up to 50.4% (61/121) if we also considered the presence of jaw claudication. This prevalence is comparable with the rates described in other studies (7, 8, 15-17). In order to consider that antiplatelet therapy has a protective effect in preventing ischemic complications, the frequency of severe ischemic events in the group of patients under antiplatelet therapy should be less than 20%. With an alpha error level of 5% and a statistical power of 95%, the sample size needed to analize this question is of at least 92 patients.

Table I. Main clinical and laboratory data of the study cohort. Results are presented as mean ± standard deviation (SD) or number of cases with frequencies.

Number of patients	121	
Age (range)	74 ± 7 (56-89)	
Women/men (ratio)	84 / 37	(2.2)
Positive TAB	88	(73%)
Risk factors for atherosclerosis	41	(34%)
Clinical features		
Headache	116	(96%)
Abnormal temporal artery	74	(61%)
Jaw claudication	51	(42%)
Malaise/anorexia/weight loss	69	(57%)
Fever	10	(8%)
Polymyalgia rheumatica	63	(52%)
% of patients with severe ischemic events*	34	(28.1%)
Visual manifestations	22	(18%)
Diplopia	2	(2%)
Transient visual loss	16	(13%)
Permanent blindness	4	(3%)
Cerebrovascular accidents	5	(4%)
Limb claudication	5	(4%)
Ischemic heart disease	2	(2%)
Baseline laboratory data		
ESR (mm/h)	94.8 ± 26.3	
C reactive protein (CRP) (mg/L; Ref value ≤5)	52.6 ± 29.4	
Hemoglobin (Hb) (g/dl)	11.24 ± 1.3	
Platelets (x 10^3 cells/mm^3)	345 ± 135	
Raised ALT/AST†	12	(10%)
Raised alkaline phosphatase†	28	(23%)

*Including visual manifestations, cerebrovascular accidents, ischemic heart disease, and limb claudication due to large artery stenosis.
†Increased ALT/AST and alkaline phosphatase was considered if values at diagnosis were ≥1.5 times the normal value.

Results

The main clinical features and laboratory data of the 121 patients included in the study are summarized in Table I. Information about the clinical characteristics of these patients has been extensively reported elsewhere (18-26). The mean duration of symptoms before the diagnosis was 3.2 months. At the time of the GCA diagnosis, 37 patients (30.5%) had already been receiving antiplatelet therapy and continued taking it during the corticosteroid treatment: 30 received aspirin (100-300 mg/day), 3 ticlopidin (250 mg/day), and 4 clopidogrel (75 mg/day). Indications for this treatment included chronic ischemic heart disease in 18 patients, atrial fibrillation in 6 and previous cerebrovascular accident in 13 patients. No evidence of secondary adverse events attributable to these drugs was observed during the follow-up.

Overall, 34 of 121 patients (28.1%) had one or more severe ischemic complications (including visual manifestations, cerebrovascular accidents, ischemic heart disease, and limb claudication due to large artery stenosis): 9 out of 37 patients (24.3%) under antiplatelet therapy and 25 out of 84 patients (29.8%) not receiving such therapy (p=0.540). Similar results were found when we also included patients with jaw claudication (59.5% *vs*. 46.4%; p=0.187).

Results of the comparative analysis between the 37 patients under antiplatelet therapy and the remaining 84 patients are summarized in Table II. The demographic characteristics were similar in both groups but, as expected, atherosclerotic risk factors were more common in patients under antiplatelet therapy (64.8 *vs*. 20%; p=0.001). When comparing clinical manifestations, no statistically significant reduction in the incidence of ischemic events (including jaw claudication, visual manifestations, cerebrovascular accidents, ischemic heart disease, and limb claudication due to large artery stenosis) was observed in this group, compared to the remaining patients. Both groups also had a similar intensity of the initial systemic inflammatory response assessed by analytic parameters. When we compared follow-up data, no significant differences in the frequency of relapses and percentage of patients recovered from GCA were found between the groups. Of interest, corticosteroid requirements among patients in long-lasting remission were lower in those under antiplatelet therapy, but the difference was not statistically significant. Similar results were found when only aspirin exposed patients (n=30) were compared to non-exposed patients.

Similar to that observed in the univariate analysis, logistic regression analysis showed that antiplatelet therapy (p=0.54, OR 1.31; 95%CI: 0.54-3.19) had not an independent protective effect against ischemic events when

Table II. Comparative analysis between patients not receiving antiaggregation therapy (group 1) or under antiaggregation therapy (group 2). Results are presented as mean ± standard deviation (SD) or number of cases with frequencies.

	Group 1 (n=84)	Group 2 (n=37)	*p*
Age	73.5 ± 7.4	76.6 ± 7.8	0.03
Women/men (ratio)	62/22 (2.8)	22/15 (1.4)	0.11
Positive TAB	62 (74%)	26 (70%)	0.73
Risk factors for atherosclerosis	17 (20%)	24 (65%)	0.001
Follow-up time, mean (range) years	3.5 (1.1-15.1)	3.6 (1.2-9.5)	0.90
Clinical features			
Headache	81 (97%)	35 (95%)	0.85
Abnormal temporal artery	55 (65%)	19 (51%)	0.14
Jaw claudication	32 (38%)	19 (51%)	0.17
Malaise/anorexia/weight loss	49 (58%)	20 (54%)	0.66
Fever	9 (11%)	1 (3%)	0.14
Polymyalgia rheumatica	44 (52%)	19 (51%)	0.91
Severe ischemic complications[*]	25 (29.8%)	9 (24.3%)	0.54
Visual manifestations	17 (20%)	5 (13%)	0.37
Diplopia	2 (2%)	0 (0%)	0.34
Transient visual loss	11 (13%)	5 (13%)	0.95
Permanent blindness	4 (5%)	0 (0%)	0.17
Cerebrovascular accidents	3 (4%)	2 (5%)	0.64
Ischemic heart disease	1 (1%)	1 (3%)	0.52
Limb claudication	4 (5%)	1 (3%)	0.60
Baseline laboratory data			
ESR (mm/h)	95.9 ± 25.5	92.5 ± 28.4	0.51
CRP (mg/L; Ref value ≤5)	56.4 ± 27.9	50.4 ± 30.1	0.67
Hb (g/dl)	11.1 ± 0.9	11.2 ± 1.4	0.62
Platelets (x 10^3 cells/mm^3)	347 ± 126	342 ± 154	0.84
Raised ALT/AST[†]	10 (12%)	2 (5%)	0.34
Raised alkaline phosphatase[†]	20 (24%)	8 (22%)	0.79
Follow-up data			
Relapses	48 (57.1%)	18 (48.6%)	0.40
% of patients recovered from GCA	60 (71.4%)	25 (67.5%)	0.66
Duration of therapy (median ±SD) (months)	36.4 ± 24.3	32.6 ± 23.8	0.64
Approximate total dose of prednisone received (g)	11.4 ± 6.3	9.7 ± 5.7	0.44

[*]Including visual manifestations, cerebrovascular accidents, ischemic heart disease, and limb claudication due to large artery stenosis.
[†]Increased ALT/AST and alkaline phosphatase was considered if values at diagnosis were ≥1.5 times the normal value.

adjusted for age, sex, and the presence of atherosclerotic risk factors

Discussion

Prevention of ischemic complications is the primary goal of GCA treatment. Since low-dose aspirin has been shown to prevent ischemic events in atherosclerotic disease, Nesher *et al*. (7) addressed in a retrospective study the issue of whether aspirin might also protect against cranial ischemic events in GCA (including visual manifestations and cerebrovascular accidents). Data on 175 patients with GCA were reviewed; the main variable of the study was the effect of aspirin on the rate of cranial ischemic complications prior to the diagnosis of GCA and following the institution of glucocorticoid therapy. At the time of diagnosis of GCA, 36 of their patients (21%) had already been receiving low-dose aspirin (100 mg/day). Despite having a higher rate of atherosclerotic risk factors (38.9% *vs*. 20%; *p*=0.03), patients receiving ongoing treatment with aspirin were less likely to present with or develop cranial ischemic complications than those untreated.

The mechanism by which low-dose aspirin may inhibit GCA-related ischemic events has not yet been fully elucidated (9, 27). The evidence suggests that aspirin may function either by reducing blood vessel inflammation or by inhibiting thrombosis. Regarding the first hypothesis, it is not known whether the anti-inflammatory action of aspirin found in animal studies using doses of 20-100 mg/kg (equivalent to 1-2 g/day in humans), extend to low-dose (100 mg/day) therapy. If the benefits of low-dose aspirin in GCA arise as a result of its well-established antiplatelet effect, we should expect similar benefits upon the use of other antiplatelet agents. Supporting this latter hypothesis, more recently Lee *et al*. have published another retrospective study confirming that antiplatelet or anticoagulant therapy may reduce the risk of ischemic events in patients with GCA (8). In this study, ischemic events (visual manifestations and cerebrovascular accidents) occurred in only 11 of 68 patients (16.2%) receiving antiplatelet or anticoagulant therapy prior to the diagnosis of GCA compared with 36 of 75 patients (48%) not receiving such therapy. In this series, the prevalence of cerebrovascular risk factors (including hypertension, diabetes, hypercholesterolemia, carotid stenosis or atrial fibrillation) was also higher in patients receiving antiplatelet or anticoagulant therapy (76.5% *vs*. 61.3%; *p*=0.07). On the basis of these studies, many clinicians have accepted the addition of low-dose aspirin to standard glucocorticoid therapy as the initial treatment of GCA, at least in those patients presenting with cranial ischemic complications, although, as stated by Spiera *et al*. in an accompanying editorial (27), the study by Lee *et al*. does not demonstrate the benefit of adding aspirin or another antiplatelet agent after the diagnosis of GCA is established. In addition, these results imply that thrombosis, in a vessel compromised by inflammation, intimal hyperplasia, and stenosis, is a major contributor to ischemic complications in GCA. This fact questions the classic histologic picture of vessel occlusion in GCA, characterized by intimal hyperplasia and not by thrombosis (2-4).

These important results compelled us to re-examine whether concomitant use of low-dose aspirin or other antiplatelet agents had an impact on the risk of severe ischemic complications and in the

outcome of patients with GCA. Using also a retrospective study design, we did not observe a statistically significant reduction in the incidence of ischemic manifestations (including jaw claudication, visual manifestations, cerebrovascular accidents, ischemic heart disease, and limb claudication due to large artery stenosis) in patients treated with low-dose aspirin or other antiplatelet agents. Similar findings have also been published recently by Gonzalez-Gay and colleagues in a retrospective analysis in 210 patients with biopsy-proven GCA (11). In this study, they analyzed, as their primary objective, the potential influence of traditional atherosclerotic risk factors on the development of severe ischemic manifestations in GCA. As a part of their analyses, they also compared the subset of patients receiving antiplatelet therapy (mainly low-dose aspirin) prior to the diagnosis of GCA with their remaining patient sample. Equally, they did not identify a significant reduction in the incidence of severe ischemic manifestations in patients under antiplatelet therapy. Together, both studies bring into question the alleged significant benefit of the antiplatelet therapy in preventing the ischemic complications of GCA. The divergent results among the different studies on this topic seem not to be related with differences among populations, since the demographic characteristics of the study populations are comparable (7, 8, 11).

Another point of interest is the potential corticosteroid-sparing effect of low-dose aspirin. The potential role of aspirin as a steroid-sparing agent in the long-term treatment of GCA has been previously suggested by Weyand and colleagues (6, 28), although, to date, this has not been thoroughly explored. In their study, using an experimental animal model of GCA (temporal arteries from humans with GCA were grafted onto immunodeficient mice), Weyand *et al*. demonstrated that glucocorticosteroids (GC) and aspirin have distinct targets. GC preferentially suppresses the production of NF-κB-dependent cytokines (such as IL-1 and IL-6) in the vessel wall, but only minimally affect the synthesis of IFN-gamma. In contrast, aspirin at doses of 20-100 mg/kg (equivalent to 1-2 g/day in humans), inhibits IFN-γ production in the inflamed arterial wall more effectively than GC, but is minimally effective in inhibiting transcription of NF-κB-dependent cytokines. Therefore, these two agents seem be complementary: GC are highly effective in treating the acute-phase response and the systemic component of GCA, while aspirin, due to its inhibition of IFN-gamma synthesis, potentially suppresses the progression of intimal hyperplasia (6). Based on the data generated by this study, combined therapy with GC and aspirin could theoretically improve the management of GCA and, perhaps, aspirin could have a steroid-sparing effect on long-term treatments (6, 28). However, recommendations for aspirin dosage to obtain this anti-inflammatory effect in humans have not yet been established.

In our study, when we analyzed follow-up data, we found no significant differences between groups in terms of frequency of relapses and percentage of patients recovered from GCA. Corticosteroid requirements among patients in long-lasting remission were lower in the aspirin-treated group, but this reduction was fairly modest, statistically non significant and thus of uncertain clinical significance.

In summary, controversy exists over whether antiplatelet therapy, specially low-dose aspirin, should be added to standard glucocorticoid therapy for GCA. Two retrospective cohort studies have recently pointed out that antiplatelet and anticoagulant therapy might reduce ischemic complications in patients with GCA (7, 8). However, in our series we did not observe a significant benefit derived from the use of antiplatelet therapy in either the incidence of severe ischemic events or the disease outcome. This is consistent with some reports from other groups (11). Due to the risks related with the chronic use of aspirin in elderly patients (29, 30), it is important to gather the experience of additional groups to help clinicians in the risk-benefit-balanced decisions that they must take on a daily basis.

Our study has several limitations due to its retrospective design and the small sample size. Its retrospective nature, however, guarantees that therapeutic decisions in terms of corticosteroid tapering were not biased by the knowledge of whether or not patients were receiving aspirin. We cannot exclude that with a greater sample size of exposed patients or using higher doses of aspirin, it could show some clinical beneficial effect on the incidence of severe ischemic complications and the disease outcome. These possibilities deserve further investigation with prospective, randomized trials to clarify decisively whether the addition of low-dose aspirin or antiplatelet drugs to glucocorticoids is more effective than corticosteroids alone.

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