ARTHRITIS & RHEUMATISM
Vol. 54, No. 10, October 2006, pp 3306–3309
DOI 10.1002/art.22141

Antiplatelet and Anticoagulant Therapy in Patients With Giant Cell Arteritis

Michael S. Lee,[1] Scott D. Smith,[2] Anat Galor,[2] and Gary S. Hoffman[2]

Objective. **Vision loss and cerebrovascular accidents often complicate giant cell arteritis (GCA). Antiplatelet and anticoagulant therapy reduce the risk of stroke in other populations. We sought to determine whether antiplatelet or anticoagulant therapy reduces ischemic complications in patients with GCA.**

Methods. **A retrospective chart review for patients with GCA was conducted. Included patients fulfilled modified 1990 American College of Rheumatology criteria for GCA. Collected information included demographic data, dates of antiplatelet or anticoagulant use, vision loss or stroke, and presence of bleeding complications and cerebrovascular risk factors.**

Results. **A total of 143 patients were included with a mean followup period of 4 years. The cohort included 109 women (76%) and 34 men (24%) with a mean age of 71.8 years. A total of 104 patients (73%) had a biopsy-proven diagnosis. Eighty-six patients (60.1%) had received long-term antiplatelet or anticoagulant therapy, including 18 (12.6%) who did not start therapy until after an ischemic event had occurred. Antiplatelet agents or anticoagulants were not used in 57 patients (39.9%). Overall, 11 of 68 patients (16.2%) had an ischemic event while receiving antiplatelet or anticoagulant therapy, compared with 36 of 75 patients (48.0%) not receiving such therapy ($P < 0.0005$). Univariate analysis failed to show a statistical difference between groups in regard to cerebrovascular risk factors, age, sex, or biopsy-proven diagnosis. Bleeding complications occurred in 2 patients receiving aspirin, 1 patient receiving warfarin, and 5 patients who did not receive anticoagulant or antiplatelet therapy.**

Conclusion. **Antiplatelet or anticoagulant therapy may reduce the risk of ischemic events in patients with GCA. An increased risk of bleeding complications was not observed.**

Giant cell arteritis (GCA) is a disease of large and medium-sized vessels that affects individuals over the age of 50 years (mean age 74 years). GCA is more common in women than in men (ratio of 2–3:1) and more common in Caucasian individuals (1,2).

Ischemic events such as vision loss and cerebrovascular accidents occur in up to 20–50% of patients with GCA (3,4). These events may herald the initial disease presentation or arise after treatment with corticosteroids has begun (5,6). Ischemia and infarction result from inflammation causing myointimal thickening, stenosis, or occlusion of vessel lumen. Thrombosis may also play a role in GCA (4).

Antiplatelet and anticoagulant therapy reduce the risks of vaso-occlusive and cardioembolic stroke (7–9). However, these agents may increase the risk of bleeding complications (9,10). Some authors have suggested that adjunctive antiplatelet (11–14) or anticoagulant (15) therapy warrants consideration in the treatment of GCA. In a retrospective study, Nesher et al (11) demonstrated that aspirin prevented the cranial ischemic complications of GCA. An accompanying editorial suggested that adjunctive aspirin would likely become a paradigm shift in the treatment of GCA (14).

In light of this single retrospective series, we sought to evaluate the hypothesis that antiplatelet or anticoagulant therapy may be efficacious in GCA. We retrospectively investigated a consecutive series of pa-

Presented in part at the Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, FL, May 2005, and the 32nd Annual Meeting of the North American Neuro-Ophthalmology Society, Tucson, AZ, February 2006.

Dr. Lee's work was supported in part by an unrestricted grant from Research to Prevent Blindness. Dr. Hoffman's work was supported in part by the Harold C. Schott Foundation and the Center for Vasculitis Care and Research.

[1]Michael S. Lee, MD: University of Minnesota, Minneapolis; [2]Scott D. Smith, MD, MPH, Anat Galor, MD, Gary S. Hoffman, MD: Cleveland Clinic Foundation, Cleveland, Ohio.

Address correspondence and reprint requests to Michael S. Lee, MD, 420 Delaware Street SE, MMC 493, Minneapolis, MN 55455. E-mail: leex2679@umn.edu.

Submitted for publication January 18, 2006; accepted in revised form June 30, 2006.

tients with GCA. The primary aim was to determine whether antiplatelet therapy or warfarin affected the rate of ischemic events. We also sought to learn whether treatment with these agents caused an increase in bleeding complications.

PATIENTS AND METHODS

The Cleveland Clinic Foundation Institutional Review Board approved a search and review of medical records to identify patients with the International Classification of Diseases, Ninth Revision code for GCA. We identified patients who presented with GCA from January 1989 through November 2004. For inclusion in this study, 3 of the following 5 criteria were required: 1) age at disease onset of ≥50 years; 2) new onset of localized headache; 3) temporal artery tenderness or reduced pulse; 4) erythrocyte sedimentation rate (ESR) ≥40 mm/hour; 5) temporal artery biopsy result consistent with GCA (16,17). Other collected information included demographic data, dates of GCA diagnosis, documented initial aspirin or warfarin use, vision loss or hemispheric stroke, last followup visit, gastrointestinal or intracranial bleeding, and cerebrovascular risk factors (e.g., diabetes mellitus, hypertension, hypercholesterolemia, carotid stenosis, and cardiac arrhythmias). An event was considered GCA-related if other signs, symptoms, or laboratory evidence of a recurrence was present. GCA-related vision loss was defined as retinal artery occlusion or ischemic optic neuropathy. Visual field loss from a retrochiasmal stroke was classified as a hemispheric stroke. Cases of transient ischemic events were not included. Bleeding complications were defined as either gastrointestinal hemorrhage/ulcer or intracranial bleeding.

Intercooled Stata 8.1 for Windows (Stata Corporation, College Station, TX) was utilized for statistical analysis. Multivariate logistic regression analysis was used to identify factors independently associated with the occurrence of an ischemic event. In order to perform survival analysis, if a patient experienced more than 1 ischemic event, the date of the first event was used. Analysis was completed using a forward-adding method of variable inclusion, retaining variables with a P value less than 0.15 in order to retain potentially confounding variables and thus identify independent risk factors for an ischemic event. A final model was generated to estimate odds ratios (ORs) associated with the use of antiplatelet or anticoagulant therapy, adjusting for age, sex, and other cerebrovascular risk factors.

RESULTS

One hundred forty-three patients met the inclusion criteria for final analysis (Table 1). There were 109 women (76%) and 34 men (24%) with a mean age of 71.8 years (range 50–93 years). The group consisted of 136 Caucasians (95%), 1 Asian (<1%), and 6 African Americans (4%). A total of 104 patients (73%) had a biopsy-proven diagnosis. The mean followup time was 53.8 months for the antiplatelet/anticoagulant-treated group and 46.7 months for the untreated group. There was a total of 45 vision loss events (31.5%) and 6 ischemic hemispheric strokes (4.2%). Of the patients with ischemic stroke, 1 had experienced both vision loss and stroke at the time of presentation. One patient was judged to have had an embolic stroke immediately following aortic valve replacement. Two patients experienced a stroke of indeterminate cause (see statistical analysis below).

Table 1. Characteristics of patients with GCA treated or not treated with antiplatelet or anticoagulant therapy*

	Treated	Not treated	P
Age, years	72.0	71.7	NS
Female, %	72.1	80	NS
ESR, mm/hour	78.2	81.0	NS
Platelet count, $\times 10^3/mm^3$	387	385	NS
Biopsy-proven diagnosis, %	73.5	72	NS
Followup, months	53.8	46.7	NS
Cerebrovascular risk factors, %	76.5	61.3	0.07
Ischemic events, %	16.2	48	<0.0005
Bleeding complications, %	3.5	8.8	NS

* Except where indicated otherwise, values are the mean. Treated patients received aspirin, clopidogrel, or warfarin. Untreated patients did not receive antiplatelet or anticoagulant therapy. GCA = giant cell arteritis; NS = not significant ($P > 0.20$); ESR = erythrocyte sedimentation rate.

All except 3 of the visual events and hemispheric strokes occurred at the time of GCA diagnosis. Of the events that occurred after the diagnosis of GCA was made, 1 involved a patient who was receiving aspirin therapy and 2 involved patients who were not.

Antiplatelet or anticoagulant therapy. Eighty-six patients (60.1%) were being treated with aspirin, clopidogrel, or warfarin at some point during the course of treatment for GCA. However, 18 patients (12.6%) did not start therapy until after an ischemic event, leaving 68 patients (47.6%) receiving antiplatelet or anticoagulant therapy and with no history of an ischemic event. Fifty-seven patients (39.9%) were not receiving antiplatelet or anticoagulant therapy. Ascertainment of occasional or intermittent aspirin dose was not possible in many cases. Overall, 11 of 68 patients (16.2%) had an ischemic event while receiving therapy compared with 36 of 75 patients (48.0%) not receiving continuous antiplatelet or anticoagulant therapy ($P < 0.0005$). There were no significant differences between the groups with regard to age, sex, or biopsy-proven diagnosis (Table 1).

Cerebrovascular risk factors. A total of 99 patients (69.2%) had one or more documented cerebrovascular risk factors such as hypertension, diabetes, hypercholesterolemia, carotid stenosis, or atrial fibrilla-

Table 2. Characteristics of patients with or without ischemic events secondary to GCA*

	Ischemic event	No ischemic event	*P*
Age, years	71.1	73.3	0.15
Female, %	67.4	80.4	0.10
ESR, mm/hour	66.3	85.5	0.03
Platelet count, $\times 10^3/mm^3$	392	383	NS
Biopsy-proven diagnosis, %	76.1	71.1	NS
Cerebrovascular risk factors, %	67.4	69.1	NS
Aspirin at time of event, %	17.4	48.5	<0.0005
Warfarin at time of event, %	4.4	13.2	0.04†
Clopidogrel at time of event, %	2	1	NS

* Except where indicated otherwise, values are the mean. An ischemic event represents vision loss or hemispheric stroke secondary to GCA. See Table 1 for definitions.
† By multivariate logistic regression analysis.

tion. Of the patients with risk factors, 53 (53.6%) were receiving antiplatelet or anticoagulant therapy, while 46 (46.5%) were not. At least 1 cerebrovascular risk factor was present in 76.5% of the patients receiving antiplatelet or anticoagulant therapy, compared with 61.3% of the patients not receiving such therapy (Table 1). One or more risk factors were present in 67.4% of the patients with an ischemic event, compared with 69.1% of the patients who did not have an ischemic event (Table 2).

Bleeding complications. A total of 8 patients experienced a bleeding complication. One patient receiving aspirin had an occipital hemorrhage. Gastrointestinal bleeding or ulceration occurred in 5 patients (3.5%) who were receiving prednisone alone, 1 (0.7%) who was taking prednisone plus aspirin, and 1 (0.7%) taking prednisone plus warfarin ($P = 0.1$)

Statistical analysis. Univariate analysis failed to show a statistical difference between groups in regard to cerebrovascular risk factors, age, sex, or a biopsy-proven diagnosis. Initial ESRs were higher in patients who did not experience an ischemic event (85.5 mm/hour versus 66.3 mm/hour; $P = 0.03$). Logistic regression analysis showed that aspirin (OR 0.18, $P < 0.0005$) and warfarin (OR 0.17, $P < 0.04$) each demonstrated an independent protective effect against ischemic events when adjusted for age, sex, and the presence of cerebrovascular risk factors.

Two patients experienced an ischemic stroke that may or may not have been related to GCA. One patient receiving warfarin had atrial fibrillation and active GCA at the time of the stroke. The other was not receiving antiplatelet or anticoagulant therapy, and available data did not indicate a definitive relationship to GCA. When these patients were excluded from the analysis, the overall results were not affected.

DISCUSSION

Our study confirms recent observations by Nesher and colleagues (11), who reported that aspirin reduced the risk of cranial ischemic complications in patients with GCA. The demographics and features of GCA in the patients in our study were very similar to those reported by others, including Nesher et al. Our study differs from that by Nesher and colleagues in that it includes patients receiving antiplatelet therapy other than aspirin as well as patients receiving warfarin. In both studies, patients were less likely to have an ischemic event if they were receiving antiplatelet therapy in addition to corticosteroids for GCA. Both studies found similar ORs for patients treated with antiplatelet agents (0.20 and 0.18). Additionally, in our study, multivariate analysis showed an OR of 0.17 for an ischemic event among patients receiving anticoagulants.

Thrombocytosis, with platelet counts of $>400{,}000/mm^3$, occurs commonly in active GCA (18,19). Liozon et al (12) suggested that patients with thrombocytosis may be more likely to experience vision loss, conceivably from an increased risk of clotting. Other studies have found no difference in outcome associated with thrombocytosis (19).

Should adjunctive antiplatelet therapy be considered in the treatment of GCA based on these data? Taken together, our study and that by Nesher and colleagues (11) show a significant reduction in the risk of ischemic events in the group treated with antiplatelet or anticoagulant therapy. Patients were generally started on antiplatelet or anticoagulant therapy because they had cerebrovascular risk factors. We would expect the group with more risk factors to experience a greater frequency of ischemic events than those without risk factors if antiplatelet or anticoagulant therapy had no effect on the outcome. However, fewer ischemic events occurred in the group receiving such therapy, making a strong argument for the use of antiplatelet or anticoagulant treatment to reduce the frequency of ischemic events in GCA.

Intracranial or gastrointestinal hemorrhage may occur more frequently with the use of antiplatelet or anticoagulant medications (9,10). Corticosteroid use may also increase the risk of gastrointestinal hemorrhage or ulceration. In our study, nonfatal bleeding complications developed in only 2 of 66 patients (3%) receiving aspirin and 1 of 20 patients (5%) receiving

warfarin. In comparison, 5 of 57 patients (8.8%) receiving prednisone alone experienced gastrointestinal bleeding or ulceration. Whether the risk of clinically apparent hemorrhage would be greater in a larger cohort is unknown.

Our study has several limitations. Retrospective studies have inherent flaws that include the lack of uniformity in record keeping and available data for acquisition. The Cleveland Clinic Foundation is a tertiary care center, and one may argue that patients seen there may not be representative of those in the general community. However, as has been the case with many recent large clinical studies of GCA, we used the 1990 American College of Rheumatology criteria for diagnosis of GCA (16,17). The disease characteristics of our patients are remarkably similar to those from other large prospective and retrospective series, suggesting that our observations are generalizable for GCA (2,3,12,16,20). We also recognize that patients may not consider aspirin a "medication" and may fail to identify it to their physicians on their list of medications. However, we have no reason to suspect that patients with or without an ischemic event would differ in the frequency of reporting this information.

Our results suggest that antiplatelet or anticoagulant therapy may reduce the risk of vision loss or hemispheric stroke in patients with GCA. An increased risk of bleeding complications was not observed in this group. Low-dose aspirin is relatively well tolerated and safe. Based on the findings of this retrospective study, we recommend that if there are no contraindications, adjunctive low-dose aspirin be considered in the treatment of patients with GCA. We also believe that our results provide a rationale for a prospective, randomized, placebo-controlled trial to further determine the role of adjunctive antiplatelet therapy in GCA.

REFERENCES

1. Salvarani C, Crowson CS, O'Fallon WM, Hunder GG, Gabriel SE. Reappraisal of the epidemiology of giant cell arteritis in Olmsted County, Minnesota, over a fifty-year period. Arthritis Rheum 2004;51:264–8.
2. Liu NH, LaBree LD, Feldon SE, Rao NA. The epidemiology of giant cell arteritis: a 12-year retrospective study. Ophthalmology 2001;108:1145–9.
3. Salvarani C, Cimino L, Macchioni P, Consonni D, Cantini F, Bajocchi G, et al. Risk factors for visual loss in an Italian population-based cohort of patients with giant cell arteritis. Arthritis Rheum 2005;53:293–7.
4. Galetta SL. Vasculitis. In: Miller NR, Newman NJ, editors. Walsh & Hoyt's clinical neuro-ophthalmology. 5th ed. Baltimore: Williams & Wilkins; 1998. p. 3755–82.
5. Hayreh SS, Zimmerman B. Visual deterioration in giant cell arteritis patients while on high doses of corticosteroid therapy. Ophthalmology 2003;110:1204–15.
6. Collazos J, Garcia-Monco C, Martin A, Rodriguez J, Gomez MA. Multiple strokes after initiation of steroid therapy in giant cell arteritis. Postgrad Med J 1994;70:228–30.
7. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71–86.
8. Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med 2001;345:1444–51.
9. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano DM, Manson JE, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293–304.
10. Weisman SM, Graham DY. Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. Arch Intern Med 2002;162:2197–202.
11. Nesher G, Berkun Y, Mates M, Baras M, Rubinow A, Sonnenblick M. Low-dose aspirin and prevention of cranial ischemic complications in giant cell arteritis. Arthritis Rheum 2004;50:1332–7.
12. Liozon E, Herrmann F, Ly K, Robert PY, Loustaud V, Soria P, et al. Risk factors for visual loss in giant cell (temporal) arteritis: a prospective study of 174 patients. Am J Med 2001;111:211–7.
13. Weyand CM, Kaiser M, Yang H, Younge B, Goronzy JJ. Therapeutic effects of acetylsalicylic acid in giant cell arteritis. Arthritis Rheum 2002;46:457–66.
14. Hellmann DB. Low-dose aspirin in the treatment of giant cell arteritis. Arthritis Rheum 2004;50:1026–7.
15. Buono LM, Foroozan R, de Virgliis M, Savino PJ. Heparin therapy in giant cell arteritis. Br J Ophthalmol 2004;88:298–301.
16. Hoffman GS, Cid MC, Hellmann DB, Guillevin L, Stone JH, Schousboe J, et al, for the International Network for the Study of Systemic Vasculitides (INSSYS). A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum 2002;46:1309–18.
17. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122–8.
18. Foroozan R, Danesh-Meyer H, Savino PJ, Gamble G, Mekari-Sabbagh ON, Sergott RC. Thrombocytosis in patients with biopsy-proven giant cell arteritis. Ophthalmology 2002;109:1267–71.
19. Costello F, Zimmerman MB, Podhajsky PA, Hayreh SS. Role of thrombocytosis in the diagnosis of giant cell arteritis and differentiation of arteritic from non-arteritic anterior ischemic optic neuropathy. Eur J Ophthalmol 2004;14:245–57.
20. Gonzalez-Gay MA, Blanco R, Rodriguez-Valverde V, Martinez-Taboada VM, Delgado-Rodriguez M, Figueroa M, et al. Permanent visual loss and cerebrovascular accidents in giant cell arteritis: predictors and response to treatment. Arthritis Rheum 1998;41:1497–504.