Antiplatelet Therapy in the Treatment of Takayasu Arteritis

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Takayasu arteritis (TA) is a chronic idiopathic inflammatory disease that affects large vessels, mainly the aorta and its major branches, including the coronary, carotid, pulmonary and renal arteries. Vessel inflammation and subsequent intimal proliferation of the arterial wall may lead to lumen stenosis and occlusion, while aneurysms may result from an inflammatory process involving the elastic lamina of the arteries. First-line medical treatment for TA is the use of corticosteroids as anti-inflammatory agents. There is evidence that long-term corticosteroid therapy contributes to improvement of angiographic features. Immunosuppressive drugs are used only as a supplementary therapy because of their adverse effects. Adjunctive antiplatelet or anti-hyper-tensive agents are recommended as second-line medical treatment in patients with TA. Studies support the use of anti-platelet agents in TA. Numano et al. reported that levels of plasma thromboxane B2 (TXB2) and platelet P-selectin were significantly higher, especially during the active phase, and plasma cyclic adenosine monophosphate levels were significantly lower in patients with TA than healthy subjects. They also showed that mean plasma levels of TXB2 and 3 μmol/L ADP-induced platelet aggregation from the affected side were significantly higher than in samples from the non-affected side, respectively. Administration of 80 mg of aspirin led to significant decreases in platelet aggregation and plasma levels of TXB2 compared with a 40-mg regimen. Furthermore, Akazawa et al. demonstrated that platelet and coagulation activities are significantly increased in patients with TA even during the inactive stages. These findings suggest that long-term treatment with aspirin is effective in preventing thrombus formation in surface-damaged blood vessels. No previous study, however, has demonstrated the clinical efficacy of long-term antiplatelet therapy in patients with TA.

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In this issue of the Journal, de Souza et al. have demonstrated that antiplatelet therapy with aspirin reduces the risk of acute ischemic events, in particular cerebrovascular and cardiovascular, in patients with TA. The aim of that study was to evaluate whether antiplatelet and anticoagulant therapy were sufficient to prevent acute ischemic events in TA patients. Forty-eight patients with TA were evaluated retrospectively for treatment and arterial ischemic events. Antiplatelet and anticoagulants were used in 62.5% and 12.5% of patients with TA, respectively. Aspirin was used by 29 of 30 patients (97%) and ticlopidine by 1 patient (3%). One patient was using aspirin and clopidogrel in combination. Most aspirin-treated patients took aspirin at a daily dose between 100 mg and 200 mg. Acute ischemic events occurred in 14 patients (29.2%). TA patients in whom an acute ischemic event occurred used significantly less antiplatelet therapy (14.3%) than those without ischemic events (82.4%), although there was no significant difference in the use of an anticoagulant. In a multivariate model, antiplatelet therapy was associated with a reduction of arterial ischemic events over time.

Giant cell arteritis (GCA) is also a chronic inflammatory disease of the large elastic arteries similarly to TA, although both have different clinical features, age of onset, and ethnic distribution. Nesher et al. demonstrated that patients receiving low-dose aspirin (75–150 mg) were 5-fold less likely to experience cranial ischemic complications compared with GCA patients who were not receiving aspirin therapy. Therefore, low-dose aspirin is recommended for all patients with GCA unless there is contraindication. A previous study using an animal model of GCA showed that aspirin and corticosteroid have complementary anti-inflammatory effects. This evidence suggests that aspirin may work on both reduction of vessel inflammation and inhibition of platelet aggregation, which may also warrant a sufficient dose of aspirin in patients with TA.

The main issue of the treatment with antiplatelet therapy is gastrointestinal (GI) hemorrhage. In previous studies, estimates of the annual risk of GI bleeding attributable to low-dose aspirin range from approximately 0.2–1.0%. The risk of fatal GI hemorrhage due to low-dose aspirin is of lower magnitude. Among 30 aspirin-treated patients with TA, only 1 (3.3%) had an episode of upper GI bleeding during the follow-up period, although the combination of steroids and aspirin may further increase the rate of upper GI bleeding. Although these safety outcomes need to be interpreted with caution due to the overall small number of patients, the findings suggest that aspirin therapy was safe, supporting its use in patients with TA in the absence of contraindications.

The de Souza study has some limitations, many of them inherent to its retrospective design. Although the size of the cohort was relatively large for an infrequent pathology such as TA, the absolute number of patients and consequently the number of arterial ischemic events was small and, thus, the use of a multivariate analysis that included several covariates may be a misleading strategy to find independent predictors.
In addition, an important feature predicting prognosis of TA, the angiographic classification that ranges from stage I to V, is surprisingly not included in the analysis. Of note, ischemic events occurred in 14 patients, who were mostly stage V (85%). Advanced stages have been associated with impaired clinical outcomes, including mortality. Therefore, although the authors concluded that antiplatelet therapy with aspirin is recommended for the entire spectrum of TA, it would have been very important to investigate its relative efficacy among different TA stages. Additionally, aspirin was the most common antiplatelet agent in the study. Therefore, the efficacy of other antiplatelet agents, such as clopidogrel or cilostazol, is not clear. Indeed, future studies examining other anti-thrombosis therapies will provide more clarity on the benefit of adjunctive antiplatelet therapy in patients with TA.

References