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Evidence-based Role of Aspirin in Giant Cell Arteritis: A Literature Review

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Abstract

Giant cell arteritis (GCA), or temporal arteritis, is a medium to large vessel vasculitis seen in the elderly. Its presentation varies from fever of unknown origin to cranial ischemic complications including complete vision loss. The early initiation of steroids is key to preventing complications of GCA. Here we discuss the role of aspirin in the treatment of GCA, both as an antithrombotic agent and its increasingly utilized anti-inflammatory properties. The aim of this review article is to examine the evidence behind the use of aspirin as an adjunct to steroids for the prevention of cranial ischemic complications.

Keywords: Aspirin, Giant cell arteritis, Prednisone, Antiplatelets, Anticoagulants

Giant cell arteritis (GCA) is a form of vasculitis affecting the medium and large sized vessels. It is a disease of the older population with an estimated mean age of 70[1] and has an incidence of 18 cases per 100,000 people in those over 50 years old.[2] GCA is more likely to affect females than males with a female-to-male preponderance of 2–6:1.[3–5] The clinical presentation varies depending on the arteries involved but the classic features of GCA include headache, scalp tenderness, jaw claudication, and visual impairment which can be insidious or acute. Constitutional symptoms of fatigue, malaise, low grade fever, anorexia and weight loss frequently accompany the classic symptoms.[6,7]

Empiric treatment should be promptly initiated upon suspicion as GCA is a medical emergency that can cause irreversible visual loss.[3,5,8] Giant cell arteritis symptoms can be successfully abated with glucocorticoids but relapses are common and can be seen during or after steroid taper. The risk of recurrent vision loss is estimated to be 7% in 3 years, while the risk of relapse increases to 77% when steroids are discontinued within the first year.[9] Extensive and prolonged use of glucocorticoids are associated with severe side effects including but not limited to weight gain, mood instability, gastric bleeding, osteoporosis and adrenal crisis. Steroid-sparing agents are therefore required in patients with frequent relapse or those at high risk of relapse to avoid these aforementioned side effects. Table 1 lists the commonly prescribed steroid-sparing agents for giant cell arteritis with their mechanism of action.

The catastrophic complications of GCA can extend beyond permanent visual loss to include cerebrovascular ischemia, scalp necrosis, tongue infarction, limb ischemia and aortic dissection.[10,11] The pathophysiology of these feared complications stems from arterial inflammation with subsequent stenosis and occlusions, the end result of which is ischemia.[11] Ischemia involving the structures of the eye give rise to a myriad of visual impairments ranging from transient visual loss (amaurosis fugax) to complete visual loss.[12]

The role of aspirin in the treatment of GCA has been debated for many years. While it was initially recommended for use in GCA by The European League Against Rheumatism (EULAR) and The British Society for Rheumatology (BSR), more recently rheumatologists have questioned its role

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Table 1. Mechanism of Action of Glucocorticoid sparing agents for giant cell arteritis.

Drug Class	Mechanism of action
Methotrexate	Inhibition of ATIC leading to intracellular accumulation of AICAR and suppressing inflammatory and immune reactions.
Tocilizumab	Interleukin-6 receptor inhibitor leading to reduction in cytokine and acute phase reactant production
Ustekinumab	IL-12 and IL-23 blockers which decreases T helper (Th) 1 and Th 17 cells.
Azathioprine	Incorporate into DNA and halts replication

given the conflicting data available from retrospective studies and concerns about the risk of gastrointestinal bleeding in the elderly.[13,14] In 2020 EULAR reversed its initial stance recommending that antiplatelet therapy in GCA be limited to patients with cardiovascular indications or at very high risk of ischemic complications. This change in viewpoint ignited the authors' curiosity to research the subject matter.[29] We performed a comprehensive literature review of articles evaluating the use of aspirin in GCA published since 2000. 72 articles were initially identified which were scrutinized and finally narrowed to 30 articles which were then reviewed in the writing of this manuscript.

Aspirin, also known as acetylsalicylic acid, irreversibly inactivates cyclooxygenase to suppress the production of prostaglandins and thromboxane A2. The blockage of thromboxane A2 formation inhibits downstream platelet aggregation which in turn mediates an anti-thrombotic effect that forms the basis of using aspirin to prevent ischemic events.[15]

In GCA ischemia occurs as inflammation results in narrowing of the vessel lumen which impedes forward blood flow. While steroids will rapidly improve the systemic symptoms of GCA, the inflammatory infiltrates in the vessel wall take longer to resolve. There is an increasingly recognized need to utilize agents that will target the inflammatory process in GCA at a molecular level. Weyand et al. undertook a prospective study using mice chimeras that had been engrafted with inflamed temporal arteries to mimic GCA that were then treated with aspirin or dexamethasone. They found that dexamethasone suppressed transcription of INF-γ by $\geq 85\%$ ($P = 0.034$), whereas aspirin suppressed its transcription by 90% ($P = 0.015$). Contrary to that, dexamethasone overwhelmingly suppressed macrophage/NF-κB production of IL-6 ($P = 0.007$) and IL-1β ($P = 0.014$), whereas the effect of aspirin was much less pronounced with IL-1β production continuing at 66% ($P = 0.223$) and IL-6 production only reducing to 51% ($P = 0.043$). They then hypothesized that if inflammation in GCA is mediated through both the NF-κB pathway (via IL-6 and IL-1β, which dexamethasone inhibits) and the INF-γ pathway (which aspirin inhibits), then simultaneous use of the two agents might provide a synergistic effect that could potentially speed up the clearance of inflammatory infiltrates in vessel wall to restore blood flow and prevent or reduce the severity of ischemic complications.[16] Kaiser and colleagues led further credence to this theory when they found a correlation between the expression levels of INF-γ and ischemic complications in GCA.[17]

Two studies carried out by Nesher and Lee have been the main catalyst for the adoption of aspirin use at the initiation of GCA treatment. Lee et al. retrospectively studied the role of antiplatelets and anticoagulation in GCA patients. Out of the 143 patients studied 104 had biopsy-proven diagnosis of GCA. 60.1% of the patients received either antiplatelets or anticoagulants with 16.2% of those patients developing ischemic events compared to the 48.0% ischemic rate in those not treated with antiplatelet nor anticoagulant agents ($P < 0.0005$). This data demonstrated the benefit of antiplatelet or anticoagulant therapy in reducing ischemic events in GCA patients, notably without an increased risk of bleeding complications.[19] Similarly, Nesher et al. published a retrospective study of 166 GCA patients in which they compared cranial ischemic complications (CICs) both at presentation and after 3-month follow up period.[18] At time of GCA diagnosis, patients who happened to be on aspirin for cardiovascular indications had a lower CIC rate (8%) on presentation compared to those not on aspirin (29%) ($p = 0.01$) despite their increased baseline risk of ischemic complications. Likewise, when the same patients were evaluated at the 3-month mark; CICs occurred in 3% of patients who were started on aspirin for GCA compared to 13% of patients in the group not treated with aspirin ($P = 0.02$). This decline in CIC from 13% to 3% would translate into 10 patients needing to be treated to prevent 1 CIC.[18] Now, this retrospective study should be interpreted with caution as it does not carry the weight a Randomized Controlled Trial. Some of the limitations of the study include the lack of a predefined protocol and also the potential that a confounding variable affecting CICs might not have been accounted for such as cardiovascular modifiers like smoking and statin use that were not included in the evaluation.

Despite its limitation, this effect remains remarkable especially given the potential risk of permanent blindness in GCA.

A case series of five patients was detailed by Alsolaimani et al. in which all GCA patients received aspirin in addition to prednisone. Two out of the five patients had full neurological recovery while three had lingering neurological sequelae.[20] Souza et al. carried out a randomized control trial of 45 GCA patients treated with aspirin and steroids. They found aspirin had a protective effect against relapse (OR 0.02, P = 0.023) after adjusting for age, gender, and ethnicity, further supporting the protective effect of aspirin as an adjunct to steroids, although some of the study participants did receive methotrexate as a steroid-sparing agent.[21]

The previously-cited studies all supported the use of aspirin in GCA but more recently authors have called into question this approach and voiced concerns about the risk of bleeding complications. Spiera et al. postulated that the main reason for conflicting results when aspirin use in GCA is evaluated is because the principal cause of ischemic complications is intimal hyperplasia and not thrombosis.[23] J Narvaez and colleagues undertook a retrospective analysis of 121 patients diagnosed with GCA using temporal artery biopsy or through fulfilment of the 1990 ACR classification criteria. They compared patients who were on antiplatelet therapy (n = 37) prior to diagnosis with continuation post-diagnosis versus a control arm of patients who did not receive antiplatelet therapy (n = 84). The rates of severe ischemic complications, defined as severe visual manifestations, cerebrovascular accidents, ischemic heart disease and limb claudication, were 24.3% (9/37) in the intervention group compared to 29.8% (25/84) with a P value of 0.54. When the definition of severe ischemic complication was expanded to include jaw claudication, the incidence of ischemic events increased to 46.4% in the intervention and 59.5% in control group (P = 0.187). This reduction in ischemic events in the antiplatelet group, while non-significant, was noted despite the increased atherosclerotic risk factors in that group. There was no significant difference between the two groups in terms of frequency of relapse, percentage recovery from GCA, or duration of treatment. The group receiving antiplatelets did appear to benefit from a lower cumulative dose of steroids.[22]

Berger and colleagues hypothesized that if platelet aggregation was the root cause of ischemia in GCA then an association should be seen between ischemic events in GCA with higher platelet size and count or platelet inhibition by aspirin. They carried out a retrospective analysis of 85 patients with GCA diagnosed through the 1990 ACR classification criteria or positive temporal artery biopsy with GCA evidence of AION or large-vessel vasculitis on PET scan. Out of the 85 patients, 26% (22/85) were treated with aspirin with a 68% incidence of ischemic events and a 32% incidence of severe ischemic events in the aspirin-treated group. Using multiple regression analysis they found that use of aspirin was associated with non-significant decreased risk of both ischemic and severe ischemic events with respective odds ratio of 0.87 (95% CI 0.25-3.08 P = 0.83) and 0.86 (95% CI 0.25-2.96 P = 0.81) Thrombocytosis and mean platelet volume (MPV) were equally associated with a non-significant increased risk of both ischemic and severe ischemic events.[24] Gonzalez-Gay et al., in 2005 also noted no difference in platelet counts between those with and without severe ischemic events using the largest published GCA cohort of 240 patients.[25] Thus, at a pathological level available literature has not been able to demonstrate with statistical significance that it is indeed the antiplatelet property of aspirin which reduces ischemic complications. A systemic review by Fraser et al. evaluating all treatments in GCA did recommend the use of aspirin in preventing ischemic complications of GCA basing their decisions on the statistically significant results of Nesher and Lee.[26] One can hypothesize that Lee et al. results was amplified because a high percentage of the cohort were treated with aspirin.[19]

Cranial ischemic complications (CICs) are usually seen at presentation but can present later during ongoing steroid therapy, posing treatment challenges. While it is not possible to prevent the CICs that are present at the time of diagnosis, it is possible to prevent the CICs that occur later. Pipitone et al. found that patients at increased risk of vision loss were more likely to be of older age, have lower ESR values, and fewer systemic symptoms.[27] In the same vein, Nesher et al. found that male gender and occurrence of transient cerebro-ophthalmic ischemic episodes (COIEs) were positive risk factors and that the presence of CIC at presentation increases the risk of subsequent CICs.[19] With that finding in mind, GCA patients at high risk of CICs should have early aggressive treatment, while those at low risk of CICs may be started on less aggressive regimens with the prospect of avoiding steroid-related adverse events.[18]

Treatment of GCA is not without risk, the most concerning one being gastrointestinal (GI) bleeding especially when high dose steroids are being utilized. As physicians living by the Hippocratic Oath of “do no harm”, it is imperative to perform a risk-

Table 2. Compares effect of aspirin on reducing ischemic complications of Gca.

Authors	Study design	N	Population/inclusion criteria	Treatment groups OR intervention	Control Group	Primary end point	Outcome treatment group
Nesher et al.	Retrospective	166	GCA on temporal artery biopsy or 1990 ACR criteria	Prednisone and ASA	Prednisone	CIC both at presentation and during follow up	ASA use reduced both: CIC at presentation (OR 0.3 p = 0.06) and CICs follow up (OR 0.2 P = 0.02)
Lee et al.	Retrospective	143	GCA diagnosed by TAB or ACR GCA criteria (1980−2004)	Prednisone plus ASA or clopidogrel or warfarin	Prednisone	Occurrence of any ischemic events.	Ischemic event rate 16.2% vs 48% (p < 0.005). Within intervention subgroups: ASA (OR = 0.18 P < 0.0005); warfarin (OR = 0.17 p < 0.04)
Narvaez	Retrospective	121	GCA diagnosed by TAB or ARC GCA criteria 1990	Prednisone plus ASA, clopidogrel or ticlopidine	Prednisone	Occurrence of severe ischemic complications	Severe ischemic complications in antiplatelet group (24.3 vs 29.8% P = 0.54)
Berger et al.	Retrospective	85	GCA diagnosed by ACR GCR criteria 1990 or positive TAB	ASA with glucocorticoids	glucocorticoids	Association of ischemic events with ASA use	ASA reduced risk of ischemic events OR 0.87 (P = 0.83) and severe ischemic events OR 0.86 (P = 0.81)
Souza et al.	Retrospective cohort	45	ACR criteria diagnosed GCA	ASA with glucocorticoids	glucocorticoids	Demographic features, clinical manifestations, treatments and outcomes of GCA in Brazilian cohort	ASA use associated with lower relapse when adjusted for age, gender
Weyand et al.	Chimeric mouse model (Experimental)		Mice chimera engrafted with inflamed temporal arteries	Injections of ASA 100 mg/kg vs indomethacin vs dexamethasone 500 μg/kg for 3 weeks	Injections of saline	Transcription of IL-1β and NF-κB	Suppression of INF-γ transcription by ASA 90% (P = 0.015) vs Dexamethasone 85% (p = 0.034) IL-1β production continued with ASA at 66% (P = 0.223) vs profound suppression by dexamethasone (P = 0.014). IL-6 production reduced by ASA to 51% (P = 0.043) vs profound suppression by dexamethasone (P = 0.007)

N- Patient Number, CIC-cranial ischemic complications, TAB- Temporal artery biopsy, GCA-giant cell arteritis, ACR- American college of rheumatology, ASA aspirin.

benefit analysis to identify patients mostly like to benefit and on the other hand recognize patients at increased risk of adverse events. Unlike rheumatoid arthritis where disease specific scores have been developed to identify increased cardiovascular risk, no GCA specific scores have been developed, thus, we recommend using the validated Atherosclerotic Cardiovascular Disease (ASCVD) score of the American College of Cardiology/American Heart Association (ACC/AHA) to identify patients at increased risk of cardiovascular events. Conversely the, the aspirin cardiovascular/gastrointestinal risk calculator is a useful tool to aid physicians outside of clinical acumen to identify patients at increased risk of GI bleeding.[28]

More recently in the field of GCA; Tocilizumab, the IL-6 inhibitor has proven its efficacy in the treatment of GCA especially in its role as a steroid sparing agent. The FDA approval came after two landmark trials. In the first trial by Villiger et al.; primary end point of complete remission at 12 weeks was achieved by 85% of the Tocilizumab compared to 40% of the placebo. This risk difference was sustained when relapse free survival at 52 weeks was seen in 85% of the Tocilizumab group compared to the 20% of the placebo group.[29] The second trial by Stone et al. showed similar results with sustained remission at 52 weeks in 56% of patients on weekly Tocilizumab, 53% in alternate weekly dosing of Tocilizumab, 14% in placebo group on 26-week steroid taper and 18% in placebo group on 52-week steroid taper.[30] It is interesting to point out that all patients enrolled in the first trial received aspirin 100 mg daily and similarly patients in the second trial all received either low dose aspirin or Clopidogrel.

1. Conclusion

The literature regarding aspirin use in GCA while initially promising has produced conflicting results. Currently, the American College of Rheumatology (ACR) recommends use of aspirin in GCA with critical or flow limiting vertebral or carotid disease while the EULAR only recommends aspirin use when patient has additional antiplatelet requirements whilst advocating individual consideration in GCA with high ischemic risk.[31,32] Prospective randomized control trials are needed to fully evaluate the efficacy of aspirin in GCA. We recommend a case-by-case approach weighing benefits against risks using validated scoring systems such as ASCVD and aspirin cardiovascular/gastrointestinal risk calculator. For GCA patients at high risk of CICs and low bleeding risk, we recommend considering adding aspirin to the treatment regimen. But if the risk of ischemic complication is low with a significant bleeding risk, then aspirin should be avoided (see Table 2).

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