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Review

Effect of antiplatelet/anticoagulant therapy on severe ischemic complications in patients with giant cell arteritis: A cumulative meta-analysis

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ABSTRACT

Objective: To evaluate the effect of antiplatelet/anticoagulant therapy on the occurrence of severe ischemic complications in GCA patients at diagnosis and while on treatment with corticosteroids (CS), and the risk of bleeding in these patients.
Methods: A comprehensive search of PubMed and the Cochrane Central Register of Controlled Trials databases was completed and supplemented by hand searching of the references of all selected articles published from 1992 through December 2012. The cumulative meta-analysis included 6 retrospective studies that provided a total of 914 GCA patients. The effect of established antiplatelet/anticoagulant therapy on the occurrence of severe ischemic complications in patients with GCA at diagnosis and on the development of new severe ischemic complications in patients with GCA after diagnosis and while on treatment with CS were evaluated; as well as the risk of bleeding in patients with GCA on concomitant treatment with CS and antiplatelet/anticoagulant therapy.
Results: Antiplatelet/anticoagulant therapy before the diagnosis of GCA was not associated with a protection to develop severe ischemic complications (OR: 0.661; 95% CI [0.287–1.520]; $p = 0.33$). However, such a therapy may prevent from severe ischemic complications after the diagnosis of GCA (OR: 0.318; [0.101–0.996]; $p = 0.049$) without increasing the risk of bleeding in patients with GCA on concomitant treatment with CS (OR: 0.658; [0.089–4.856]; $p = 0.682$).
Conclusions: Antiplatelet/anticoagulant therapy prior to the diagnosis of GCA was not associated with reduction in severe ischemic complications. However, antiplatelet/anticoagulant therapy demonstrated a marginal benefit when used together with CS therapy in patients with established GCA without associated bleeding risk.

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1. Introduction

The main goal in the treatment of giant cell arteritis (GCA) is to prevent the development of severe ischemic events, mainly permanent visual loss (PVL) and cerebrovascular accidents (CVA). Unfortunately, the majority of severe ischemic complications develop before the diagnosis of GCA [1]. Therefore, early diagnosis and treatment are especially important, because once high-dose corticosteroid (CS) therapy has been started, the risk of developing ischemic events dramatically decrease [2,3].

Several factors have been associated with a higher risk of severe ischemic complications: age, history of previous hypertension or ischemic heart disease, previous cranial ischemic manifestations (jaw claudication and amaurosis fugax), absence of systemic symptoms (fever and/or weight loss), thrombocytosis, or the lack of typical acute phase reactants (anemia, high ESR or circulating IL-6 levels) [4–8]. More recently, two studies [9,10] suggested that patients receiving ongoing treatment with antiplatelet/anticoagulation therapy at the time of diagnosis of GCA were less likely to present with or to develop severe ischemic complications.

Since these initial studies [9,10], it has been accepted by most physicians attending GCA patients that the addition of low-dose acetyl salicylic acid (ASA) to high-dose CS therapy is part of the standard of care of these patients. In fact, the initial study by Nesher and colleagues [9] merits a rotund conclusion from an Editorial: "we should change our initial treatment of GCA to include not only prednisone but also low-dose aspirin" [11]. Furthermore, the recent EULAR recommendations for the management of large vessel vasculitis [12] include the use of low-dose aspirin in all patients with GCA (level of evidence 3, strength of recommendation C). The authors stated that the addition of low-dose aspirin (75–150 mg/day) protects against such events and should be prescribed to all patients in the absence of contraindications [12]. However, and probably based on the fact that not all the studies have found a protective effect of antiplatelet/anticoagulant therapy [7,8,13,14] in preventing severe ischemic complications, the authors include in the research agenda the role of thromboprophylaxis for primary prevention of vascular outcomes in GCA [12].

In view of these contradictory observations, the goal of this study was to evaluate: a) the effect of established antiplatelet/anticoagulant therapy on the occurrence of severe ischemic complications in patients with GCA at diagnosis; b) the effect of antiplatelet/anticoagulant therapy on the development of new severe ischemic complications in patients with GCA after diagnosis and while on treatment with CS; and, c) the risk of bleeding in patients with GCA on concomitant treatment with CS and antiplatelet/anticoagulant therapy.

2. Methods

2.1. Data sources and searches

As no clinical trials were found in the initial search, we searched for all articles that tested the effect of antiplatelet/anticoagulant therapy on the occurrence of severe ischemic complications in patients with GCA. A comprehensive search of PubMed and the Cochrane Central Register of Controlled Trials databases was completed and supplemented by hand searching of the references of all selected articles. "Giant Cell Arteritis"[MeSH] AND "Platelet Aggregation Inhibitors"[MeSH] without restriction to any language (January 1, 1992, through December 31, 2012). The search strategy was in accordance with the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group [15]. This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at: http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42011001631.

2.2. Study selection

Articles that included patients with GCA and data on the effect antiplatelet/anticoagulant therapy on the occurrence of severe ischemic complications were reviewed as shown in the flow chart (Fig. 1).

2.3. Data extraction and quality assessment

Information was collected by two investigators (VMMT and MLH) on study design, study sample, characteristics of the study population, interventions, severe ischemic complications before and after diagnosis, and bleeding complications. The disagreements were resolved by consensus. Abstracted data are shown in Tables 1 and 2, and Supplementary Table 1.

Three reviewers (MLH, PMC and JN) independently assessed the methodological quality of selected studies using the Newcastle–Ottawa quality assessment scale for cohort studies [17], and considered items included the STROBE statement [18] in order to highlight gaps in reporting or execution in studies. Disagreement among reviewers was discussed, and agreement was reached by consensus.

We rated the quality of evidence using GRADE (Grading of Recommendations Assessment, Development and Evaluation), which provides an explicit and comprehensive method to rate the quality of evidence [19]. Evidence summaries were prepared for each research question by using the GRADE Profiler (GRADEpro), version 3.6 (McMaster University, Hamilton, Ontario, Canada). Recommendations were rated as high, moderate, low or very low [20].

2.4. Statistical analysis

We tested for heterogeneity using Cochran's Q (considered significant for $p < 0.10$) and quantified its extent with I^2 [21]. Because individual studies differed with regard to various important clinical and methodological characteristics, we used random-effects model. Combined odds ratio (OR) and associated 95% confidence intervals (CI) were obtained by using a DerSimonian and Laird random-effects model [22]. Publication bias was examined by funnel plot [23,24] and Egger's test [25] as shown in Supplementary Fig. 1. We also conducted a cumulative meta-analysis [26] whereby studies were pooled chronologically and presented in order of publication. Statistics were performed using Comprehensive Meta-analysis [27].

3. Results

3.1. Characteristics of the study populations included in the meta-analysis

The computerized bibliographic search revealed six studies that included a total of 914 patients with GCA (Table 1). All the studies, published between 2004 and 2009, were retrospective and developed during a similar period of time ranging in duration from ten to twenty