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Review

A scoping review of the use of non-biologic disease modifying anti-rheumatic drugs in the management of large vessel vasculitis

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ABSTRACT

Takayasu's arteritis (TA) and Giant cell arteritis (GCA) comprise the large vessel vasculitides (LVV). Patients with LVV are treated with disease-modifying anti-rheumatic drugs (DMARDs), both conventional (cDMARDs) and biologic (bDMARDs). We undertook a scoping review to assess the effectiveness of cDMARDs in TA and GCA. We could identify 11 studies in TA and 18 studies in GCA. There were only 3 randomized controlled trials on methotrexate, one on hydroxychloroquine and two on cyclosporine in GCA, the others being case series (including all studies on TA). Most of these studies had small patient numbers (median 15 in TA and 27 in GCA). Outcome measures reported in different studies were heterogenous. Overall, methotrexate, leflunomide, azathioprine, mycophenolate mofetil and cyclophosphamide were effective in TA (low quality of evidence). Methotrexate (high quality of evidence), hydroxychloroquine and cyclosporine (moderate quality of evidence) appeared to be ineffective in GCA. Azathioprine (moderate quality of evidence), leflunomide, mycophenolate mofetil, cyclophosphamide and dapsone (low quality of evidence) were effective in GCA. There exists a paucity of high quality evidence to guide use of cDMARDs in TA and GCA. There is an unmet need to conduct large multi-centric randomized placebo-controlled trials to accurately assess the utility on cDMARDs in LVV.

Contents

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1. Introduction

Large vessel vasculitides (LVV) are inflammatory diseases predominantly affecting large arteries, resulting in scarring and stenosis. Takayasu's arteritis (TA) and Giant cell arteritis (GCA) are recognized as the two forms of large vessel vasculitis. Whereas TA usually affects young females and is more common in Asian countries, GCA usually affects older patients, is characteristically associated with temporal artery involvement, has more prominent constitutional features and is more common in Western countries.

The American College of Rheumatology (ACR) proposed classification criteria for TA and GCA in 1990 [1,2]. Both TA and GCA are considered as rare diseases [3]. Management of LVV involves initial induction therapy using corticosteroids. This is followed by maintenance therapy using conventional disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, mycophenolate mofetil, azathioprine or cytotoxic drugs such as cyclophosphamide. Patients who fail conventional DMARDs are managed with biological agents such as anti-tumor necrosis factor alpha (TNF-α) agents (infliximab, etanercept, adalimumab, golimumab), tocilizumab, abatacept and rituximab [4].

Assessment of outcomes in large vessel vasculitis is challenging. Active disease is often associated with increases in erythrocyte sedimentation rate (ESR) or serum C-reactive protein (CRP), especially in GCA. The same, however, does not always hold true for TA, wherein aortic biopsies suggestive of active disease have been found to be associated with normal acute phase reactants in peripheral blood, and vice versa [5,6]. Ability to stop prednisolone or lower the dose of prednisolone below 5 mg/day and reduction in frequency of relapses have been used as outcome measures in GCA [7]. The National Institutes of Health (NIH) criteria were described in 1994 to assess disease activity in TA [8]. These criteria require new onset or worsening of two of the following four points for TA to be considered active: ESR > 20 mm/h, constitutional features like fever and malaise, features suggestive of vascular involvement like bruits and pulse loss and angiographic features consistent with TA. The disease extent index in TA (DEI.Tak) was devised by the Indian Rheumatology Association Core Group on Vasculitis (IRAVAS) from the Birmingham Vasculitis Activity Score (BVAS) used to assess disease activity in small vessel vasculitis, and validated externally [9]. It comprises 75 items scored in eleven different domains, with weightage given for cardiovascular features. Items are scored if they are present in the past 6 months, irrespective of whether they are due to active disease or are the consequences of scarring due to previous vascular inflammation. The Indian Takayasu Clinical Activity Score (ITAS2010), and its modification which takes into account acute phase reactants (ITAS-A) scores features which are new or worse in the past 3 months, hence is a score for active disease. Features in six different domains are scored, with weightage for renal, cardiovascular and neurologic features [10]. Serial angiography [conventional, computerized tomography (CT) or magnetic resonance (MR)] demonstrating increase in severity of affected vessels as well as involvement of newer blood vessels has been proposed to be an end point signifying vascular progression in TA as well as in GCA. Other modalities such as positron-emission tomography computerized tomography (PET CT) have been shown to signify vessel wall inflammation characterized by uptake in the vessel wall, which reduces following immunosuppressive therapy, and hence may hold promise as a potential outcome measure. Validated clinical outcome measures for assessing damage are not yet described in published literature [11–13]. Patient reported outcomes assessing quality of life using the World Health Organization (WHO) Short Form 36 (SF-36) and the hospital anxiety and depression scale (HADS) have recently been assessed in a large cohort of patients with TA [14]. Other than the NIH criteria for TA, most outcome measures do not integrate clinical and angiographic information. Hence, measurement of outcomes in LVV is heterogenous and an area of ongoing research.

Biologic DMARDs are costly and often, out of the reach of patients in developing countries. Hence, most patients with TA and GCA hailing from these countries have to be managed with conventional DMARDs (cDMARDs) in addition to steroids. There is lack of a consolidated systematic review of literature on the use of non-biologic DMARDs in the management of LVV. Hence, we decided to undertake a scoping review of the existing literature on the use of cDMARDs in the management of LVV to assess the feasibility of further systematic reviews in the subject and evaluate the need to generate evidence to guide therapy in these conditions.

2. Search strategy

The methodology for undertaking scoping reviews proposed by Arksey and O'Malley was adopted [15]. The database Scopus (which includes data from Medline) was searched individually for TA and GCA. For TA, the search terms used were "Takayasu arteritis" or "Takayasu's arteritis" in combination with "methotrexate", "azathioprine", "cyclophosphamide", "mycophenolate", "leflunomide", "sulfasalazine", "hydroxychloroquine", "chloroquine", "cyclosporine", "tacrolimus", "sirolimus", "everolimus", "dapsone", "mizoribine". Similarly, for GCA, the databases were searched using "Giant cell arteritis" or "temporal arteritis" in combination with the same search terms for medications as above. In addition, the Cochrane Central Register of Controlled Trials (CENTRAL), LILACS database, SCIELO database and Indmed database were searched for articles on TA and GCA. The conference proceedings of the annual conferences of the American College of Rheumatology (2009–2015), British Society for Rheumatology (2001–2016), European League Against Rheumatism (2001–2016), Indian Rheumatology Association (2006–2014) and the Asia Pacific League Against Rheumatism (2008, 2010, 2012–2015) were searched for articles on TA and GCA. The World Health Organization International Clinical Trials Registry Platform (ICTRP) was searched to identify ongoing studies of relevance to the systematic review. The results of the search are summarized in Fig. 1 derived from the PRISMA guidelines [16] and presented in detail in the supplementary tables S1, S2 and S3. The titles retrieved and abstracts were screened to identify relevant articles. Narrative reviews and case reports were excluded from analysis. Randomized controlled trials (RCT) were analyzed wherever available. In their absence, case series (which included at least data of 3 patients and reported intervention-specific outcomes) were analyzed and presented. Studies were included irrespective of the outcome measures reported, whether clinical, angiographic, inflammatory markers, composite measures (NIH criteria or ITAS) or patient-related outcomes such as quality of life.

3. Results and discussion

3.1. Takayasu's arteritis

Overall, we could identify 10 different studies on cDMARDS in TA (with another a longer term follow-up of a previously reported study). The median number of patients enrolled in each study was 15 [interquartile range (IQR) 9–19]. The outcomes studied in each study are represented in Table 1. The individual studies are discussed below and summarized in Tables 2 and 3.