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Pharmacological therapy for the prevention and management of cardiomyopathy in Duchenne muscular dystrophy: A systematic review

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Abstract

Cardiomyopathy is a major source of morbidity and mortality in Duchenne muscular dystrophy (DMD) patients now that respiratory care has improved. There is currently no definitive evidence guiding the management of DMD-associated cardiomyopathy (DMD-CM). The objective of this systematic review was to evaluate the effectiveness of pharmacotherapies for the prevention and/or management of DMD-CM and to determine the optimal timing to commence these interventions. A systematic search was conducted in January 2016 using MEDLINE, EMBASE and CINAHL databases and grey literature sources for studies evaluating the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta-blockers or aldosterone antagonists. Study quality assessment was conducted using the Downs and Black quality assessment checklist. PRISMA reporting guidelines were used. Of the 15 studies included in this review, most were of low methodological quality. Meta-analysis was not possible due to heterogeneity of studies. ACE inhibitors, angiotensin receptor blockers, beta-blockers and/or aldosterone antagonists tended to improve or preserve left ventricular systolic function and delay the progression of DMD-CM. While there is evidence supporting the use of heart failure medication in patients with DMD, data regarding these interventions for delaying the onset of DMD-CM and when to initiate therapy are lacking. PROSPERO registration: CRD42015029555.

Keywords: Duchenne muscular dystrophy; Cardiomyopathy; Heart failure

1. Introduction

Duchenne muscular dystrophy (DMD) is the most common and severe form of childhood muscular dystrophies, affecting 1 in 3600–6000 live male births [1]. DMD is an X-linked recessive disease characterized by the absence of or defect in the sarcolemmal protein dystrophin. The lack of dystrophin ultimately results in progressive muscle degeneration [2,3]. Patients are typically diagnosed between the ages of 3 and 7 years, when their physical ability diverges noticeably from their peers. Loss of independent ambulation occurs by 13 years of age [4–6]. Without intervention, premature death associated with respiratory or cardiac failure occurred in the late teens [7]. Improved medical management with long-term glucocorticoid therapy and non-invasive ventilation has prolonged survival, with patients now having a possible life expectancy into their fourth decade [1,8]. Improved respiratory care has unmasked cardiomyopathy as a major source of morbidity and mortality [9]. In the dystrophin-deficient myocardium, fibrosis caused by the degeneration of cardiomyocytes proceeds to dilated cardiomyopathy and is further complicated by heart failure and arrhythmia [10,11]. Onset of DMD-associated cardiomyopathy (DMD-CM) occurs at a mean age of 14–15 years and is a universal consequence by adulthood [12,13].

There is currently no consensus regarding the appropriate pharmacological management of DMD-CM and the optimal time to initiate pharmacotherapy [1,14]. In 2010, the DMD Care Considerations Group published consensus-based recommendations for DMD patients, which advised the use of angiotensin-converting enzyme (ACE) inhibitors as first-line therapy for DMD-CM [1,15]. The use of ACE inhibitors has now become widespread in the DMD population. In patients who are unable to tolerate ACE inhibitors, angiotensin receptor

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blockers (ARBs) may be used [16]. An expert Working Group recently published updated cardiac care recommendations, which recommend that ACE inhibitor/ARB therapy should be initiated by the age of 10 years, however it is unclear if earlier therapy is warranted. While a beta-blocker (BB) is often initiated after ACE inhibitor/ARB therapy for progressive cardiac decline, recommendations for their use remain variable [14]. Aldosterone antagonism has recently demonstrated favourable effects on cardiac function in DMD and the use of an aldosterone antagonist (AA) is currently under further investigation [17].

The objective of this systematic review is to evaluate the effectiveness of pharmacological therapies for the prevention and management of DMD-CM and to determine the optimal timing to commence these interventions. This review aims to summarize and critically appraise the current body of scientific literature relating to the use of ACE inhibitors, ARBs, BBs and AAs in the DMD population.

2. Materials and methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. The protocol of this systematic review was registered in PROSPERO (CRD42015029555), an international database of prospectively registered systematic reviews in health and social care.

2.1. Search strategy

A systematic search was conducted using MEDLINE (Ovid), EMBASE and CINAHL databases. A grey literature search was conducted using Web of Science™ Core Collection, BIOSIS Previews®, ClinicalTrials.gov, International Clinical Trials Registry Platform, UK Clinical Trials Gateway, UK Clinical Research Network Study Portfolio, Cochrane Center Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Electronic Theses Online Services (EThoS), Networked Digital Library on Theses and Dissertations, Theses Canada Portal, ProQuest Dissertations and Theses, Centers for Disease Control and Prevention, and U.S. Food and Drug Administration. Searches were conducted in October 2015, and updated in January 2016. A comprehensive search strategy was developed with guidance from a research librarian using terms related to DMD, cardiomyopathy, ACE inhibitor, ARB, BB, AA and additional heart failure medications. The search strategies employed database- and platform-specific terminology and syntax. Alerts were set up for each database to receive publication notifications for relevant newly published articles. See Appendix A for detailed search strategies and search results.

2.2. Inclusion and exclusion criteria

The PICOS (population, intervention, comparator, outcomes, study design) approach was used to specify the inclusion and exclusion criteria [19]. The population was defined as male patients of any age who have a diagnosis of DMD confirmed by mutation analysis of the DMD gene or by the absence of dystrophin protein expression on muscle biopsy, and a phenotype consistent with DMD. The interventions under investigation were ACE inhibitors, ARBs, BBs and AAs. Studies were not excluded based on types of control groups used or lack thereof. Outcomes of interest included both surrogate measures of cardiac function and clinical outcomes. The primary outcomes were changes in left ventricular ejection fraction (LVEF) and fractional shortening (FS) measured using echocardiography, cardiac magnetic resonance imaging (cMRI) or radionuclide ventriculography. Canadian Cardiovascular Society paediatric heart failure guidelines define left ventricular (LV) systolic dysfunction as LVEF<50% and/or FS<25% [20], while abnormal LVEF in adults is commonly defined as <55% by echocardiography or <60% by cMRI [21–24]. Secondary outcomes included the following measures by echocardiography, cMRI or radionuclide ventriculography: left ventricular end diastolic and systolic diameters (LVEDd and LVESd), left ventricular end diastolic and systolic volumes (LVEDv and LVESv), left ventricular mass (LVM) and heart rate (HR). Peak left ventricular circumferential strain (ε_{cc}) and myocardial fibrosis evident by late gadolinium enhancement were also of interest as they have been found to be early markers of myocardial damage before the onset of ventricular dysfunction [25,26]. Additional clinical outcomes of interest included levels of blood biomarkers indicative of heart failure, adverse events, hospital admissions due to heart failure, signs and symptoms of congestive heart failure, arrhythmias and survival. Types of records included were full-text research studies (experimental or observational) with a sample size greater than 1 DMD patients, published in English. Non-research articles such as review articles, editorials, commentaries and case reports were excluded. Records were not excluded based on country or date of publication.

2.3. Study selection

All records were imported into EPPI Reviewer 4 [27]. Duplicate records were removed prior to screening. Two authors (BE and RR) independently screened records against the inclusion and exclusion criteria in three consecutive stages by title, abstract and full-text. Kappa statistics were calculated following each stage to measure agreement between authors. Kappa values between 0.40 and 0.59 were considered to reflect fair agreement, between 0.60 and 0.74 to reflect good agreement and 0.75 or more to reflect excellent agreement [28]. Any disagreements at each stage were resolved by consensus. Reference lists of included studies and excluded non-original data studies were searched to ensure no records were omitted from the search strategy. When full-text articles corresponding to relevant conference abstracts could not be located, authors were contacted and asked to provide full reports. Authors of studies that included patients with other muscular dystrophies were contacted and asked to provide data on DMD patients exclusively when a subgroup analysis was not already provided.

2.4. Data abstraction

Two authors (BE and EZ) independently extracted data from the included studies in the following areas: study