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Journal of Stem Cell Research & Therapeutics

Mini Review

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Integrated treatment regime for duchenne muscular dystrophy

Abstract

Duchenne muscular dystrophy (DMD), a genetic neuromuscular disorder, has a pernicious influence on skeletal and cardiac muscle tissue and results in a significant decline in the life span of those affected. The destruction is mainly attributed to perpetuating inflammation and fibrosis. This review explores the potential of a comprehensive therapeutic approach with an objective to minimize ongoing damage and reconstitute normal tissue.

Keywords: duchenne muscular dystrophy, chronic inflammation, muscle fibrosis, human adipose derived stem cells, pleiotropy, anti fibrotic effects

Volume 1 Issue 4 - 2016

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Received: July 29, 2016 | **Published:** September 27, 2016

Abbreviations: DMD, duchenne muscular dystrophy; hASCs, human adipose derived stem cells; TGFB, transforming growth factor beta; OPN, osteopontin; ACEIs, angiotensin converting enzyme inhibitors; ROS, reactive oxygen species

Introduction

Duchenne muscular dystrophy (DMD) is the most common hereditary neuromuscular disease affecting all races and ethnic groups, with a sex linked inheritance pattern of 1 in 3500 male births. The underlying genetic defect results in the loss of a structural protein called dystrophin that normally serves to provide mechanical stability during muscle contraction. As a result of this loss, there is enhanced myofibre damage/ necrosis, and this forms a prelude to chronic inflammation and significant bystander tissue damage. This destruction of muscle tissue progresses faster than the body's ability to compensate by regeneration.[1,2] These patients are wheel chair bound by late adolescence and also suffer extensive damage to the cardiac muscles. Death usually occurs as a result of respiratory failure, intractable heart failure or pneumonia.[1,2]

Despite our increasing knowledge of the genetic causation and pathology of the disease, current treatment strategies are limited to symptomatic management with glucocorticoids[3] which when used long term can cause debilitating side effects. There is a need to formulate a multimodal therapeutic strategy that will reduce our reliance solely on steroids and manage the disease at various stages of its pathogenesis.

Gene restoration therapy (that serves to restore dystrophin expression in muscle cell) by Allogenic healthy adult Stem cells 'complemented' by a vast array of pharmacological approaches are proposed with particular promise in disease management.

In this review, in addition to understanding potential areas of target, drugs that are currently used in some common medical conditions are explored for their 'pleiotropic' effects in treating DMD.

Value of human adipose derived stem cells (hASCs)

hASCs are adult Mesenchymal stem cells (MSCs) sourced from fat tissue, that have an inherent ability for self- renewal, proliferation, and differentiation towards mature tissues, depending on the surrounding microenvironment/inductive media.[4,5] Such characteristics inherent to stem cells also constitute the essence of regenerative medicine.

The relative ease with which they can be procured, the higher concentration of stem cells per gram of fat and their ability to differentiate into multiple lineages of cells[5] make them a popular therapeutic choice. *In vivo* studies showed that transplantation of hASCs in mdx mice (animal model of DMD) restored substantial dystrophin expression in them.[6]

Human *in vitro* study results reinforce this observation and support the idea that hASCs could be an important tool of muscle cell therapy. It has been suggested that hASCs restore dystrophin expression when co-cultured with DMD myoblasts primarily by cellular fusion. Their ability to transdifferentiate into muscle cells is also of importance in the proposed cell based treatment.[7]

Pharmacological approach

It is essential to first understand the pathophysiology of muscle damage and repair to identify suitable targets for pharmacotherapy. Muscle fibres that lack dystrophin succumb to physiological stresses that normal muscle fibres can resist. Death of these fibres heralds an inflammatory response. Phagocytes (neutrophils and macrophages) are brought in to clear the debris and make space for growth of new muscle tissue. However, as long as the new cells being produced lack the normal dystrophin protein, the cycle of cell death and inflammation will perpetuate. There is thus, chronic inflammation that occurs on a massive scale so as to cause significant bystander tissue damage and fibrosis.[1,8] This can affect both skeletal and cardiac muscle tissue leading to progressive muscle weakness and heart failure respectively.

Glucocorticoids are being routinely employed in the treatment of DMD by virtue of their anti-inflammatory effects. However, their use is limited in duration as there is scarcity of evidence to suggest beneficial effects when used long term.[9] This calls for a need to look for alternative treatment options for DMD.

Drugs with anti-fibrotic potential

Fibrosis, is an inevitable consequence of chronic inflammation.

It significantly attenuates muscle function by competing with regenerating tissue for space and also affects the success of stem cell engraftment. Therefore, anti-fibrotic therapy, apart from its individual benefits, may be a necessary addition to cell therapy as well.[10]

Studies on mdx mice have demonstrated the potential of several drugs as anti-fibrotics. Angiotensin receptor blockers (ARBs) such as Losartan are widely used as anti-hypertensive medication. They act by blocking the effects of angiotensin II that besides causing physiological vasoconstriction and water retention by kidneys, is also known to increase fibrosis by promoting transforming growth factor beta (TGFB) signaling.[11]

Increased expression of Osteopontin (OPN) has been demonstrated in muscle biopsies of DMD patients. Recently, Vetrone et al.[12] demonstrated genetic ablation of osteopontin altered the in-flammatory response and led to reduced TGFB expression thus, attenuating diaphragm and cardiac muscle fibrosis in mdx mice. These findings suggest that osteopontin may also represent a promising therapeutic target in DMD.[12]

Eplerenone

In DMD, Progressive myocardial damage is well underway before left ventricular ejection fraction becomes abnormal. Exertional symptoms and signs of myocardial disease are typically absent because skeletal muscle disease progressively restricts functional capacity in these patients. Myocardial involvement can thus, go undetected until advanced fibrosis.

A recent human study[13] demonstrated that the early use of Eplerenone (a mineralocorticoid receptor antagonist) in addition to background clinician directed therapy of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) attenuated the progressive decline in left ventricular systolic function.

These drugs are commonly prescribed for heart failure and through mechanisms that are unclear, have shown to reduce progressive left ventricular strain over 12 months. Cystitatin C, a biomarker for renal function, remained fairly constant in both test and control groups of the study. Elevated serum potassium, a potential complication of mineralocorticoid receptor antagonism was not observed in non-hemolysed blood samples.[13]

Simvastatin

Statins have been rarely tested as a therapy for any inherited muscle disease. This is primarily due to the perceived risk of muscle related symptoms that can occur with statin use. A recent review of several randomised, placebo controlled studies showed that the incidence of adverse, statin-related muscle symptoms was almost identical for statin treated and placebo control patients.[14] Simvastatin, relatively more lipophilic than other statin drugs, has better uptake by muscle tissue and is known to reduce damage mediated by free radicals (reactive oxygen species-ROS) generated in mdx muscle. This retains muscle strength and prolongs ambulation.[15]

Conclusion

Duchenne muscular dystrophy is lethal, characterized by protracted inflammation and fibrosis of muscle. There is limited choice for treatment, in practice, despite enhanced understanding of the disease pathogenesis. Comprehensive approach with a combination of stem cells and drugs with beneficial pleiotropic effects such as those that can potentially reduce inflammation, fibrosis and progressive cardiac dysfunction can prove to be of great benefit to optimally treat DMD. Existing evidence is promising and more studies are needed to explore the efficacy of these drugs in com-binatorial treatment approach.

Acknowledgements

None.

Conflict of interest

The author declares no conflict of interest.

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Citation: Kareti S, Kapadia A, Dravida S. Integrated treatment regime for duchenne muscular dystrophy. *J Stem Cell Res Ther.* 2016;1(4):176–177.
DOI: 10.15406/jsrt.2016.01.00030