The breakthroughs and barriers to clinical utilization of in vivo cellular therapies in the management of osteoarthritis in humans: A review

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Abstract
Osteoarthritis is a debilitating illness that is commonly characterized by swelling, pain, stillness and limited function of the joints. It is a degenerative disease that has affected over 7% of the world’s population and is responsible for over 2% of all DALYs. It is one of the most common clinical presentations and the most common joint pathology among adults. From non-pharmacological, to pharmacological and even surgical modalities, there are a myriad of therapies for its symptomatic treatment, but no cure. Advances in research for a cure have started exploring molecular mechanisms, such as genetics and regenerative medicine. Regenerative medicine focuses on stem cellular harvest, transplants and manipulations. Sources of MSC are currently BMSC and ADSC. Application of this therapy have moved from an invasive approach to a non-invasive approach. Recent advances in stem cell therapies have focused on MSCs, EVs and exosomes, for their effective and promising results so far. As thousands of more case studies and researches are currently going on around the world, this study will be taking a systematic look in to the breakthroughs and barriers these researchers have discovered or encountered in the course of their research and how this affects the propensity to clinical adoption and utilization of stem cellular therapies in the treatment of osteoarthritis.

Keywords: MSC, BMSC and ADSC

1. Introduction
The global burden of osteoarthritis (OA) has been on a progressive increase, currently affecting approximately 7% of the world’s population [1]. The Disability Adjusted Life Years (DALYs) associated with OA affects approximately 2% of the world’s human population [1-2]. Although the global burden of disease is most significant in high and higher-middle income countries, the prevalence in lower-middle- and low-income countries are now witnessing a significant rise. These lower economic countries also have factors such as poor health facilities and other social determinants, thus propagating a worse burden of disease and DALYs [1-3]. In fact, the true burden of OA is actually underestimated [1-2].

However, many people consider it a physiologic path of aging, and not a real disease pathology of its own [6]. In fact, it is not featured in the global strategic plans for non-communicable diseases [4]. This mentality is also shared by practitioners, as patients have reported varying levels of neglect and down-play of their genuine concerns and complaints [5]. This abandon in combination with varying levels of therapeutic nihilism on the path of the medical professionals, worsens the personal, economic and social tolls these patients have to bear [4]. One might wonder if this abandon is the reason for positive progress in the management of OA not making as much head-way as treatments of other musculoskeletal diseases and chronic pathologies or, if this slow progress is the reason for the abandon on the side of the health professionals [5, 6]. Nevertheless, with a myriad of treatment options, some of which are not so therapeutically significant, the financial and pathological burden are borne by often ill-informed patients [7-9]. Notwithstanding, tremendous progress has been made in the public health understanding of the disease, the global burden and pathogenesis of the disease [10].
However, as regards an effective mode of treatment and management, a myriad of non-pharmacological, pharmacological and surgical treatments are available, but no cure yet [13]. In clinical practice, commonly used therapies such as non-steroidal anti-inflammatory drugs and glucocorticoids have moderate effectiveness with substantial side effects on the long run [12-13]. Recent strategies have tried hydroxychloroquine (HC) but several studies have failed to produce effective satisfactory results [14-15]. A lot of researches are still going, such as genetic studies that have made significant findings in the genomic risk factors of OA [16-17], the anabolic BMP-7 and anti-catabolic MMP-13 inhibitor drug trials [18-19]. Regenerative cellular therapies (BMSC, ADSC and MSC) and so on [20-22].

Discussion
Regenerative therapies have shown a lot of promise from multiple case studies being carried out around the world. It utilizes transplanted Stem cells to help in regeneration of the damaged area. Stem cells may be acquired from bone marrow (BMSC) and adipocytes (ADSC), and other areas rich in mesenchymal stem cells (MSC). Unlike initially, when transplantation used to be via invasive surgery, it is now transplanted autologous via intra-articular injections [23-24]. This studies on MSC utilization in human trial have shown effective results.

When MSC is transplanted into the joint compartment it elicits an immunomodulatory and chondroprotective effect that lasts a while, leading to a cascade of activities. These actions are mediated in a paracrine manner [25]. Exposure to inflammatory signals develop and promotes secretions from the MSC [26]. It produces Extracellular Vehicles (EVs), which basically are small phospholipid-bilayer-enclosed particles carrying many cytoplasmic components [27-28]. In the body, EVs play numerous roles, metabolic and mRNA transcription roles [29]. Amongst the EVs, exosomes are the most therapeutically palatable so far, and hence the most studied [30]. Consensus of studies carried out on MSC, EVs and exosomes applied for treatment of cartilage pathologies and knee osteoarthritis had promising positive effects [31].

Understanding these mechanisms, more purified studies utilizing EVs were done. These studies have been conducted on an in vitro and in vivo level. In vitro, properties such as anti-catabolic, immunomodulatory and regenerative properties were assigned to EVs and secretomes. While on in vivo pre-clinical application, studies showed that there were positive effects on the joint and confirmed effectiveness of EV injections as a minimally invasive therapy [32]. Furthermore, when exosomes were used in an animal-based study, they improved the gait abnormality patters in OA and MSC secretomes provided early pain reduction [33-34]. It has proven to be an ever-advancing field.

Furthermore, more breakthroughs have been seen in understanding the knowledge and future prospects that mesenchymal based therapy may hold. In fact, the promise EVs have shown also distinguishes them as promising potential next-generation biomarkers to predict the pathophysiological state of the joint [31]. Hence, the role of cellular therapies in even OA primary prevention and assessment. More studies are currently being conducted on its potentials in the management of other forms of arthritis, such as rheumatic arthritis. The adoption of intra-articular form of transplantation from an initial invasive surgical method, the sequestration of stem cells from adipose tissues and focused therapies that have isolation and utilization of EVs and exosomes are very significant breakthrough in yet [21, 23, 33-34].

Although, studies have identified some modifiable and non-modifiable characteristics and barriers to effective utilization of MSC therapies, such as age, gender and oxygen concentration (Normoxic vs. hypoxic) conditions which may affect cell proliferation and regeneration in varying degrees [35-36]. A pilot study that quantitatively assessed the barriers to clinical development and adoption of cellular therapies found that the major barriers that existed were cost-effectiveness, efficacy, reimbursement and regulations. The study also went further to suggest future studies answering questions of regulators, as well as a broader clinical community [37], the promising potentials shown by stem cell therapies are still palpable.

Conclusion
However, with so many concurrent studies being carried out on stem cell therapies all around the world, with a lot of significant studies not even being published, it is hard to keep detailed track of the milestones each researcher is attaining [22]. We need to also understand the progress and observations made in case control trials that have attempted to utilize these therapies in human based trials. As the end game is to aim towards clinical utilization of the cellular therapies in order to provide evidence based and improved management options to alleviate the burden of disease and DALYs experienced by OA patients. There is thus a need to have a directory or a study that aims at streamlining and properly classifying for sake of research, clinical application and learning, the essential studies and findings as regards in vivo utilization of cellular therapies in OA.

Conflict of interest
The Author’s declares no conflict of interest.

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References


