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Research Article

INTRA-ARTICULAR INJECTION OF AN EXTRACELLULAR VESICLE ISOLATE PRODUCT TO TREAT HIP OSTEOARTHRITIS

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ABSTRACT

This case report will introduce the concept of using an acellular mesenchymal stem cell (MSC) derived extracellular vesicle isolate product (EVIP) containing active growth factors (GFs) and exosomes to treat hip osteoarthritis (OA) as well as the rationale of why acellular may replace all current cellular biologic therapies both autogenous and allogeneic presently in use.

INTRODUCTION

Hip osteoarthritis (OA) has demonstrated, in both cadaver and radiographic studies, to affect up to 55 million patients over the age of 60.[1] Patients with hip OA have pain, crepitus, loss of motion, and decreased ability to weight bear or ambulate. Limiting the ability to ambulate severely impairs activities of daily living. The nonsurgical treatments forhip OA according to the American Academy of Orthopedic Surgeons (AAOS),include weight loss, gentle exercise, and the use of non-steroidal anti-inflammatory medications. The surgical treatment forhip OA is total hip arthroplasty (THA).[2] The AAOS does not recommend hip arthroscopy or the use of any Hyaluronic Acid injections.

Over the last few years, it has become increasingly understood by researchers and clinicians that the clinical efficacy of utilizing mesenchymal stem cells (MSCs) to treat osteoarthritis (OA) is not dependent on the cells differentiating into articular cartilage but entirely on their paracrine release of growth factors (GFs) and exosomes. Living MSCs are not required to accomplish the release of GFs and exosomes into an arthritic joint.[22,23] This case report will introduce the concept of using an acellular MSC derived extracellular vesicle isolate product(EVIP) containing active growth factors and exosomes to treat hipOAas well as the rationale of why acellular may replace all current cellular biologic therapies both autogenous and allogeneic presently in use.

MATERIALS AND METHODS

This is a case report of an EVIP injection for the treatment of hiposteoarthritis. OA is defined by swelling, pain, and stiffness in the hipjoint. Symptoms are typically worsened by weight-bearing and ambulation.Radiographs and MRI scanning wereused tograde osteoarthritis of the hip joint from one to four using the Kellgen-Lawrence scale.[12]

The patient is a 63-year-old retired Chicago Fireman. He presented with increasingpain in the left groin and a progressive loss of ability to continue his daily health club fitness routine. He experienced a progressive loss of hip mobility.MRI scanning and radiographs of the left hip joint were compatible with Kellgren-Lawrence Grade 3osteoarthritic changes of the left hip joint. On physical examination, he had an antalgic limp and a positive Trendelenburg sign. Passive ROM of the hip joint was associated with the reproduction of severe groin pain, crepitus, and a loss of internal rotation. The patient had a BMI of 27. NSAIDs had failed to provide adequate pain relief. The patient was seriously considering total hip arthroplasty. In an attempt to avoid surgery, he elected to

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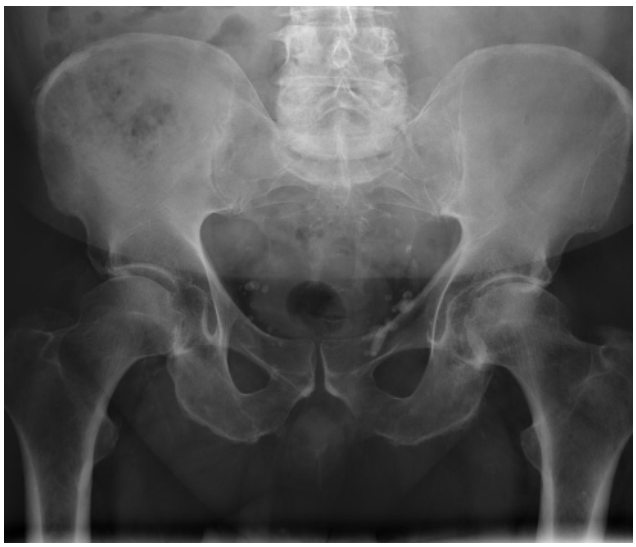
have an injection of an EVIP containing active GFs and exosomes into his hip.

Radiographs of apelvis are shown in Figure 1. This x-ray shows a normal right hip and grade three OA hip on the left.



Theleft hip was sterilized with betadine skin prep. A 20-gauge spinal needle was placed through ananterolateral approach into the hipjoint. Needle placement was verified by fluoroscopy. At this point,2cc of the frozen EVIP (ExoFlo-Direct Biologics, St. Louis MO)was thawed to room temperature and placed into the joint. The patient was put on restricted physical activity for oneweek following the procedure. A passive, low-resistance range of motion was encouraged immediately. The patient returned to fullactivities at two weeks.

CLINICAL RESULTS

At the three-month follow-up, the patient had returned to his previous fitness routine without limitation. He is no longerlimited in his exercise profile and has enjoyed the return of a functional pain-free hip ROM. He has returned to full activities without restrictions.

DISCUSSION

The hip is a di-arthrodial joint with a synovial lining and a joint capsule. The synovial capsule containsnumerous synovial MSCs (more than those found in bone marrow or adipose tissue). These MSCs have more chondrogenic potential than bone or adipose MSCs.[8,9] During the development of OA, pro-inflammatory growth factors are produced by these synovial MSCs. This creates a chronically inflamed,painful joint environment. Bone marrow concentrate (BMC) contains on average only about 2,500 MSCs per cc.[24] Despite the incredibly small number of MSCs found in BMC; there is an extensive amount of literature reporting the clinical efficacy in animals and humans using BMC for the treatment of OA.[3-17] This effect cannot be dependent upon BMC/MSC cell survival or differentiation. Thisefficaciousness must be from the release of acellular paracrine factors. The future of the biologic treatment of OA will be the utilization of acellular MSC derived growth factors and especially exosomes.

The exosome is a tiny 30 to 150 nanometer-sized (1 billionth of a meter) bi-phospholipid membrane-enclosed structure created by the Golgi body or apparatus. An MSC (12 to18 microns) is 1,000 times larger than an exosome. The diameter of a hair is 80,000 nanometers. Exosomes contain growth factors, signaling lipids, and microand messengerRNA. The RNA contents within exosomes mediate most of their anti-inflammatory effects. The RNA is placed into an exosome along with numerous peptide growth factors. These paracrine factors can be placed into any joint in concentrations of 100,000 or more times that of any cellular MSC treatment. These growth factor proteins and exosomes will function in a paracrine fashion to both, directly and indirectlyalter the inflammatory environment of any painful arthritic joint back to a normal non-painful physiologic environment.

Future acellular treatment of OA will involve a two-front attack. First, highly concentrated anti-inflammatory MSC derived growth factors are injected into an arthritic joint. These growth factors will enter the nucleus of the recipient synovial MSC. The EVIP growth factors will stimulatethe transcription of mRNA containing instructions for the production of continuous anti-inflammatory secretomes, chemokines, and cytokines. These will be released from the recipient synovial MSC into the synovial fluid. Second, the highly concentrated exosomes from the EVIP will enter recipient synovial MSCs to deliver their mRNA. This mRNA will undergo direct translation in the recipient synovial MSC ribosomes to produce anti-inflammatory secretomes, cytokines, and chemokines.

These salubrious effects could last months or years. This acellular biologic treatment can all be achieved with a single arthritic joint injection, without requiring the morbidity and cost of obtaining autogenous MSCs. The future of regenerative medicine in orthopedics and spine may well be the utilization of highly concentrated acellular MSC derived growth factors and especially exosomes.[18-21]

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