

A Physical Therapy Algorithm in the Setting of Orthopaedic Immunobiologics for Unicompartamental Knee Osteoarthritis

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Signaling cell treatments, often referred to erroneously as “stem cell treatments” and “regenerative therapies” are not uniform between clinics and often do not even represent scientifically justified management strategies. In fact, a recent article in the Journal of Bone and Joint surgery illustrated that of the more than 895 clinics claiming to offer “regenerative treatments”, 96% were in violation of both ethical and legal professional standards by making false treatment claims [1]. Sadly, widespread provider unfamiliarity with molecular mechanisms over the last decade has led to widespread patient exploitation with appropriate treatments delayed and patient trust defeated in many settings. Gaining a better understanding of the immunological signaling basis for autologous orthopedic immunobiologics provides the knowledge to make sound clinical decisions where signaling cell treatments are considered.

An adequate work up includes thorough history and physical with appropriate clearance obtained from primary physicians when indicated. Initially, patients with poor alignment or multi-compartment involvement with extensive joint disease on radiographs were not considered good candidates for cell treatments. Recently, these concerns have been refuted by us and other authors who point to clinical and molecular evidence otherwise including excellent clinical results in the setting of more pronounced Kellgren-Lawrence stages. Patients who have “bone-on-bone” changes can be expected to have up to two to five years of at least fifty percent pain relief. Having an unaffected weight bearing compartment facilitates the subchondral healing response and when managed exquisitely, can lead to clinical regression of osteoarthritis symptoms reflected by structural changes. Subchondral nanoplasty techniques that restore Young’s modulus to the stiff bone seek to accomplish that end.

Patients are typically indicated as likely appropriate by history, examination and appropriate weight bearing radiographs including long-standing films. Magnetic resonance imaging Cartigram® (GE Healthcare®, Chicago, IL) sequencing including T2 wetmap and Terracon images define proteoglycan parameters and suggests the potential for chondrocyte differentiation, specialization and migration into new matrix. Patients are not offered the procedure until they are declared candidates and fully understand all risks, benefits and options to treatment, including no treatment. Full informed consent is established, and the procedure is described using the word, “experimental” during full disclosure. Patients are made aware that in spite of our clinically proven success based on prospectively collected data, the procedure is used off-label in this setting and there is no third-party indication or reimbursement for signaling cell arthritis treatment.

In the pre-procedure setting, there is nutrition consultation and patients are trained on the potential benefits of an alkaline diet. Dietary supplementation may be provided and typically includes N-acetylcysteine, ubiquinone, quercetin and NAD+ that patients typically subscribe to for twelve weeks. Clinical consultation prompts laboratory studies and focuses evaluation. An executive lab panel plus is drawn. The labs are necessary and obtained to exclude blood born cancers, infection, anemia and to ensure there is no platelet deficiency (thrombocytopenia). The labs also demonstrate any nutritional deficiency requiring supplementation.

Patients have an advanced concept MR imaging study called a CartiGram® (GE Health®, Chicago, IL) that clearly provides in living color the greatest detail in the extracellular matrix where cartilage cells reside. This advancement in appendicular imaging technology is consistent with the ongoing paradigm shift from reactive to proactive medicine. The axial imaging counterpart, apparent diffusion coefficient (ADC)/diffusion weighted imaging has recently worked its way into clinical medicine and promises to play a big role in the regenerative techniques that presently in use and on the horizon. These advanced imaging techniques predict the clinical onset of arthritis symptoms long before patients present for treatment and should play a larger role in the prevention of disease.

An ideal initial cell harvest is critical to achieve the most therapeutically valuable cell counts. While isopycnic separation is the current gold standard, other looming FDA approved technologies promise to eclipse current cell isolation methods and provide an order of magnitude greater cell delivery, which may further enhance results. Orthopedic and neurosurgeons have the most experience harvesting bone marrow from the anterior iliac crest, where bone turnover is high due to gravitational impact loading along the gluteal pillar with locomotion from heel strike to toe off. Techniques to extract immune cells, mesenchymal stem cells, hematopoietic stem cells, dendritic cells, endothelial cells, pericytes, inflammatory and nucleated cells have been elaborated on at length elsewhere and are beyond the scope of the article. Total nucleated cell counts should be obtained in all patients who undergo signaling cell treatments. Samples from bone marrow aspirate, platelet poor plasma, growth factor concentrate, and bone marrow concentrate should be kept for enzyme linked immunosorbent assay. Samples of effusate may indicate the stage of arthritis and ELISA correlates well to clinical report and condition. Most patients experience two to four years of symptoms after the onset of knee pain due to clinical arthritis, after which joint destruction is eminent. Proteome cytokine shifts in the effusion account for clinical experience of symptoms and wax and wane over a four-year period during which the joint undergoes continual and ultimately end stage destruction. At this point, the opposite weight bearing compartment of the same joint is mechanically involved and disease progression is rapid, leading to deformity and transfer lesions to other articulations.

Multimodality ancillary involvement is critical to achieve long term results and patient satisfaction with their investment. Patients must re-establish normal concavity compression in full extension of the knee joint prior to becoming candidates for the procedure. This ensures full surface area of contact. Failure to accomplish this leads to rim/edge loading akin to internal rotation contracture at the glenohumeral joint. Edge loading equates to third body wear from a physical standpoint. Edge loading is biomechanically coupled to plasma membrane bound second messenger systems through integrin and cadherin mechanoreceptors that incite immunomodulatory catabolic signaling pathways and lead to joint destruction. Patients often initially present with contracture of the posteromedial (varus knee) or posterolateral (valgus knee) corner of the knee that must undergo manual stretching to accomplish results and can take 6 - 12 weeks of a formal therapy program. Patients must achieve their full range of motion or cannot become excellent candidates for signaling cell based nanoplasty procedures.

Static and dynamic unloader bracing is extremely helpful in the pre-procedural setting. All of our patients undergo evaluation by a physical therapist with expertise in gait and locomotion. Balance and gait optimization in all degrees of freedom in stance and throughout locomotion are primary. Subchondral remodeling is the key to a good result in all patients who undergo signaling cell treatments and the weight bearing mechanical axis must be tuned at the time of signaling cell treatment using a combination of unloader bracing for six weeks when gravity dependent following the procedure and an additional six-week period of brace use with impact activities. Patients typically use the appropriate heel wedge orthotics for one to two years to maintain the new mechanical axis and facilitate subchondral bone remodeling.

PreHab

Ideally, in most patients over sixty, a three-week pre-habilitation phase focuses on balance and gait patterns, core range of motion and strengthening and appendicular range of motion and strengthening including weight bearing frontal and transverse plane hip strengthening and stabilization. Patient treatment is critically individualized and the prehabilitation phase may last longer based on circumstance. Often, patients find adequate relief with an exercise program and conservative management strategies even when they have

been told their only option is knee replacement. It must be understood that restoration of full passive and active knee extension range of motion must be achieved to avoid expectation/result mismatch following the procedure. Often, manual stretching is indicated and can take 8 - 12 weeks to achieve the desired resolution of posteriorly based capsular and intrinsic ligamentous contractures.

Younger, more active impact athletes may be more resistant to prehabilitation until they understand the importance of subchondral remodeling in restoring tissue elasticity (Young's Modulus). The attached infographic is helpful in educating patients on the concepts behind both the disease and the treatment.

Below, we describe our basic rehabilitation program for arthritic knee pain patients who elect to undergo signaling cell treatment with primed marrow concentrates. The program is meant to serve as a guide and/or platform that can be modified as the field evolves and is not exhaustive.

Rehabilitation following signaling cell injection for the knee

General guidelines/goals for iSC patients

- Consultation comes from the referring physician and may be more or less specific than current widespread recommendations. Equal assurance of physician and therapist availability is essential for the atypical case where urgent discussion is in the patient's best interest. Any ROM directives AND impact loading restrictions are made clear.
- Unless otherwise indicated therapy will not begin until 14 days post-procedure during which time the active inflammatory phase of healing subsides.
- Restoring balance, full AROM, strength, and most importantly function is the ultimate goal of physical therapy. The final phase of therapy is activity-directed and often specific.
- Participation in a home exercise program (HEP) to supplement in-office therapy visits is essential to maximizing outcomes and regenerative potential.
- Clear communication and consideration of the patient's prior level of function, personal goals, and comorbidities is essential to establishing trust and a successful working relationship between patient and therapist and avoid expectation/result mismatch.
- In-office therapy visits may be scheduled 1 - 3 times per week, including consideration of the patient's schedule availability, distance traveled and financial concerns (if these are limiting factors encouraging one session per week over the course of several weeks is more conducive to a successful outcome rather than more frequent sessions over a shorter duration).
- Progression from one phase to the next is individualized depending on each patient's progression, tolerance to pain, and long-term goals and is not necessarily time dependent. Patients with diabetes or other metabolic considerations typically require more extensive therapy programs, particularly when there is capsular contracture.

Phase 1: (2 weeks)

- Purpose: Initiate active range of motion (AROM) exercises and improve quality of gait mechanics and limb mobility.
- Goal: Achieve full pain-free AROM for flexion, extension and rotation as compared bilaterally, normal patella mobility, and lower extremity flexibility.
- Exercises can be performed once daily unless otherwise indicated.
- Do not force motion or encourage ballistic exercises. Perform all activities deliberately and with control. Avoid sudden movements and sharp, stabbing sensations. Encourage a gradual "stretching" throughout sets and repetitions rather than pushing through the pain.

- If the patient has access to a pool, practicing normal gait mechanics or performing the weight bearing exercises below may be helpful in this setting initially.
- Begin as needed with non-weight bearing quad sets, straight leg raises, heel slides, hip abduction/adduction, pillow squeezes for isometric adduction, and ankle pumps 2 - 3 sets of 10 repetitions.
- NuStep® for 5 - 10 minutes level 5/10.
- Once 90 - 100 degrees of flexion is achieved initiate forward/backward revolutions on a stationary bike with no resistance and work toward completing full revolutions without excessive hip hiking or plantarflexion on the affected side and with minimal discomfort.
- Walking pace gait drills such as marching, toe walking, long steps, backwards steps and leg curls in or out of the parallel bars depending on the patient's balance/fall risk.
- Elliptical beginning with 3 - 5 minutes with no resistance with progressive duration.
- Address any lower extremity flexibility issues as necessary for the hamstrings, iliotibial band, hip rotators, gastroc/soleus, etc. 3 - 5 repetitions with a 20 second hold.
- Ice and/or vasopneumatic compression as needed for 10 - 20 minutes to reduce post-exercise pain and to reduce/control joint effusion can be considered but should not begin until after 14 - 21 days to avoid any extrinsic anti-inflammatory/anti-healing mechanism.

Phase 2: (2 - 6 weeks)

- Purpose: Initiate low impact closed-chain quadriceps strengthening exercises as well as exercises for any additional lower extremity strength deficits discovered during the initial evaluation. Initiate basic lower extremity proprioceptive exercises.
- Goal: Achieve full strength in all planes (grade 5/5 manual muscle testing) with proper mechanics and improve lower extremity proprioception.
- Encourage proper mechanics and neuromuscular control throughout progression of the strength phase.
- Exercises are to be performed every OTHER day for the first six weeks until tolerated otherwise.
- Terminal knee extensions with resistance tubing 30 repetitions.
- Standing calf raises 30 repetitions.
- Double leg press with light to moderate weight for 2 - 3 sets of 10 repetitions, progressing to sets of 15 repetitions.
- Single leg press with light to moderate weight for 2 - 3 sets of 10 repetitions, progressing to sets of 15 repetitions.
- Step ups forward and laterally on a step, mini trampoline, and BOSU 1 - 3 sets of 10.
- Double leg wall slides with a Swiss ball (within any range of motion restrictions for weight bearing flexion).
- Progress to single leg wall slides with a Swiss ball (within any range of motion restrictions for weight bearing flexion) when strength and neuromuscular control allow.
- Double leg sit-to-stands on a plyometric box with a weighted medicine ball 2 - 3 sets of 10 repetitions, progressing to 15 repetitions.
- Progress to single leg sit-to-stands on a plyometric box with a weighted medicine ball 2 - 3 sets of 10 repetitions, progressing to 15 repetitions when strength and neuromuscular control allow.
- Single leg balance/proprioceptive exercises on a level surface with upper extremity activities such as Theraband rows, biceps curls, triceps pushdowns, ropes, etc. 2 - 3 sets of 10 repetitions, progressing to 15 repetitions.

- Progress single leg balance/proprioceptive exercises to unlevel surfaces of increasing difficulty, such as on a 1/2 foam roll or BOSU 2 - 3 sets of 10 repetitions, progressing to 15 repetitions.
- Ice and/or vasopneumatic compression as needed only for 10 - 20 minutes to reduce post-exercise pain and to reduce/control joint effusion.

Phase 3: (6 weeks and beyond)

- Purpose: Progress towards sports-specific or activity-specific goals.
- Goal: Return to patient's prior level of function or beyond, whether the goal is for a specific sport, activity, or simply a return to an independent pain-free daily function.
- Consider that all patients do not have the same goals. Communication is key to establishing these goals and developing a plan to achieve them.
- Progress strengthening and proprioceptive exercises from previous phases, integrating these knee and lower extremity-specific exercises into core and full body movements to replicate functional movements and activities.
- Progress with impact loading only per physician.
- Progress with sports-specific activities such as accelerating, decelerating, cutting, pivoting, etc. only per physician.
- Encourage discussion between patient, therapist, and physician for ultimate long-term activity restrictions.
- Ensure the patient has the necessary written HEP including both pictures and descriptions and is safe and independent with this prior to discharge.
- Consider special equipment for patients who intend to return to impact activity as part of their recreational or vocational pursuits. The AlterG® (Fremont, CA) anti-gravity treadmill is an example.

Bibliography

1. Kingery, *et al.* "Online Direct to Consumer Advertising of Stem Cell Therapy for Musculoskeletal Injury and Disease". *Journal of Bone and Joint Surgery - American Volume* 102.1 (2020): 2-9.

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