Protocol Title: A Prospective Randomized Trial of Biologic Augmentation with Mesenchymal Stem Cells in patients Undergoing Arthroscopic Rotator Cuff Repair

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PI: Brian J. Cole, MD, MBA

1. Purpose of the study –

The purpose of this study is to compare the clinical outcome of arthroscopic rotator cuff repair with and without augmentation with MSCs. Important secondary endpoints include the incidence of persistent structural defects in the tendon following surgery and the incidence of post-operative stiffness.

2. Background & significance –

Mesenchymal stem cells (MSCs) have the potential to differentiate into a variety of adult cells and to provide a source of growth factors for tissue regeneration. They have been used to augment several orthopedic surgical procedures, including rotator cuff repair. Specifically, biologic augmentation of rotator cuff repair with MSCs has been shown to improve healing outcomes compared to standard rotator cuff repair. Furthermore, studies have shown that MSCs used in rotator cuff repair improve tendon integrity, which decreases the likelihood of re-tear that may occur as a result of normal rotator cuff tendon degeneration over time. In addition, stem cells may provide a more favorable biologic environment for recreation of a more normal tendon-bone interface following tendon repair. Ideally, their use can potentially reduce the risk of re-injury or improve muscle function that has been compromised following tendon disruption. The hypothesis is that there will be improved clinical outcomes and reduced incidence of recurrent structural defects in patients undergoing repair with MSCs as compared to the control group.

3. Design & procedures –

This research project will evaluate the efficacy of biologic augmentation of arthroscopic rotator cuff repair with bone marrow-derived mesenchymal stem cells (MSCs) as measured by validated patient reported outcome measures. This study will be conducted as a prospective, randomized trial of 130 patients undergoing arthroscopic repair of full thickness rotator cuff tears with or without MSCs

The primary outcome measure will be the American Shoulder and Elbow Surgeons (ASES) score at one-year follow-up. Important secondary outcome measures include shoulder examination findings (range of motion, shoulder strength, and Rowe Score) and additional validated patient reported outcome measures (PROMs) about shoulder function, symptoms, daily activities, sports/recreation, and general health (the visual analog pain scale (VAS), Constant score, Simple Shoulder Test (SST), SANE score, and VR-12 Health Assessment). Subjects will undergo an MRI scan at 1 year post-operatively to determine the integrity of the repair with comparisons to standard of care, preoperative MRI anatomy and tear description at the time of surgery.

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Secondary endpoints will include structural integrity of the tendon using MRI scan, and functional outcome using objective examination findings. A relationship between use of MSCs, pain, and stiffness may be determined as well.

4. Selection of Subjects –

Patients ages 18-70 who are determined by medical chart review and confirmed by standard of care procedures to have a full thickness rotator cuff tear and elect to have surgery will be invited to participate in this study. Potential subjects will have to meet all of the inclusion criterion and none of the exclusion criterion to participate in the study. Once a patient has met the pre-operative criteria, s/he will be offered the opportunity to participate in this study.

Eligibility

Inclusion Criteria

- Patients ages 18-70
- Patient is determined to have a full thickness rotator cuff tear (1-3 cm) or partial tear converted to a full-thickness tear–on the standard of care, pre-operative MRI scan or found arthroscopically—and is scheduled to undergo surgical repair. Pre-operative MRI data is solely abstracted from the chart.
- Written informed consent is obtained

Exclusion Criteria

- Revision surgery
- Irreparable tear or partial repair
- Any patient lacking decisional capability
- Subscapularis involvement
- Diagnosed musculoskeletal cancer or any diagnosed cancer, other than musculoskeletal if not on long term remission (e.g. at least 5 years or negative biopsy at last exam), except basal cell carcinoma
- Patients who are at higher risk for post-surgical bleeding (e.g., bleeding disorder; taking anticoagulants except low dose aspirin) or post-surgical infection (e.g., taking immunosuppressants; have a severe infection or a history of serious infection or use of systemic steroids)
- Known history of HIV, or has active Hepatitis B or active Hepatitis C
- Alcohol and drug (medication) abuse
- Pregnant or breast feeding women. Females of childbearing potential must agree to use an acceptable birth control method during study participation.
- Patients that have received PRP, other platelet-based product, or investigational treatment in another cell/biologic study for the target shoulder in the 12 months prior to the injection procedure
- Any clinically significant finding that would place the patient at health risk, impact the study, or affect the completion of the study

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- Any psychiatric illness that would prevent comprehension of the details and nature of the study and interfere with follow-up clinic visits
- Contraindications to MR imaging

5. Subject recruitment and compensation –

Patients age 18-70 who are determined by medical chart review and confirmed by standard of care procedures to have a full thickness rotator cuff tear and elect to have surgery will be invited to participate in this study. Potential subjects will have to meet all of the inclusion criterion and none of the exclusion criterion to participate in the study.

Subject will not be compensated for their participation in this study.

6. Consent process –

The patient must be made fully aware of the protocol requirements and s/he must acknowledge his/her understanding and agreement prior to signing the informed consent. Informed consent will be obtained pre-operatively in the office setting or with an econsent through potential subject email via Rush approved, secured electronic platform, Patient IQ. Only patients recommended to undergo full thickness rotator cuff surgery by the treating surgeon will be offered enrollment in the study. Once patients are enrolled, randomization will occur prior to surgery.

The enrollment period will be ongoing until 130 patients are enrolled and all patients will be tracked for 1 year. Follow-up will take place at 7-10 days, 1 month, 6 months, and 12 months. PROMs will be obtained annually for 5 years.

7. Study Interventions –

Timeline of Events

1. Prior to signing the consent, all patients will have obtained a pre-operative MRI and standardized outlet view radiograph of their shoulder as part of their customary evaluation. Pre-operative shoulder exam will be performed, PROMs, and baseline data obtained. Pre-operative data regarding Goutalier staging will be recorded. Pre-operative MRI and shoulder exam data will solely be abstracted from charts. Pre-operative MRI and shoulder exams are not performed for research purposes.
2. Once informed consent is obtained, the patient will be randomized prior to surgery to either the MSC or non-MSC group.
3. Using clinically accepted methods, bone marrow aspiration (from hip, proximal humerus or tibia) will be performed through a small incision prior to arthroscopy in the group undergoing MSC augmentation. A small incision will be made on patients who are not undergoing MSC augmentation in order to maintain patient blinding.

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4. Patient will undergo full thickness rotator cuff repair using a double row, TOE anchor/suture technique. Acromioplasty will be performed in all patients. Alternate procedures such as biceps tenotomy/tenodesis, distal clavicle excision will be performed at the discretion of the surgeon and recorded.
5. Intra-operative data, including size of tear, degree of retraction, and tendon quality, will be obtained during surgery.
6. MSC injection or no MSC injection will be performed according to randomization.
    a. For MSC patients, a total of 6 mL of BMAC will be injected: 3 mL in the tendon at the junction between the bone and tendon; 3 mL in the bone at the site of the footprint
7. Identical rehabilitation using a standard accelerated protocol will be employed.
8. Subjects will return to the office for a follow-up visit at 6 weeks after surgery. VAS, SANE score and passive range of motion will be measured.
9. Subjects will return to the office for a follow-up visit at 6 months after surgery. PROMs and shoulder examination will be obtained.
10. Subjects will return to the office for a follow-up visit at 12 months after surgery. PROMs, shoulder examination and MRI will be obtained.
11. PROMs will be collected annually for 5 years.

	Pre-op	**Rotator Cuff Surgery**	**7-10 days FU**	**1 mo. FU**	**6 mo. FU**	**12 mo. FU**	**24 mo. FU**	**48 mo. FU**	**60 mo. FU**
PROMs	X		X (VAS only)	X	X	X	X	X	X
Shoulder examination			X	X	X	X			
Outlet view radiograph	X								
Intra-operative data collection		X							
MRI of shoulder						X			
Informed Consent	X								

Study Flow Sheet

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Bone Marrow Concentrate Preparation

MSC injection (BMAC) will be prepared from the aspirated bone marrow using the Arthrex Angel System (Arthrex, Naples, FL). This automated centrifuge system rapidly concentrates cellular contents and growth factors in bone marrow aspirate using flow cytometry.

8. Risk/benefit assessment –

There is no direct benefit to the patient for their participation in this study. The results will contribute to the improvement in treatment of full thickness rotator cuff tears in future patients undergoing arthroscopic repair. The study will help determine whether the use of MSCs is needed in these patients with regard to functional outcome and pain relief. Additionally, the study may help conclude whether the use of MSCs is associated with increased pain and stiffness following surgery.

Alternatives to Participation

The alternative to participation in this study is not to participate. Patients who decline to participate will be offered to proceed with the recommended rotator cuff repair, which is the current standard of care. They will return to the office for postoperative follow-up per the rehab protocol for the specific procedure performed.

9. Costs to the subject

There are no additional costs that will be incurred by subjects involved in this study.

All standard of care procedures and costs will be billed to patient insurance.

10. Data Analysis and Statistical Considerations –

A power analysis was conducted based on previously published data by MacDonald *et al.*[1] They reported ASES scores at 2-year follow-up between patients undergoing rotator cuff repair with and without acromioplasty and found a 95% confidence interval of -13.0 to 3.2 for the score difference. Using the reported standard deviation from these 2 study groups, 10 a minimal clinically important difference (MCID) of 10 points in the ASES score,[2,3] and group size of 45 patients each, we would be powered at 81.1% to detect a difference. Due to several reasons, we have had to increase our enrollment number from 100 to 130 participants. We have set a new enrollment goal of 65 patients in each of the groups for the current investigation to account for attrition.

11. Data & Safety Monitoring–

Safety monitoring of subjects will occur throughout the duration of the study.

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12. Data Storage & Confidentiality –

Data will be stored on a password-protected computer with the data maintained on a secure Rush server on Patient IQ. Subjects will be de-identified via the use of a separate document correlating subjects' Athena medical record numbers with a study ID assigned for the sole purpose of this study. At the end of data collection, that key will be destroyed using the Rush secured document disposal service. No social security numbers, addresses, or other personal information will be recorded. Files will not be shared with non-study personnel. Any presentations or publications that result from this study will not identify any subjects individually and may present the data results in an aggregated form.

REFERENCES:

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