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Allograft Tissue Implantation and Inflammatory-Immune Model Considerations for the Treatment of Osteoarthritis

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Abstract

Object: The purported role of inflammation in degenerative joint disease has increasingly been linked. Coincidentally, the effects upon the immune system by inflammation have rendered inflammatory-immune considerations in the treatment of degenerative joint disease as a result.

Setting: Clinical practice.

Methods: Total of 77 subjects. 18 males/24 females were randomized for amniotic allograft tissue implantation with the remainder receiving corticosteroid injection (40 mg Kenalog). Serum blood work was obtained randomly (13 of the 42 total allograft tissue implantation treatment population).

Results: Reduction of pain greater than 30% translating to functional improvement manifested in significant improvement in SF-36 results (Role-Physical and Bodily-Pain domains) was seen in the allograft tissue implantation population (shoulder/knee/hip joint patient population) at three months with the majority extending to six months. These results were not seen in the repeat corticosteroid population. In the glenohumeral joint population, (15/17) receiving allograft tissue implantation reported statistically significant improvement in SF-36 results (Role-Physical and Bodily-Pain domains) and (14/17) reported improved active range of motion with reduction of pain versus (2/10) receiving repeat corticosteroid injection reporting these subjective/objective findings at the three month interval. This benefit was sustained in (10/14) at six months. In the patellofemoral segment, (15/16) test patients reported benefit in the same SF-36 domains coupled with improved active functional range of motion and reduction of pain as compared to (8/20) in the repeat corticosteroid population at three months. At six months, benefit was retained in the allograft tissue population (12/16) versus (2/20) in the repeat corticosteroid population. In the femoroacetabular joint test population, (8/9) reported SF-36 improvement in the corresponding domains coupled with improved active joint range of motion and reduction of pain of at least 30%. (1/5) in the corticosteroid administration subjects reported the same benefit at three months. (8/9) allograft treated subjects preserved benefit at six months with (0/5) corticosteroid patients demonstrated benefit.

Conclusion: As part of targeted multimodal treatment considerations, neuropeptide and amniotic allograft tissue may play an adjuvant role in degenerative joint disease addressment via purported inflammatory-immune pathways.

Keywords: Allograft; Tissue implantation; Osteoarthritis; Inflammation

Introduction

The relevance of adjuvant addressment of inflammation has increasingly grown more prominent. As the shift of treatment relevance has centered on functionality with basic and advanced activities of daily living, so has there been a shift in focus to biomechanics. As an example, the goal of improvement of range of motion about a joint has most notably been tagged to its implication with overall integrated movement with the rest of the kinetic chain. More specifically, addressment of inflammation which is seen as a hindrance to not only joint specific decline in motion and pain but also in affecting the surrounding joints in a similar manner, functional activity is now defined. Specifically, insights into the PI3/AKT/mTOR biochemical pathways with its suggestive links and relation to apoptosis have increasingly been utilized in purported treatment targets as such (Beale) [1-3]. With likely activated programmed cell death, implications in degenerative/inflammatory processes are seen (Cansfield). Examples of this include degenerative osteoarthritic changes seen in weight bearing joints such as the patellofemoral joint. With advancement of degenerative change occurring at this level, biomechanical deficits concomitantly occur as the body is seen compensating, offering assistance in more proximal weight bearing joints (i.e., femoroacetabular and zygapophyseal joints in the lumbar spine). This distribution in mechanical load offers a mediation facilitating a functional activity, in this case ambulation [4,5]. Similarly, with upper extremity activities of daily living, the required and repetitive load borne upon the glenohumeral joint necessitates a functional active range of motion of ninety degrees of external rotation and abduction to perform optimally. Therefore, treatment strategies incorporating regenerative/restorative via inflammatory/immune considerations across the involved interactive kinetic chain has been increasing sought. The use of targeted multimodal analgesic regimens incorporating interventional and adjunctive medicinal means is increasingly being utilized.

Subjects

A total of 77 patients were included in the study. 18 males and 24 females were randomized for amniotic allograft with the remainder to

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receiving repeat corticosteroid injection. Patient population embodied ages 35-72. Clinical diagnosis of osteoarthritis of the glenohumeral joint/rotator cuff impingement (determined by the treating orthopedic surgeon/Physiatrists) was present in 15 cases. Clinical Diagnosis of Osteoarthritis of the patellofemoral joint (grade 2-3 corresponding to 50-75% loss of joint space as determined by the treating Orthopedist/Physiatrist) was present in 18 cases [6,7]. Radiographic evidence of complete rotator cuff tear, biceps tendon tear, acromioclavicular joint dislocation, or clavicular/humoral head fracture was exclusionary features. Similarly, radiographic evidence of meniscal tear, anterior cruciate/posterior cruciate/medial or lateral collateral ligament tear/baker's cyst was exclusionary, moreover. History of acute trauma was an exclusionary feature, in addition [8-10]. In 9 cases, clinical diagnosis (determined by treating Orthopedic surgeon/Physiatrist) of osteoarthritis of the femoroacetabular joint was made. Concomitant radiographic joint space loss of at least 50% was documented. Exclusion criteria included history of trochanteric/femoral neck fracture within the previous six months. Complete joint space loss was an exclusion criterion, moreover [11].

Procedure

Serum blood work was measured pre-treatment and at one and three months. Blood work parameters included inflammatory and immune mediator markers. Specifically Free IGF-1, Free T3, Free T4, TSH, cortisol, serum pregnenolone, Free Testosterone, Erythrocyte sedimentation rate, IgG, IgM, FSH, LH, Free Testosterone levels. Goniometric measurement of joint range of motion was utilized. Concomitantly, functional relevance was measured. The functional measurement scale utilized was the SF-36 health survey. Functionally, joint dependent active range of motion pre-and post-treatment were measured via a goniometer.

All treatment subjects had a prior history of physical therapy and corticosteroid injection without sustained benefit (defined by benefit greater than 4 months duration). Subsequently, patients were randomized to receive repeat corticosteroid injection (all patients last corticosteroid injection was greater than six months prior with reemergent symptoms) or amniotic allograft tissue implantation secondary to pain and persistent functional deficits with basic/advanced activities of daily living. Coincidentally, select patients (in both the allograft tissue implantation and repeat corticosteroid cohorts) were randomized to being given LR3IGF-1 to adjuvantly assist with inflammation and help to promote functional recovery for the duration of 1-2 months, moreover. SF-36 scores were measured pre-treatment, three and six months post treatment.

Materials

40 mg Kenalog coupled with 2 cc of 0.25% bupivacaine or Cryopreserved Amniotic allograft tissue (Skye, Palingen) were utilized.

Results

Amniotic allograft tissue has been increasingly studied in degenerative inflammatory diseases (Buckland). With purported mesodermal/ectodermal derived elements optimally promoted in connective tissue (and to a lesser extent neural/dermal) elements via the placenta, its adjuvant usage in the addressment of inflammation has grown. Its growing involvement in treatment strategies includes dermal wound healing, neurodegenerative conditions, and musculoskeletal degenerative processes (Abdo, Fazelli). This study has sought to further prior work in a more robust manner offering both subjective/objective data that is meaningful from a functional gain standpoint.

The utilization of IGF-1 has been implicated in improving inflammatory levels, improving hormone resistance levels, and addressing immune-mediated factors. It's inclusion in rehabilitation regimens to promote healing and recovery is increasingly being utilized/considered (Ferbert). Amongst the purported rationale for its efficacy includes stem cell and rejuvenatory factor migration in neuromuscular disease (Ferbert). Thus, to adjuvantly address inflammation and to promote the healing process, functional restoration has incorporated advanced treatment considerations. More direct inclusion of treatment measures to address degenerative inflammation may serve to further these treatment goals and improve upon overall functional outcomes. In the glenohumeral osteoarthritic patient, documented Improvement of range of motion most notably with external rotation and abduction was seen. The functional goal of 90 degrees of active external rotation and abduction translating to improved functionality with activities of daily living was seen in 15/17 patients (p value less than 0.01) There was an improvement of perceived pain at the three month interval measured by Visual analog Scale of greater than 30% concomitantly in 14/17. Persistence of greater than 30% (3 grade levels on VAS scale) was seen at 6 month interval in 10/14 that had seen benefit at the three month point (p less than 0.01). In the 10 patients randomized to repeat corticosteroid injection within the medial compartmental space, 8/10 did not receive benefit at the three month interval with the remainder not receiving benefit greater than 30% benefit on VAS pain scale score at the three month point. Of note, in the 2 patients reporting VAS benefit (pain improvement not over 30%), translation to functional improvement (SF-36) was not seen at three months and six months (Role-Physical and Bodily-Pain domains). Moreover, again with a significance value of p less than 0.01, SF-36 domains of Role-Physical and Bodily-Pain domains showed a statistically significant improvement with the allograft tissue sect as opposed to the bio comparator corticosteroid treatment patient population. In the patellofemoral segment, attainment of active range of motion actively to 90 degrees of active flexion and less than 5 degrees of full extension was seen in 15/16 patients (p less than 0.01). Similarly, the improved range of motion translated to improved functional independence, in this case mobility/functional transfers/and ambulation (Role-Physical and Bodily Pain domains). With a degenerative grade ranging from Grade 2-3 correlating with loss of patellofemoral space of approximately 50-70%, improved functional independence was seen across this population sample. This improved functional independence was preserved at the six month interval in 12/16 that had perceived benefit at the three month interval. This corresponded to a calculated p value of less than 0.01) VAS improvement was preserved by12/16 (p less than 0.01), in addition. In the twenty patients randomized to receive repeat corticosteroid injection, 8/20 reported benefit from a pain scale (VAS) standpoint. Similar to the shoulder degenerative joint disease cohort, however, 2/20 receiving initial benefit at three months reported benefit at the six month interval. As seen in the glenohumeral study segment, a statistically significant separation from the bio-comparator corticosteroid population was seen in the allograft tissue implantation patient portion (p less than 0.01).

In the femoroacetabular osteoarthritic cohort, 8/9 individuals reported improved pain relief via the VAS (Visual Analog Scale) of greater than 30% translating to improved functional mobility and functional transfers by the three month interval. This attained benefit was preserved at the 6 month measuring interval in 6 of the 8. Statistically, this has corresponded to a confidence interval of p less than 0.01). VAS improvement at 6 month interval was preserved in all 8. In the five patients randomized to receive intra-articular femoroacetabular

corticosteroid injection, 1/5 reported VAS (pain scale score benefit) reduction of 30%. The lone patient subjectively stating pain benefit did not have SF-36 correlation at three nor six months (Role-Physical and Bodily-Pain domains).

Meaningful reduction of pain is juxtaposed to translation of management of pain to improved functional independence with basic/advanced activities of daily living. Measuring quality of life through a series of eight domains incorporating physical, emotional, social, environmental aspects provides a more meaningful comprehensive insight to patient improvement. With a p value of less than 0.05 statistically significant improvement was seen in the domains of pain (21,22) and Role-Physical domains (13-16) in the patients receiving benefit via measurement of the SF-36 short form questionnaire. Statistical significance was sustained at 6 month interval, moreover.

As previously mentioned, selectively and randomized treatment patients were provided with LR3-IGF1. The subcutaneously administered dose range of 20 mcg to 60 mcg was provided. Serum Blood work revealed increased levels of Free IGF-levels in 5/7 males. Free IGF-1 levels were increased in 3/5 females of note (p value less than 0.05) A total of 13 of the total treatment cohort was concomitantly and randomly treated with LR3-IGF1 (of the 42 total treatment population). 9 patients were randomly selected from the allograft tissue treatment population while 6 were randomly selected from the repeat corticosteroid injection population.

Discussion

Synergistic and progressive benefit in addressment of inflammation has been increasingly sought. Minimally invasive means to assist from a regenerative perspective and to facilitate functional rehabilitational goals has become paramount in treatment goals, moreover. In the current treatment population, the primary focus was the study of functional restoration. With the degenerative process, there is evidence of inflammation playing a central role. With elements of the inflammation cascade produced, immune mediators as well likely become affected. This inflammatory-immune mediated complex has increasingly been studied and has been the focus of many forward treatment regimens with the sole aim being the patient's restoration of function. Indeed, pre-treatment levels in the majority of the study population revealed lower levels of free IGF-1 and evidence of hormone resistance seen in chronic inflammation states (decreased Free T3/4, elevated TSH, and elevated serum glucose/HgBA1C levels).

It is understood that chronic corticosteroid administration can lead to further degeneration of the connective tissue elements, moreover. Additionally, current treatment regimens have oftentimes lead to the utilization of a variety of viscosupplementation alternatives with conflicting long-term results.

Increasingly and alternatively the consideration of allograft tissue/adult mesenchymal cells has become a more prominent consideration in multimodal treatment regimens. Tuoheti et al. delineated that within supraspinatus tendinopathies, advancement of cell apoptosis is seen. The furtherance and propagation of "programmed cell death" alters the healing process (presumably via inflammatory pathways; PI3k/mTOR) likely impair collagen synthesis and alter immune function. Increased cellularity and fibrosis was found to ensue. Angiofibroblastic hyperplasia (Nirschl) specifically was defined. This process is similarly seen in other tendinopathies (Nirschl) and can be extrapolated in consideration with degenerative joint disease. Edwards and Calandruccio have studied whole blood administration and Platelet Rich Plasma injections for the treatment of lateral epicondylitis. At 9.5 months no outcome differential was seen between the treatment regimens. The common thought is that whole blood administration and PRP promote growth factor migration and vascularity, both of which aid in healing and promote collagen formation. As aforementioned, patient functionality has been the focus. In this study, the patient cohort with degenerative osteoarthritis of the shoulder majorly saw a reduction of pain (greater than 30% reduction) translating to improved functionality (Table 1). This was manifested as an improved active range of motion translating to improved ease and capability to perform overhead activities and reach (requiring 90 degrees of abduction and external rotation). Similarly, the patient cohort with degenerative osteoarthritic change in the patellofemoral joint space (grade 2-3 with corresponding loss of joint space of approximately 50-75%), majorly had improved pain scores (30% or above) translating to improved functional capacity (improved SF-36). In the majority of cases, this level of functional independence was retained at the six month point, moreover. In this case, improved independence with functional transfers and walking distance was seen in the majority of cases. Treatment implications support the utilization of allograft tissue implantation in functional recovery. With suggestion of improved active range of motion, and coupled with multimodal treatment regimens incorporating medicinal, interventional, and rehabilitative modalities, the kinetic chain may be more beneficially addressed translating to more meaningful management of pain translating to functional recovery. Singh et al has studied concomitant usage of PRP and Mesenchymal stem cell treatment in the treatment of lateral epicondylitis with pain efficacy measured over 5 years offering additional support. In totality of function, considerations across the entire kinetic chain must be implemented. The inflammatory/degenerative cascade seen in osteoarthritis of the knee certainly contributes to bio mechanical deficits promoting affect/degeneration of the femoroacetabular joint. With the concept of targeted multimodal analgesia incorporating elements of rehabilitational/interventional/appropriate medicinal means, oftentimes the femoroacetabular joint becomes a familiar culprit included in the patient's pain symptomology and thus overall functional decline in functional independence. In this study, once more, concomitant utilization of amniotic allograft tissue has supported possible relevance with pain reduction and overall functional improvement for the treatment subjects. Longitudinal furtherance of study is once more recommended.

In the current study and across the diagnosis treatment array, it is interesting to note that at the three month and even moreso six month interval the VAS pain scale improvement of at least 30% was not only attained but retained in the treatment population. Specifically, inclusive of degenerative joint disease involving the shoulder/hip/knee, the results support plausible benefit with regards to pain reduction in upwards of six months. Furtherance of study examining to ongoing benefit extent past the studied timeframe is certainly warranted (Table 2).

The current treatment strategies for degenerative joint disease has included conservative measures including physical therapy and adjuvant modalities not wholly inclusive off superficial cold, moist heat, and interferential electrical stimulation. Medicinal options have included topical compounds, NSAIDS, and even opioid medications. With failed conservative measures, corticosteroid injection is currently a favored treatment option. With its possible longstanding detrimental effects, options have been sought and utilized. Viscosupplementation results have been conflicting. Similarly, longitudinal results are equally concerning. The advent of adult mesenchymal stem cell usage has mirrored amniotic allograft tissue implantation consideration. With growth factor promotion (VEGF/FGF/BGF) and immunomodulatory

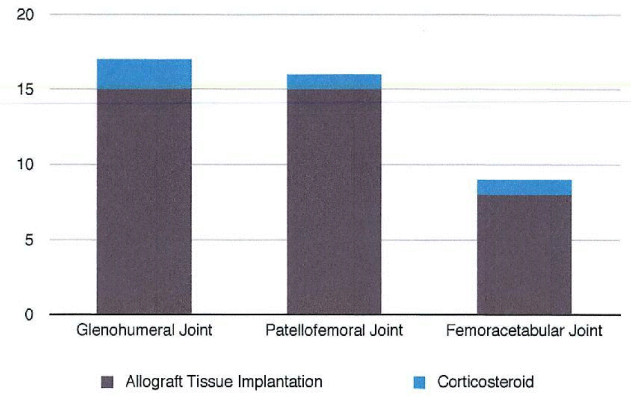

Table 1: Functional active joint range of motion with reduction of pain.

Domain	Allograft tissue Implantation	Corticosteroid	P-Value
Role-Physical 3 Months	7.53	4	<0.01
Bodily Pain 3 Months	2.6	4.8	<0.01
Role-Physical 6 Months	7	4	<0.01
Bodily Pain 6 Months	3.12	5.02	<0.01

Table 2: Functional active joint range of motion with reduction of pain.

benefit (Interleukin 1/3/6/TNF alpha inflammatory marker purported reduction), amniotic allograft tissue usage results inclusive in treatment considerations continues to be encouraging. Stem cell administration has been linked with increased IGF-1 levels. By itself, collagen regeneration, improved immunity, and improved healing have been observed. In a similarly synergistic effort, the combination of peptide and allograft tissue implantation may have similar results. Upon inspection, the implication of improved hormonal resistance translating to additional functional gain has been suggested. Furtherance of study is necessary.

In examining the treatment population, rehabilitation benefit was realized with administration of IGF-1 inclusive in their rehabilitation regimen. An implied functional and pain improvement was seen after plateau was reached with adjunctive utilization of allograft tissue.

Of additional note, 5/12 patients had a history of type 2 Diabetes Mellitus and 4/12 were diagnosed with thyroid disorder. Incidental note of improved HGBA1c (less than 10) was seen in 4/5 test patients. Improved thyroid hormone levels (improved Free T3/4 levels) was seen in 3/4 test subjects. Furtherance of study again is encouraged to further delineate the clinical significance and relevance.

After plateau of functional recovery (deemed by physiatrist/physical therapist), additional functional benefit was seen with allograft issue implantation as compared to the corticosteroid injection treatment cohort. Incremental improvement of management of pain coupled with rehabilitation gains is implied.

Clear separation of percentage benefit may be of some debate as a targeted multimodal analgesic regimen has become standard of care. However, with the focus on the inflammatory-immune model for treatment modification, the benefit of the multimodal treatment may indeed be synergistic. Additionally, possible treatment considerations including neuropeptides (LR3-IGF1) may play a role.

Study Limitations

This study has much strength but is not without limitations. Although the test number sample was significant, the array of joint sites tested was also extensive. Furtherance of double-blinded study focusing on the individual joints would be optimal going forward. Another consideration would be test dosage amount. 2cc of allograft tissue was utilized in the test patients. Variance of this dosage was not used. Additional study assessing the efficacy of repeat dosing should be considered. A significant focus of this study has been the relevance of improved functional gain and independence. Future research should focus on additional supportive functional scales coupled with a more clear separation of benefit individually and separately with regards to neuropeptides and allograft tissue.

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