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Randomized Control Trial

Viable Disc Tissue Allograft Supplementation; One- and Two-level Treatment of Degenerated Intervertebral Discs in Patients with Chronic Discogenic Low Back Pain: One Year Results of the VAST Randomized Controlled Trial

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Background: A viable disc tissue allograft has been developed to supplement tissue loss associated with degenerative lumbar disc disease and the development of chronic discogenic lower back pain.

Objectives: Viable disc allograft was injected into painful degenerated discs to evaluate safety and determine whether it can improve pain and function.

Study Design: Patients received an active treatment of allograft or saline, or continued with nonsurgical management (NSM). Prior to entering the study, patients had back pain for a minimum of 6 months before treatment that was recalcitrant to nonoperative treatment modalities. Standardized outcome measures were used to evaluate the patient's condition before and after treatment. Primary endpoints included improvement in Oswestry Disability Index (ODI) and Visual Analog Scale of Pain Intensity (VASPI). Conventional radiographs and magnetic resonance imaging scans were used to assess disc space height and spinal alignment, and to determine the degree of disc degeneration. Patients were followed for one year after enrollment. The NSM group could cross over to the allograft group after 3 months.

Setting: This multicenter trial was completed in outpatient surgical centers and office injection suites. A total of 218 patients with chronic low back pain secondary to single-level or 2-level degenerative disc disease were enrolled. Inclusion criteria included pretreatment VASPI ≥ 40 mm, ODI score ≥ 40 and symptoms present longer than 6 months. Patients were blinded and randomized to receive intradiscal injections of either viable disc allograft or saline. Patients randomized to the NSM group continued existing treatment. Patients were assessed at 6 and 12 months. Adverse events (AEs) were continually assessed.

Methods: The VAST trial is a prospective, multicenter, blind, randomized clinical trial (RCT) for patients with single-level or 2-level degenerative lumbar disc disease.

Results: At 12 months, clinically meaningful improvements in mean VASPI and ODI scores were achieved in the investigational allograft and saline groups. A responder analysis demonstrated a clinically meaningful reduction in ODI of ≥ 15 points at 12 months that was statistically significant; 76.5% of patients randomized to allograft were responders ($P = 0.03$) compared to 56.7% in the saline group. A responder group characterized by a ≥ 20 point reduction in pain at 12 months achieved a statistically significant reduction in pain compared to the saline group ($P = 0.022$). In the allograft group, 11 safety adverse events occurred in 141 patients (3.5%) and there were no persistently symptomatic AEs.

Limitations: Limitations of this study include a comparison to saline that has been shown to be more representative of an active comparator as opposed to a placebo. In addition, 36 patients were lost to follow-up; this loss resulted in the saline and NSM/crossover groups being smaller than the predetermined group size to have an appropriately powered analysis.

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Conclusions: This large, prospective blinded RCT demonstrated safety and efficacy results indicating that viable disc tissue allograft may be a beneficial nonsurgical treatment for patients who have chronically painful lumbar degenerative discs. Further studies would be optimal to confirm efficacy

Key words: Viable disc tissue allograft, discogenic back pain, allograft supplementation, degenerative disc disease, low back pain, intervertebral disc, intradiscal injection

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Low back pain and referred leg pain are often associated with the development of internal disruption of the disc (IDD) in the lumbar spine (1-4). Alteration of the proteoglycan composition of the central nucleus pulposus can lead to changes in intradiscal pressure and the tissue's ability to handle mechanical loading and stresses. The natural history of pain secondary to IDD tends to be chronic and persistent (5). Chronic low back pain has a substantial economic impact, constituting the second leading cause of missed work, the most common cause of disability worldwide, and resulting in more than half of the opioids prescribed in the United States (6-9). Treatment for discogenic low back pain has varied from nonsurgical management (NSM) (10) to epidural injections (11), intradiscal therapy (12-14), disc arthroplasty (15), and fusion (16-18). Despite many treatments being available, no consensus exists as to the best treatment approach.

Supplementing the intervertebral disc in an intermediate stage of IDD with processed allogeneic disc tissue may support biomechanical function and overcome a loading imbalance resulting from tissue loss and disruption. Several clinical trials have tested both autologous and allogeneic human cellular/tissue therapies in patients with painful IDD and have reported improvements in pain and function (13,19). These early trials have reported on small sample sizes and clinical applications that are limited by the strict inclusion criteria and/or lack of durability.

The Viable Allograft Supplemented Disc Regeneration in the Treatment of Patients with Low Back Pain With or Without Disc Herniation (VAST) Trial was designed as a large, blind, prospective, randomized controlled trial (RCT) to assess patients with discogenic back pain who were treated with disc tissue allograft supplementation. The primary objective of the study was to assess safety and improvement from baseline in 2 clinical endpoints at 12 months. This study reports the one-year data from the VAST Trial assessing the safety and effectiveness of allogenic disc tissue supplementation.

Methods

Trial Design

The VAST Trial is a multicenter, blind, prospective, randomized study. patients were enrolled, and data were gathered under jurisdiction and oversight from the Sterling Institutional Review Board (Atlanta, GA) from August 2017 through March 2020. (Fig. 1). Outcomes of the trial were based on assessment of 2 primary endpoints at 12 months, and secondary endpoints at 6 and 12 months following viable disc tissue allograft supplementation of the intervertebral disc or discs which were compared to saline and sustained NSM. The patients treated had been diagnosed with discogenic pain attributable to disc degeneration as determined by magnetic resonance imaging (MRI), physical examination, and subject-reported pain.

Patients

Patient eligibility included adult patients with one or 2 painful and moderately degenerated lumbar intervertebral discs categorized as modified Pfirrmann grades of disc degeneration grades 3 through 6. Identification of painful discs was done with radiographs, MRI imaging, physical examination, and discography. Enrollment was further limited to patients with a pretreatment Visual Analog Scale of Pain Intensity (VASPI) score ≥ 40 mm, Oswestry Disability Index (ODI) Score ≥ 40, Body Mass Index < 35, symptoms present longer than 6 months, mental capacity to comply with protocol requirements for the 12-month study duration, and no contraindications determined by MRI (Table 1). Radiographic evidence of minimal or no instability was also required with translational instability of ≤ 5 mm on flexion and extension x-rays and angular instability of ≤ 5°. Patients with spondyloarthropathies, prior lumbar spine surgery, Modic type 3 endplate changes, greater than mild facet joint arthrosis, or spinal stenosis were ex-

cluded. All inclusion and exclusion criteria are listed in a pilot study of 25 patients (20).

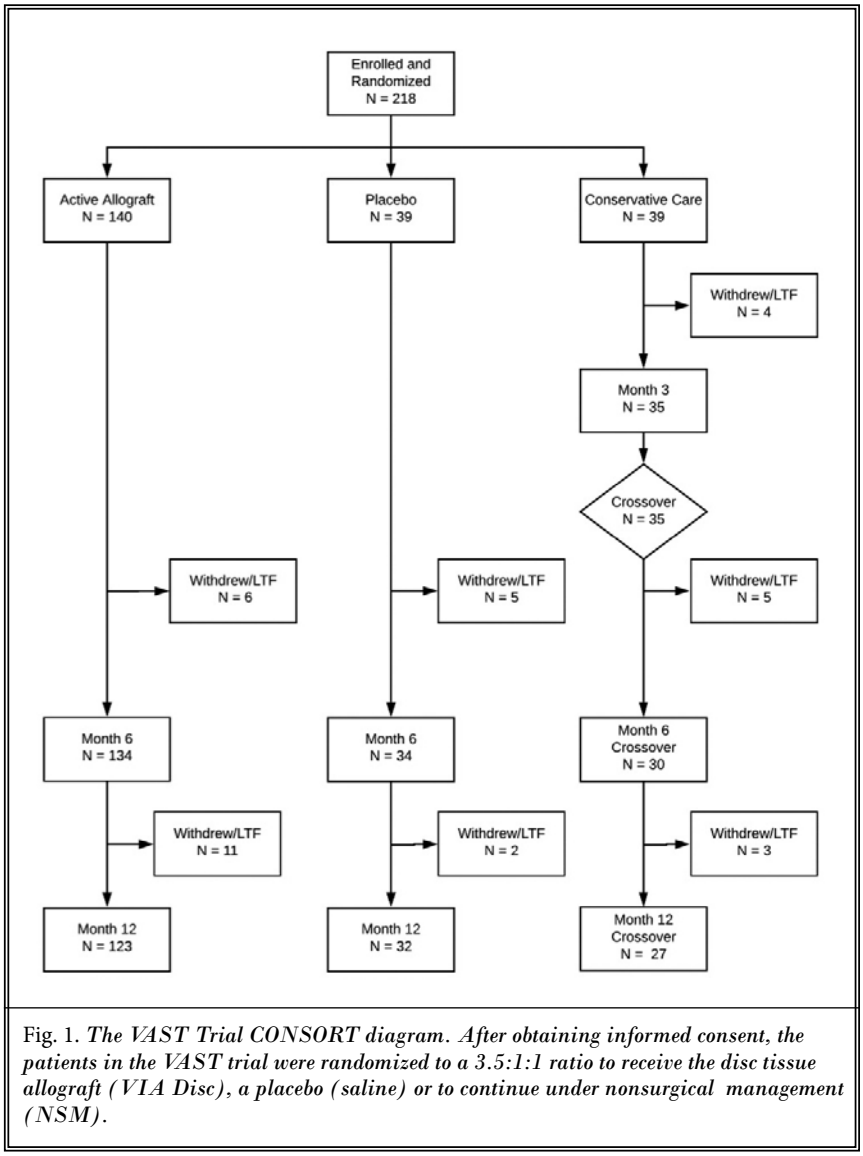

Fig. 1. *The VAST Trial CONSORT diagram. After obtaining informed consent, the patients in the VAST trial were randomized to a 3.5:1:1 ratio to receive the disc tissue allograft (VIA Disc), a placebo (saline) or to continue under nonsurgical management (NSM).*

Interventions

Upon confirmation of eligibility, baseline measurements were collected and retained at individual study sites, and clinical data were monitored independently and entered by a third party (MileStone Contract Research Organization, San Diego, CA). Patients randomized to the investigational active treatment or the saline group underwent intradiscal injections into the center of the lumbar intervertebral disc with either the viable disc allograft (VIA Disc Allograft, VIVEX Biologics, Inc, Miami, FL) (20) or saline.

The procedure was performed under fluoroscopic guidance with primarily local anesthesia or in combination with moderate conscious sedation in an outpatient setting. Placement of the needle was confirmed on fluoroscopic imaging or computed tomography . A total of 1.75 mL of viable disc allograft or saline was injected into the affected disc. In patients treated for 2 levels of disc degeneration, the procedure was repeated with an additional dose of the randomized treatment.

Clinical Outcomes

Each patient completed pre- and postoperative questionnaires in person at each clinic visit, including at baseline prior to treatment. Following the injection procedure, the 2 co-primary endpoints and secondary outcomes were assessed at 6 and 12 months in all cohorts. Patients randomized to the NSM treatment group were seen at 3 months following their initial enrollment in the study. At 3 months, if patients randomized to the NSM group experienced a 10% increase in pain or a 9-point increase in ODI, they were offered an option to cross over to the allograft treatment. This group was then followed at 6 and 12 months following their investigational treatment with the allograft disc tissue.

Secondary outcomes included Short Form 36, x-ray, and MRI measurements, adverse event and serious adverse event (AE/SAE) rates, hospitalization rate, re-operation rate, and resource utilization. Safety data were gathered by the occurrence of treatment and procedure-related AEs and SAEs, study patient withdrawal, and subsequent surgical interventions. In addition, changes in clinical laboratory values and neurological assessments over the course of the study were used to confirm safety.

Table 1. *Demographics and baseline characteristics. Modified intention-to-treat population.*

	Active Allograft n = 140	Placebo n = 39	Conservative Care n = 39
Age, years			
Mean ± SD (n)	42.76 ± 9.63 (140)	43.23 ± 10.83 (39)	42.23 ± 10.90 (39)
Median (Min, Max)	42.00 (19.00, 65.00)	42.00 (20.00, 73.00)	44.00 (19.00, 60.00)
Gender			
Women	43.6% (61/140)	38.5% (15/39)	46.2% (18/39)
Men	56.4% (79/140)	61.5% (24/39)	53.8% (21/39)
Ethnicity			
Hispanic	3.6% (5/140)	7.7% (3/39)	7.7% (3/39)
Non-Hispanic	80.7% (113/140)	76.9% (30/39)	76.9% (30/39)
Body Mass Index, kg/m^2			
Mean ± SD (n)	27.80 ± 4.66 (139)	28.47 ± 4.27 (39)	26.22 ± 5.10 (39)
Median (Min, Max)	28.00 (18.00, 50.20)	28.65 (17.80, 35.40)	26.20 (17.00, 35.40)
Smoking History			
Never	64.3% (90/140)	46.2% (18/39)	66.7% (26/39)
Past Smoker	25.0% (35/140)	35.9% (14/39)	20.5% (8/39)
Current Smoker	10.0% (14/140)	15.8% (6/39)	12.8% (5/39)
History of Endocrine or Metabolic Disorders			
Yes	6.4% (9/140)	12.8% (5/39)	7.7% (3/39)
No	89.3% (125/140)	84.6% (33/39)	92.3% (36/39)
Levels of Treatment			
1 level	57.9% (81/140)	51.3% (20/39)	56.4% (22/39)
2 levels	41.4% (58/140)	48.7% (19/39)	30.8% (12/39)

Patients could report more than one race so numbers may be greater than the total.

Patient Harms and Adverse Events

All AEs were collected, reported, and evaluated by an independent committee for treatment and procedure relationship. All AEs are reported on the ClinicalTrials.gov web site (21). The AEs were systematically classified into preferred terms and system organ class according to the Medical Dictionary for Regulatory Activities using the verbatim language reported by investigators into the case report forms.

Sample Size

The VAST Trial was approved to enroll up to 220 patients randomized to receive viable allograft, or saline, or continued NSM in a 3.5:1:1 ratio at 15 clinical sites.

Randomization – Sequence Generation

The design of the study accepted the premise that NSM would not yield satisfactory outcomes at 12 months after inclusion in the study, so a provision for crossover was included. At 3 months, if patients randomized to the NSM group experienced a 10% increase in pain or a 9-point increase in ODI, the patients were offered an option to cross over to the allograft treatment.

Randomization – Allocation Concealment

A total of 218 patients met the enrollment criteria and were enrolled in the trial. Assignment to allograft, placebo, or continued NSM was done in a randomized manner after informed consent was obtained.

Randomization – Masking

All patients receiving the active treatment or saline were treated identically, apart from the material being injected and the number of levels treated. Patients were blinded to the preparation and delivery of their treatment.

Statistical Methods

The primary endpoints were the change in ODI and average back pain on the VASPI at 12 months after treatment. The hypothesis for both the ODI and the VASPI were: Ho: $\tilde{x}1 = \tilde{x}2 = \tilde{x}3$, where $\tilde{x}1$ was the median pre-post difference in the active allograft group, $\tilde{x}2$ was the median pre-post difference in the placebo group, and $\tilde{x}3$ was the median pre-post difference in the conservative care group. The null hypothesis for this endpoint states that there was no difference in change in ODI and VASPI at 12 months among the 3 treatment groups. The alternative hypothesis was that there was a difference in change in the endpoints at 12 months among the 3 treatment groups.

For both the ODI and the VASPI, the pre-post difference of the groups was compared using the Kruskal-Wallis test at a 2-sided α-level of 0.05. If the result for either test was significant, then the Dwass, Steel, Critchlow-Fligner Method would be used to assess all pairwise comparisons for that endpoint.

AE rates, SAE rates, hospitalization rates, and re-operation rates were summarized by treatment group and compared using the χ^2 test of independence or Fisher's exact test, as appropriate.

Results

A total of 224 patients were enrolled; 6 withdrew prior to receiving treatment, leaving 218 patients. Thirty-six patients voluntarily withdrew or were lost to follow-up prior to the 12-month assessment. One patients terminated the study early due to an AE; 182 patients completed the study. The patients ranged in age from 19 to 73 years (Table 1). Ages varied slightly among the study groups, with the mean age of the patients in the allograft, saline, and NSM/crossover groups being 42.8, 43.2, and 42.2 years old, respectively. Variation in gender was evident in the groups with 43.6%, 38.5%, and 46.2% women in the allograft, saline, and NSM/crossover groups respectively, and 56.4%, 61.5%, and 53.8% men in the same groups for a decidedly male predominance (Table 2). One or 2 levels were treated in each of the 218 patients, resulting in 301 total levels being treated in the allograft, saline, and crossover groups. The degree of disc degenerated was evenly represented in the patients who were appropriately classified according to the modified Pfirrmann scores, but there were also 58 patients with at least one treated level that was outside of the predefined levels of degeneration for inclusion. The analysis of age, gender, and number of levels treated were consistent with the overall results and not driven by one subgroup (Fig. 2). However, it was noted that younger patients had a more favorable outcome compared to older patients in regard to the ODI improvement with an overall

Table 2. *VAST safety data summary.*

A. Serious Adverse Events (SAEs)

	Active Allograft		Placebo		Conservative Care		Crossover	
	Number of Events N	Number of Patients with Events % (n/N)	Number of Events N	Number of Patients with Events % (n/N)	Number of Events N	Number of Patients with Events % (n/N)	Number of Events N	Number of Patients with Events % (n/N)
Total Number of SAEs	6	1.4% (2/141)	0	0.0% (0/38)	0	0.0% (0/39)	0	0.0% (0/35)
General Disorders and Administration Site Conditions	1	0.7% (1/141)	0	0.0% (0/38)	0	0.0% (0/39)	0	0.0% (0/35)
Pain	1	0.7% (1/141)	0	0.0% (0/38)	0	0.0% (0/39)	0	0.0% (0/35)
Infections and Infestations	3	1.4% (2/141)	0	0.0% (0/38)	0	0.0% (0/39)	0	0.0% (0/35)
Bacteremia	1	0.7% (1/141)	0	0.0% (0/38)	0	0.0% (0/39)	0	0.0% (0/35)
Osteomyelitis	2	1.4% (2/141)	0	0.0% (0/38)	0	0.0% (0/39)	0	0.0% (0/35)
Musculoskeletal and Connective Tissue Disorders	2	1.4% (2/141)	0	0.0% (0/38)	0	0.0% (0/39)	0	0.0% (0/35)
Back Pain	2	1.4% (2/141)	0	0.0% (0/38)	0	0.0% (0/39)	0	0.0% (0/35)

Note: Patients were analyzed according to the treatment received at baseline regardless of initial randomization.
Note: Related includes Definitely Related, Related, Probably Related, Possibly Related and Unknown. Relation was determined by independent reviewers.
Note: Crossover includes any Conservation Care Subjects that crossed over and received Active Allograft Treatment.

B. Hospitalization and Reoperation Rate at 12 Months After Treatment

	Active Allograft		Placebo		Conservative Care/Crossover		
	Number of Events N	Number of Patients with Events % (n/N)	Number of Events N	Number of Patients with Events % (n/N)	Number of Events N	Number of Subjects with Events % (n/N)	Overall *P*-value [2]
Hospitalization Rate	9	3.6% (5/141)	0	0.0% (0/39)	1	2.6% (1/39)	.0832
Spinal Procedure Rate [1]	2	1.4% (2/140)	0	0.0% (0/39)	2	5.1% (2/39)	.289

[1] A patient is considered reoperated on if they underwent a procedure for lower back pain. Patient 13-028 in the Active Allograft group had elective hip surgery unrelated to back pain that was not counted.
[2] *P*-value is derived from Fisher's Exact Test

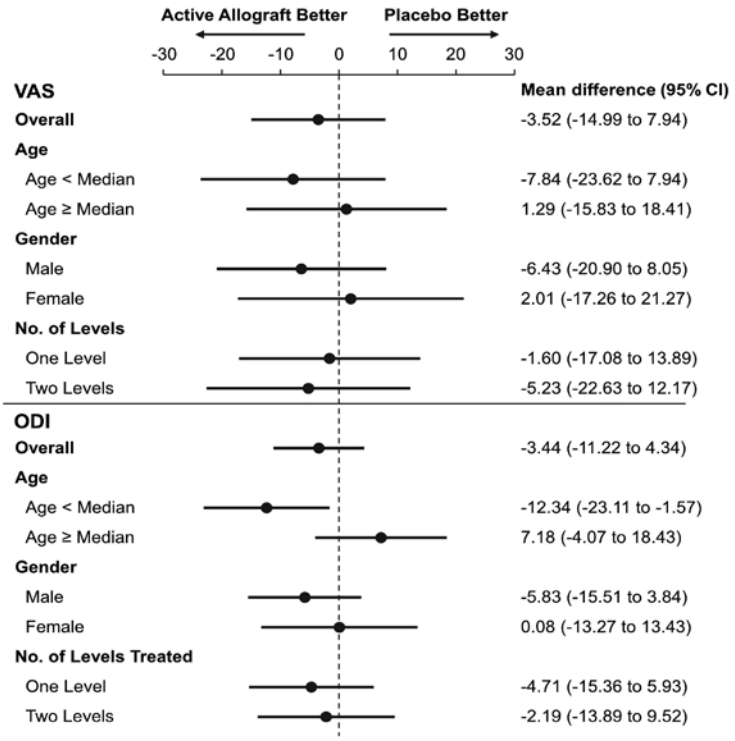

Fig. 2. *Subgroup analysis for age, gender and levels treated on response measured by VAS and ODI at 12 months. The analysis of age, gender, and number of levels treated were consistent with the overall results and not driven by one subgroup. However, it was noted that younger patients had a more favorable outcome compared to older patients.*

P-value of 0.004 for patients less than the median age and an overall *P*-value of 0.244 for the ODI improvement in patients older than the median age.

Procedures

Mean procedure duration was between 10 and 11 minutes for both the allograft and the saline groups for one level, and between 14 and 15 minutes for 2 levels. Approximately 43% of the 301 lumbar discs treated were at L5-S1, 42% at L4-5, 11% at L3-4, 4% at L2-3, and one level was treated at L1-2.

Clinical Outcomes

Clinically meaningful improvements were observed with the viable disc allograft, with a mean reduction in ODI of 27 (Fig. 3) and in VASPI pain score of 34 (Fig. 4) at 12 months post-procedure. Both pain and function worsened in the NSM patients over the first 3 months. All patients in this group crossed over to the investigational allograft treatment group. The magnitude of symptomatic improvement assessed by ODI and VASPI was similar between patients receiving the active allograft and NSM following crossover as both received the same active treatment; one randomized and blinded, the other open label.

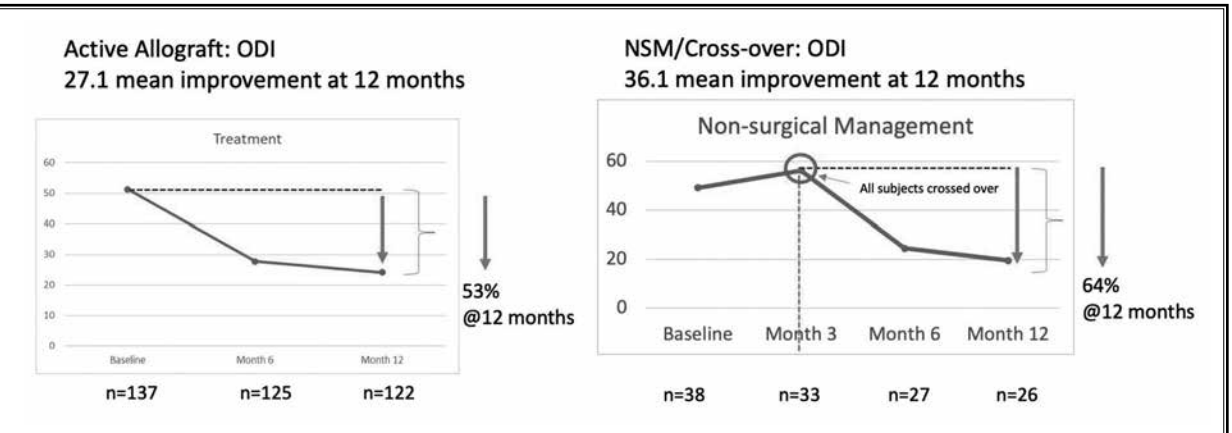

Fig. 3. *Oswestry Disability Index mean improvement with active allograft and cross over groups treated with cellular allograft. The active allograft had a 27.1 point mean improvement in ODI at 12 months (a 53% decrease) and the NSM/crossover group had a 36.1 point mean improvement (64% decrease) at 12 months.*

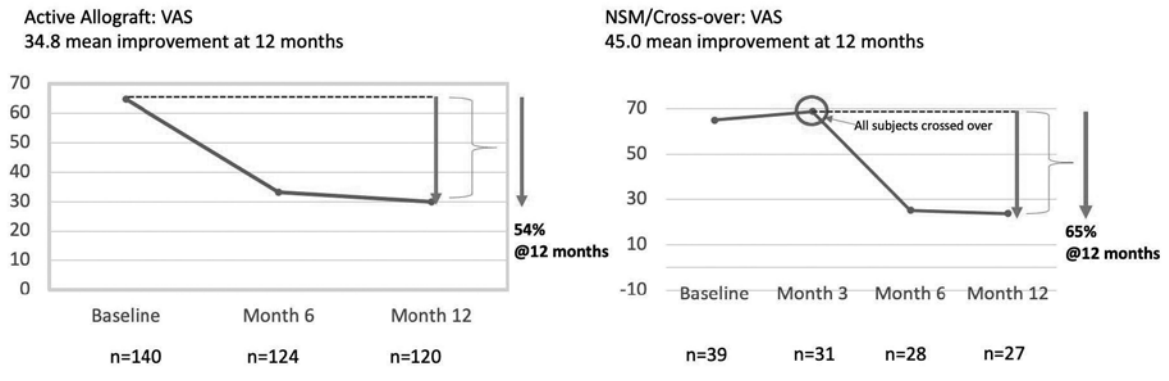

Fig. 4. *Visual Analog Scale mean improvement with active allograft and cross over groups treated with cellular allograft. The active allograft had a 34.8 point mean improvement in VAPI at 12 months (a 54% decrease) and the NSM/crossover group had a 45.0 point mean improvement (65% decrease) at 12 months.*

Pain improved 54% at one year in patients receiving the allograft, which was accompanied by 53% improvement in ODI. Patients receiving NSM following crossover attained a 65% improvement in pain at 12 months combined with a 64% improvement in ODI.

The mean pain reduction at 12 months was 30.5, 34.0, and 46.7 for the saline, allograft, and NSM/crossover groups, respectively, and the mean functional improvement was 23.9, 27.4, and 36.5 for the saline, allograft, and NSM/crossover groups respectively (Fig. 5). A comparison of group means between ODI and VASPI outcomes among the 3 groups, or between the allograft and saline treatment groups, did not reach statistical significance at 12 ≤ months.

The VASPI and ODI results for patients treated at 2 intervertebral disc levels were comparable to patients receiving treatment at one level (Fig. 6). Although the differences in pain and function were not statistically significant, the patients with 2 disc levels treated had a minimally greater clinical improvement than patients receiving treatment at a single level.

Nonsurgical Management (NSM) Group

Thirty-nine patients were randomized into the NSM group. These patients continued with their nonoperative care including pain management and physical therapy and failed to make any significant improvements when evaluated at the 3-month follow-up time frame. Clinical assessment of 35 patients at the 3 months following randomization into the NSM group was completed, demonstrated that they continued to report pain and functional disabilities. All crossed over into the investigational allograft treatment group. Twenty-seven completed the 12-month follow-up. Improvements were similar in both ODI and VAS for the active allograft and NSM crossover groups with pain and functional improvements of almost identical magnitudes.

Responder Group Clinical Outcomes

The modified intention-to-treat population showed significant difference between the allograft and saline groups in a planned analysis of the ODI responders with ≥ 15-point reduction (P = 0.030) and an exploratory analysis of ≥ 10-point reduction (P = 0.008) (Fig. 7). In the planned responder analysis of patients achieving a 50% reduction in pain at 12 months, groups receiving saline (53.5%), disc allograft (62.5%), and NSM/crossover allograft (69.6%) did not demonstrate significant differences (P = 0.467). In additional post hoc analyses, patients who had no back pain, as defined by a VAS score ≤ 20 at 12 months, 43.3%, 50%, and 56.5% of the saline, allograft, and NSM/crossover patients, respectively, reached this low level of pain (P = 0.632). In a responder group characterized by a ≥ 20 point reduction in pain at 12 months, 66.7% and 91.3% of those in the randomized allograft and NSM/crossover allograft groupsachieved a statistically significant reduction in pain compared to the saline treatment group that had a 56.7% reduction in pain (P = 0.022) (Fig. 8).

Patient Harms and Adverse Events

All patient harms and AEs are reported in

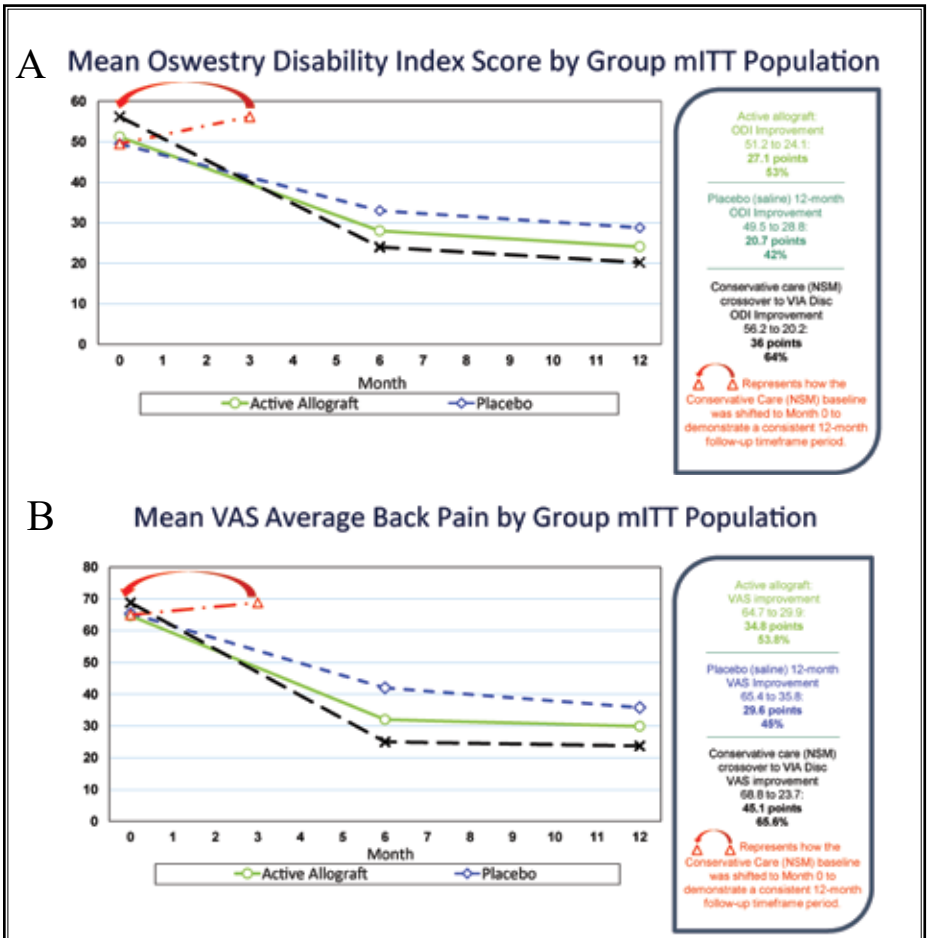

Fig. 5. *A) ODI function scores of 179 patients showed reduction of disability for the saline and active allograft groups but increased disability in the conservative care/NSM group up to month 3 when all patients in this group crossed over to cellular allograft injection. Subsequently all groups experienced a reduction in disability. The saline, active allograft and conservative care to crossover groups had reductions in pain of 23.9, 27.4, and 36.5 points respectively on the ODI scale corresponding to reductions in disability of 42%, 53% and 64%. B) VAS pain scores of 178 patients showed reduction of pain for the saline and active allograft groups but increased pain in the conservative care/NSM group up to month 3 when all patients in this group crossed over to cellular allograft injection. Subsequently all groups experienced a reduction in pain. The saline, active allograft and conservative care to crossover groups had reductions in pain of 30.5, 34.0, and 46.7 points respectively on the VAS scale corresponding to reductions in pain of 45%, 54% and 65%.*

the clinical trial registry on www.clinicaltrials.gov (NCT03709901). There were both a greater total number of AEs and proportion of patients reporting an AE in the allograft group than in either the saline or NSM/crossover group. In the allograft group, there were 66 total events (29.8% of 141 patients) compared to 5 total events (13.2% of 38 patients) in the saline group. There was one total event in the NSM group (2.6% of 39 patients), and 8 total events (11.4% of 35 patients) in the crossover group (P = 0.021). In the allograft group, there were 23 potentially related events (11.3% of patients) compared to no events in the saline group or the NSM group, and 7 events (8.6% of patients) in the crossover group. Most events in the allograft group were musculoskeletal and connective tissue disorders with 41 total events (22.0% of patients) and 14 related events (9.2% of patients). Of these events, the most common was back pain with 22 total events (14.9% of patients) and 8 related events (5.7% of patients), whereas no patients from the saline group and 2.9% of the crossover group reported back pain as a related AE.

The allograft group had a total of 11 SAEs (3.5% of 141 patients) while there were no serious events in the saline or NSM groups, and one event (2.6% of patients) in the crossover group (P = 0.832) (Table 2). Of the 11 SAEs in the allograft group, 6 were considered possibly related to treatment and/or procedure, including pain, back pain, bacteremia, and osteomyelitis. The one SAE in the crossover group was considered not related to treatment or procedure.

Discussion

Treatment efforts for painful degenerative disc disease have recently been focused on the cellular repair of damaged disc tissues (22,23). Biologic materials that have been injected into the intervertebral

disc include fibrin sealant, hyaluronic acid, placental tissue matrices, isolated growth factors, juvenile chondrocytes, platelet rich plasma, and mesenchymal stem cells (13,14,19-21,24). A recent subgroup analysis of these studies showed that stem cells were more effective than chondrocytes resulting in significantly less pain (19,23,25). Based, in part, upon these early and promising findings, a human cellular formulation and micronized allograft disc tissue was developed. The VAST trial represents the first, large, prospective RCT designed to measure the safety and efficacy of disc tissue allograft supplementation in the treatment of painful lumbar IDD.

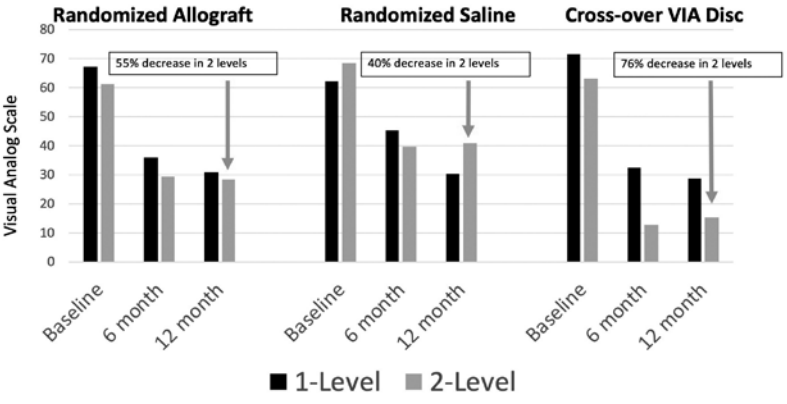

Fig. 6. *The VAS scores obtained at baseline, 6 months, and 12 months show lower levels of pain in patients that received active allograft at 2 levels (gray bars) compared to those patients who received it at one level (black bars). The patients who received saline in 2 of their intervertebral discs had a higher level of pain at 12 months than those who received it in one disc.*

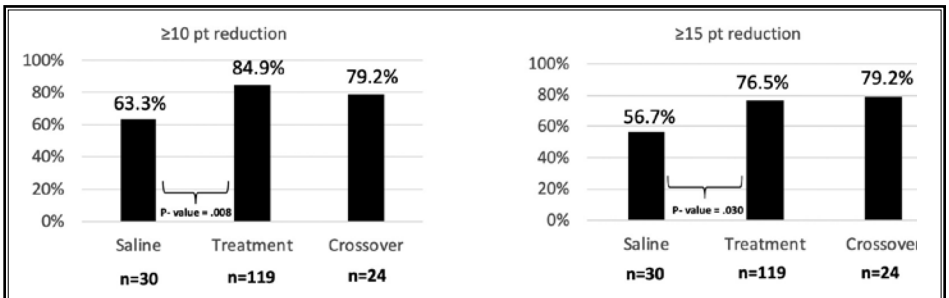

Fig. 7. *The patient responder analysis of the Oswestry Disability Index (ODI) at 12 months shows a statistically significant improvement in function for the patients who responded with a ≥ 10 and ≥ 15-point ODI reduction versus saline treatment. The Minimal Clinically Important Difference (MCID) for the functional response was 15 and this was statistically significant at P = 0.030.*

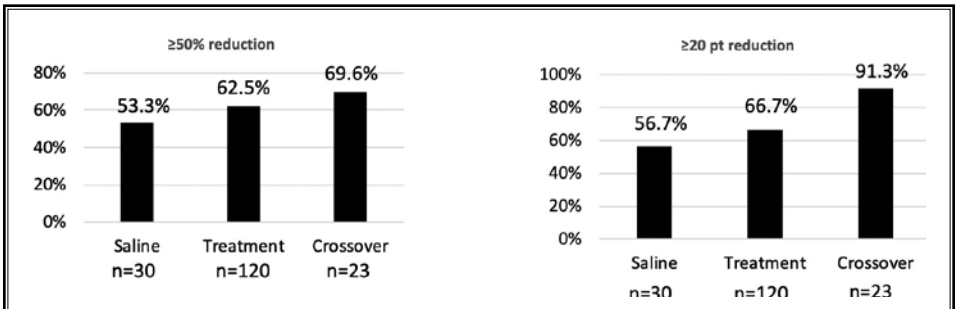

Fig. 8. *Planned responder analysis of ≥ 50% VAS improvement (P = .467) and ≥ 20-point VAS improvements (P = .022). The patient responder analysis of the Visual Analog Scale (VAS) at 12 months shows in the planned responder analysis groups where patients achieved a greater than 50% reduction in back pain at 12 months, 53.3%, 62.5% and 69.6% of patients receiving saline, allograft, and NSM/crossover treatments achieved this level, respectively (P = .467). In a responder group characterized by a ≥ 20 point reduction in pain at 12 months, 66.7% and 91.3% of the allograft and NSM/crossover patients respectively, achieved a statistically significant reduction in pain compared to the saline treatment group that had a 56.7% reduction in pain (P = 0.022).*

Limitations

Limitations of this study include a significant loss to follow-up over the course of the study and using an active comparator treatment arm. Thirty-six patients were lost to follow-up during the study, either because their perceived improvement prompted discontinuation, or whether a treatment failure caused them to seek other clinical options. A multiple imputation analysis was performed to address missing data specifically caused by those lost to follow-up and demonstrated that the results from this analysis were consistent with the pri-

mary analysis. With the randomization scheme, loss to follow-up resulted in saline and NSM/crossover groups that were smaller than the predetermined group size to have an appropriately powered analysis.

Additional limitations include the duration of follow-up being limited to one year as well as the treatment that was limited to 2 levels and therefore cannot be extrapolated to patients with more than 2 levels of IDD and discogenic low back pain.

There was a disproportionately larger number of smokers in the saline group. Smoking is known to contribute to degenerative disc disease and the larger number of patients in the allograft group that had never smoked creates an imbalance in the groups for a known exacerbating factor for DDD. This is a factor that limits the randomness of the groups.

Saline intradiscal injections may be associated with certain limitations when used as a control in RCTs (24). Although data directly comparing saline to placebo in this clinical setting are not available, several studies have been published indicating that saline may elicit clinical responses in excess of those expected for a placebo control. RCTs investigating the efficacy of injections in disc degeneration, disc herniations, or disc/back pain have reported on the use of intradiscal saline injections (26,27). Across these studies, differences between the control and comparator arms were generally smaller in those studies using saline as a control than those using placebo. Similarly, the responses observed in this study (45% reduction of pain in the saline cohort, Fig. 5) suggest a far higher than expected response for the control arm, indicating that saline injections may be more representative of an active comparator rather than a placebo.

Generalizability

The need for an effective treatment for stable discogenic low back pain is necessary as the existing treatments are marginally effective and often very expensive (28-35). The VAST study is the largest RCT to show clinically meaningful outcomes for a viable disc tissue allograft with approximately 3 times the summed total patients from 6 studies assessed in the random-effects analysis by Wu et al (19); none of which were randomized or compared to another treatment. If all of the treated intervertebral discs are considered, the 301 levels in the VAST trial outnumbers the discs treated in the Wu analysis by a factor of four-fold. With the inclusion of 2 levels of disc degeneration for treatment, this VAST study is reflective of patients commonly seen in clinical practice with discogenic low back pain (36,37).

Interpretation

This blinded RCT demonstrates that viable disc tissue allograft is safe and suggests that it may be an effective nonsurgical treatment for patients who have chronically painful lumbar degenerative discs. Clinical benefits were seen in functional activities and reduction in pain out to 12 months. Thirty-five patients (35/39; 90%) in the NSM group failed nonoperative treatment regimens and at 3 months into the study they elected to crossover into the investigational active treatment allograft group.

The comparatively better pain and functional results in the crossover group may partially be due to a placebo effect given that all of the patients knew they had an option to receive active treatment if their NSM treatment was insufficient to control their symptoms. The patients in the crossover group also tended to have consistent noninterventional treatments for their back pain which could have played a role in their symptom improvement compared to the allograft group.

The treatment or procedure-related AE rate over 12 months was 11.3% with 23 total AEs across 141 patients treated with allograft. The most common AE was back pain, which is an AE that is known to occur after intradiscal injection, such as discography, and this was by far the most common AE noted in the patients receiving intradiscal injections (38,39). The treatment or procedure-related SAE rate over 12 months was 1.4% with 6 total SAEs across 141 patients treated with allograft. Most events in the allograft group were musculoskeletal and connective tissue disorders with back pain the most commonly reported event. The group injected with saline had back pain as their most commonly reported AE. Bacteremia and osteomyelitis accounted for 3 of these events in 2 patients. Osteomyelitis or discitis is a serious adverse event that is known to occur after intradiscal injections, such as discography, and has been reported in the literature ranging from 0.2% to 4.92% of patients (40,41). The rate of osteomyelitis observed in this study falls within the expected range. This safety profile reflects an extension of the previous reported safety data (20).

Conclusions

This large prospective, blinded RCT showed clinical improvements across all 3 treatment groups. A statistically significant difference was not shown when comparing the mean difference among groups. However, statistically significant differences were achieved in 2 of 3 ODI subgroups and one VASPI subgroup in patients treated with allograft disc supplementation compared to a saline placebo with durable results out to 12 months. Thirty-five patients (35/39; 90%) in the NSM group failed nonoperative treatment regimens and at 3 months into the study they elected to crossover into the investigational active treatment allograft group. The proportional improvements in pain and function were nearly identical in patients receiving an allograft regardless of the timing of administration during the trial. The patients treated with viable disc tissue allograft also exhibited significantly higher functional responder rates than the saline arm, indicating promising benefits for patients with painful lumbar degenerative discs. Patients that were treated with 2-level treatments with allograft did better than those receiving one-level treatment, but this difference was not statistically significant nor was this difference seen in the patients receiving saline. The safety profile of the supplemental allograft was demonstrated to carry a risk similar to discography. Further clinical studies are needed to investigate the efficacy of viable disc tissue supplementation with a more accurate neutral comparator in the clinical design to better understand this treatment's therapeutic effect.

Trial Registration

This trial is registered on www.clinicaltrials.gov (NCT03709901).

Author Contributions

DPB and TG contributed to study design. DPB, TTD, MJP, KA, EY, GLW, RB, WT, SG, and ML enrolled patients and collected data. DPB, TTD, MJP, KA, MPL, HJM, TG, and ML contributed to data interpretation, manuscript development, and content approval. DPB, TTD, MJP, KA, MPL, HJM, TG, and ML were publication committee members and made final decisions about data submission.

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