

Randomized Controlled Trial of Micronized Dehydrated Human Amnion/Chorion Membrane (dHACM) Injection Compared to Placebo for the Treatment of Plantar Fasciitis

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Abstract

Background: Failure of conservative management to reduce/eliminate symptoms of plantar fasciitis (PF) may indicate need for advanced treatments. This study reports Level I evidence supporting 3-month safety and efficacy of micronized dehydrated human amnion/chorion membrane (dHACM) injection as a treatment for PF.

Methods: A prospective, single-blind, randomized controlled trial was conducted at 14 sites in the United States. Subjects were randomized to receive 1 injection, in the affected area, of micronized dHACM (n=73) or 0.9% sodium chloride placebo (n=72). Safety/efficacy assessments were conducted at 4 weeks, 8 weeks, 3 months, 6 months, and 12 months postinjection, using visual analog scale (VAS) for pain, Foot Function Index–Revised (FFI-R) score, and presence/absence of adverse events. Primary outcome was mean change in VAS score between baseline and 3 months expressed as difference in means for treatment versus control subjects. Secondary outcome was mean change in FFI-R score between baseline and 3 months expressed as difference in means for treatment versus control subjects.

Results: Baseline VAS scores were similar between groups. At the 3-month follow-up, mean VAS scores in the treatment group were 76% lower compared with a 45% reduction for controls ($P < .0001$), FFI-R scores for treatment subjects had mean reduction of 60% versus baseline, whereas control subjects had mean reduction of 40% versus baseline ($P = .0004$). Of 4 serious adverse events, none were related to study procedures.

Conclusion: Pain reduction and functional improvement outcomes were statistically significant and clinically relevant, supporting use of micronized dHACM injection as a safe and effective treatment for PF.

Level of Evidence: Level I, prospective randomized trial.

Keywords: dehydrated human amnion/chorion membrane, chronic pain, plantar fasciitis

Inflammation of the plantar fascia, or plantar fasciitis, is a common condition. In the United States, approximately 1 million outpatient visits are made annually for plantar fasciitis.¹⁶ Plantar fasciitis is characterized by classic signs of inflammation, including pain, swelling, and loss of function. It frequently presents as heel pain that is most severe during the first few steps after prolonged inactivity or is exacerbated by increased activity. A diagnosis of plantar fasciitis is generally based on patient-reported symptoms, history, and physical examination.

Historically, plantar fasciitis was believed to be a chronic inflammatory condition. However, recent histopathologic

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studies of tissue from people with plantar fasciitis demonstrate changes similar to tendinopathy and to chronic problems at the sites where tendons or ligaments insert into bone (entheses).⁶ These conditions involve collagen degeneration, fiber disorientation, increased ground substance, and an absence of inflammatory cells. Thus, the underlying pathology of plantar fasciitis may be more degenerative than solely inflammatory.⁶

The current recommended treatment of acute tendonitis or tenosynovitis, which may also be applicable to plantar fasciitis, generally focuses on the need for resting the affected tendon and avoiding exacerbation of the underlying inflammatory condition. Rest, ice, compression, and elevation (RICE) are typically recommended as a first-line treatment.² Heat, splinting, and anti-inflammatory analgesics such as aspirin or nonsteroidal anti-inflammatory drugs can complement the initial recommended treatment. Dedicated heel cord stretching and massage may be effective in treating this condition.⁵

Plantar fasciitis can be a challenging and frustrating condition for both patient and clinician as several months to even years of treatment may be required before symptoms subside with conservative management.⁴ During this prolonged treatment interval, a degenerative process related to repetitive micro-tearing and inflammation of the plantar fascia may occur, and the pain from chronic inflammation and injury to the connective tissue becomes refractory to conservative management.^{17,19} Treatments that can interrupt the process of degeneration before long-term damage has occurred are desirable from both clinical and financial perspectives.¹⁹

Given the prolonged and often recurrent treatment periods, and in particularly acute or refractory conditions, a number of newer treatment methods have been used with varying levels of success. These treatments include low-level laser therapy, ultrasound, extracorporeal shock wave therapy, topical nitroglycerine, and endoscopic and open operative procedures.¹ For most of these treatment modalities, there is little, or no, Level I scientific evidence available to support their efficacy as a treatment for plantar fasciitis. Injection of corticosteroids in the area of inflammation or the peritendinous sheaths is also frequently employed, although this is somewhat unsatisfactory in that injected steroids are not without complications and cannot be used repeatedly. Regular use of corticosteroid injections has been associated with tendon rupture and tissue atrophy.¹³ Given the variability of efficacy, significant cost, and untoward side effects of current therapies, additional evidence-based treatment options are needed.

Physicians and researchers have hypothesized that growth factors and/or stem cells may provide benefit as a treatment for tendinopathies with the potential to reverse the degenerative process and encourage the regeneration of healthy tendon.¹ Human amniotic membrane contains

essential, active, healing growth factors. Amniotic membrane is a unique material containing collagen types IV, V, and VII, and is composed of structural extracellular matrix, which also includes specialized proteins, fibronectin, laminins, proteoglycans, and glycosaminoglycans. In vivo and in vitro studies have shown that the biochemical properties of amniotic membrane help to modulate inflammation and enhance soft tissue healing, with antibacterial and pain reduction properties.¹⁴ Tissue repair is mediated through the growth factors contained in the membrane tissue.

An effort to harness the natural healing properties inherent in amniotic tissue in a way that allows for its use in a variety of treatment modalities has resulted in a commercially available dehydrated human amnion/chorion membrane (dHACM) allograft. A proprietary PURION process, in use since 2006, safely and gently separates placental tissues obtained from screened and tested donors, cleans and reassembles layers, and then dehydrates the tissue.⁸ The dHACM allografts are available in sheet/membrane, mesh, and micronized configurations for homologous use in operative, soft tissue, tendon, and nerve applications. A micronized dHACM processed through the PURION process (AmnioFix Injectable, MiMedx Group Inc, Marietta, GA) is injectable when suspended in 0.9% sodium chloride.

In 2013, results of an 8-week, 45-patient, single-center, randomized controlled feasibility study showed that micronized dHACM allograft injection was effective in reducing pain and improving function for patients diagnosed with chronic plantar fasciitis.²⁰ Our purpose was to provide additional evidence regarding the safety and efficacy of micronized dHACM as a treatment for plantar fasciitis with a large, multicenter, prospective, single-blinded, randomized controlled trial of micronized dHACM injection compared to saline placebo injection in patients diagnosed with plantar fasciitis.

Methods

Subjects were enrolled in a prospective, single-blind, randomized controlled trial conducted at 14 clinical sites across the United States from March 2015 through July 2017. In order to achieve a representative enrollment, 7 study sites were located on the East Coast, 2 in the Midwest, and 5 on the West Coast. Of these 14 centers, 9 sites were affiliated with hospital systems and 5 were private practices. The study sponsor (MiMedx Group Inc) was responsible for choosing qualified investigators, ensuring proper monitoring of the investigation, and ensuring that the US Food and Drug administration (FDA) and all participating investigators were promptly informed of significant new adverse events or risks identified during the course of the study.

Patients presenting to the study sites and having a diagnosis of plantar fasciitis were assessed for study eligibility

Table 1. Study Inclusion and Exclusion Criteria.**Inclusion Criteria**

1. Confirmed diagnosis of plantar fasciitis for ≥ 1 mo (30 d) and ≤ 18 mo by the investigator
2. VAS pain scale of ≥ 45 mm at randomization
3. Plantar fasciitis with conservative treatment for ≥ 1 mo (30 d), including any of the following modalities:
 - RICE
 - Stretching exercises
 - NSAIDs
 - Orthotics
4. Diagnostic radiograph within 6 months of enrollment showing view of calcaneus negative for calcaneal fracture or structural abnormalities
5. BMI ≤ 40
6. Age ≥ 21 y and < 80 y
7. Ability to sign informed consent and release of medical information forms

Exclusion Criteria

1. Prior surgery or trauma to the affected site
2. Subjects requiring bilateral plantar fasciitis treatment at time of enrollment
3. Prior use of any lower limb injection therapy, including corticosteroids or PRP in either limb within the last 3 months
4. Has diabetes either type I or type II
5. Systemic disorders associated with enthesopathy (disorder of entheses, ie, bone attachments) such as Gout, Reiter syndrome, rheumatoid arthritis, etc
6. The presence of diagnosed comorbidities that can be confused with or can exacerbate the condition—to be assessed by radiograph—including but not limited to:
 - calcaneal stress fracture
 - nerve entrapment syndrome (diagnosed as Baxter nerve syndrome)
 - fat pad atrophy
 - acute traumatic rupture of the plantar fascia
 - calcaneal tumor
 - tarsal tunnel syndrome (diagnosed)
 - significant bone deformity of the foot that may interfere with the study
7. Affected site exhibits clinical signs and symptoms of infection
8. Known allergy or known sensitivity to aminoglycosides
9. Clinically significant abnormal laboratory tests at baseline, including CBC, PT/PTT/INR, liver function and creatinine, as determined by the investigator
10. Subjects who are nonambulatory
11. History of *more than 14 days treatment* with immunosuppressants (including systemic corticosteroids) or cytotoxic chemotherapy within 30 d prior to enrollment, or who are anticipated to require such medications during the course of the study
12. Prior radiation at the site
13. Use of any investigational drug(s) or therapeutic device(s) within 3 mo preceding enrollment
14. Immune disorders including systemic lupus erythematosus (SLE), fibromyalgia, acquired immunodeficiency syndrome (AIDS), or human immunodeficiency virus (HIV)
15. History of any condition (including drug or alcohol abuse, medical or psychiatric condition) that is likely to impair understanding or compliance with the study protocol, in the judgment of the investigator
16. Pregnancy at enrollment or within last 6 months, women who are breastfeeding, or women of childbearing potential who are planning to become pregnant during the time of the study OR are unwilling/unable to use acceptable methods of contraception (birth control pills, barriers, or abstinence)
17. Workers' compensation subjects

Abbreviations: BMI, body mass index; CBC, complete blood count; INR, international normalized ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; PT, prothrombin time; PTT, partial thromboplastin time; RICE, rest, ice, compression, elevation; VAS, visual analog scale.

based on inclusion and exclusion criteria presented in Table 1. Eligible patients who agreed to participate in the study read and signed an institutional review board (IRB)–approved informed consent form prior to any study involvement. The study protocol underwent full review and was approved by the Western Institutional Review Board (WIRB) for 5 sites whereas the remaining 9 sites had their respective local IRB review and approve the study. The study was preregistered in ClinicalTrials.gov (NCT02427191) and

was submitted as a Phase 2B Investigational New Drug (IND) to the FDA under the IND number 16095.

Randomization to the study group assignment was generated via an online, password-protected, centralized, and automated randomization routine. At the time of randomization, site staff used a secure online tool log in, verified that the subject met all eligibility requirements, confirmed subject consent, and then proceeded with the request for patient group assignment. This study employed a variable

block design with block sizes of 4, 6, and 8 for randomization. Once a patient was randomized, the site and sponsor were notified of the assignment and identifier of the patient.

Consenting subjects were randomized in a 1:1 ratio to receive either micronized dehydrated human amnion/chorion membrane (micronized dHACM) injection (treatment group) or 0.9% sodium chloride, USP placebo injection (control group). Each subject received 1 injection of either 1 mL micronized dHACM or placebo. The treatment group received 1 injection of sterile micronized dHACM. The micronized dHACM product, packaged in double-pouched, single-use, glass vial, contains 40 mg of the product. Prior to injection, the vial was filled by the physician with 1 mL of 0.9% sodium chloride solution as the vehicle to suspend the micronized dHACM. The placebo injection was composed of 1 mL sterile 0.9% sodium chloride solution. Injections were performed using a standard 3-mL syringe with a 22- to 25-gauge needle. For both groups, the injection site was chosen along the medial side of the index foot, 3 to 4 cm superior to the most painful area of the plantar fasciitis. The needle was pointed downwards from horizontal and advanced until it traversed resistant fascia. The investigator was encouraged to assist dorsiflexion of foot to render the plantar fascia taut and easy to identify. The use of topical anesthetics at the injection site was permitted and used at investigator discretion; however, these products could not be mixed and administered simultaneously with the micronized dHACM or placebo material.

Although the nature of the treatment precluded blinding of clinical staff, patients were blinded to their treatment assignment and unaware if they were receiving micronized dHACM or placebo. Postinjection, all subjects were provided with a controlled ankle motion (CAM) boot and instructed to wear it for the first 2 weeks. They were also provided with a night splint to wear in the evenings. After the second week postinjection, the patient could gradually return to tennis shoes with an over-the-counter orthotic as tolerated, and by week 4 allowed to resume normal activity.

For the purposes of this study report, data were analyzed to conduct an evaluation of safety and efficacy after the 3-month follow-up visit. Per study protocol, study visits were conducted at 4 weeks, 8 weeks, and 3 months, with additional long-term follow-up visits at 6 and 12 months postinjection. Initially, there was to be additional follow-up at 24 months, but the protocol was modified to allow for the final study visit to occur at 12 months (after consultation with FDA). At each study visit, pain was assessed using the visual analog scale (VAS) for pain, function was assessed by the Foot Function Index-Revised (FFI-R), and presence or absence of adverse events was assessed and documented.

Primary efficacy endpoint was the change in VAS score for pain for subjects between baseline and 3 months

expressed as the difference in means between the micronized dHACM treatment group versus the placebo control group.

The VAS for pain is a unidimensional measure of pain intensity, which has been widely used in diverse adult populations, including those with rheumatic diseases.⁷ The VAS for pain is a single-item scale which is most commonly anchored by “no pain” (score of 0) and “pain as bad as it could be” or “worst imaginable pain” (score of 100 [100-mm scale]). It was self-completed by the subject at each visit.

To assess safety, all adverse events experienced by patients during the course of the trial were collected by site and reviewed by the Clinical Events Committee. This reporting also included the classification of an event as a serious adverse event, the determination of the severity of the event, and an assessment of events considered possibly related to the micronized dHACM product or to the injection procedure.

Secondary endpoint for this study was the mean change in functional score as assessed by the Foot Function Index-Revised (FFI-R) at 3 months in the treatment group versus the control group. The FFI-R is a self-reporting measure that assesses multiple dimensions of foot function based on patient-centered values.^{2,3} The FFI-R assessment quantifies the impact of foot pathology on pain, disability, and activity limitation in patients, as well as psychosocial activities and quality of life related to foot health. Study subjects completed the FFI-R assessment at each visit.

Study Participants

A total of 154 subjects were screened for entry into the trial and 147 were ultimately enrolled and randomly assigned to one of the 2 groups (treatment or control). One hundred forty-five subjects received an injection of either micronized dHACM or placebo and were in the intent-to-treat population, with 73 subjects in the treatment group and 72 subjects in the control group. Five subjects, 3 in the treatment group and 2 in the control group, did not have data for their 3-month visit because of a missed visit or were lost to follow-up (Figure 1). Their last known observation was carried forward (LOCF) for final analysis of 3-month outcomes.

Clinical Characteristics

Patient demographics and clinical characteristics are presented in Table 2. Of the 145 randomized and treated subjects, the majority (84) were female (57.9%) and Caucasian (125/86.2%). Overall, 67 (46.2%) were considered obese with a BMI greater than 29.9, and 94 (64.8%) were between the ages of 40 and 60 years. Subjects in the control group had a mean age of 53.0 years, which was greater than the

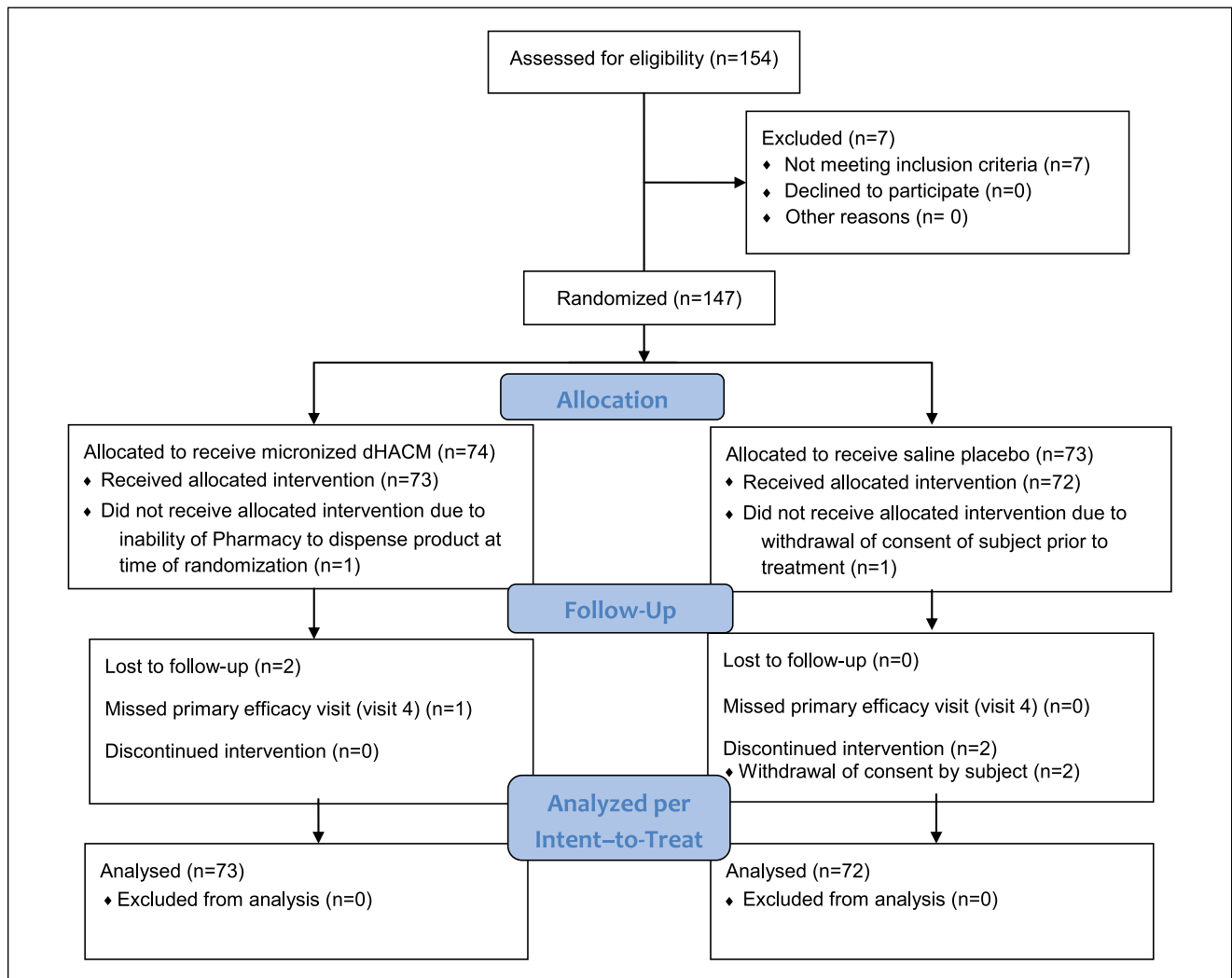


Figure 1. Consort flow diagram.

mean age of 48.7 years for those in the treatment group. All subjects had been receiving conservative treatment with RICE and orthotics for plantar fasciitis symptoms for at least 30 days prior to study enrollment.

Statistical Methods

Sample size determination was conducted using PASS 15 Sample Size software, with estimates based on tests for 2 groups of pre-post scores. This analysis assesses the superiority of micronized dHACM plus 0.9% sodium chloride solution over 0.9% sodium chloride solution placebo alone in the treatment of plantar fasciitis. Group sample sizes of 58 in treatment group and 58 in the control group achieved 90% power to detect a difference between the mean difference scores. Assuming a dropout rate of 10%, group sample sizes of 65 in each group would mitigate the risk of losing sufficient power for analysis over time. The main

point of interest in this test was to compare the change across time in the treatment group to the change across time in the control group. Assumptions for this analysis include a 20-point difference in the mean change of treatment group minus the mean change of the control group with a standard deviation of 34.7 at both time points with an overall correlation between time points of 0.55. The test statistic used was a 2-sided, 2-sample *t* test on the paired differences.

The intent-to-treat population (all randomized patients receiving treatment) was used as the basis for the demographics, efficacy, and safety analyses. Efficacy analyses were conducted using a 2-sided 0.05 significance level and a 2-sample *t* test on the paired differences; demographic analyses were conducted using a 2-sample *t* test for continuous data and Fisher exact test for categorical variables. For missing values, the last known value was used as the final outcome. A linear mixed model (LMM), which is a method

Table 2. Demographics and Clinical Characteristics.^a

	Treatment (n=73)	Control (n=72)	P Value
Gender			.3140
Female	39 (53.4%)	45 (62.5%)	
Male	34 (46.6%)	27 (37.5%)	
Age, y	48.7 ± 11.0	53.0 ± 9.0	.0112
	49 (21, 69)	53 (28, 74)	
Race			.2324
American Indian or Alaska Native	0 (0%)	3 (4.2%)	
Asian	3 (4.1%)	2 (2.8%)	
Black or African American	5 (6.8%)	4 (5.6%)	
Caucasian	62 (84.9%)	63 (87.5%)	
Other	3 (4.1%)	0 (0%)	
Ethnicity			>.9999
Hispanic or Latino	10 (13.7%)	9 (12.5%)	
Not Hispanic or Latino	63 (86.3%)	63 (87.5%)	
BMI	29.5 ± 4.4	29.4 ± 4.6	.8853
	29.5 (21.2, 37.1)	29.3 (19.8, 39.2)	
Obese (BMI >29.9)	35 (48.0%)	32 (44.4%)	.7399
Duration of PF symptoms at enrollment (d)	179.3 ± 101.7	205.8 ± 124.4	.1640
	167.5 (31, 505)	183.0 (42, 541)	
VAS pain score (BL)	71.2 ± 13.0	70.8 ± 11.6	.8347
FFI-R score (BL)	59.5 ± 21.3	55.4 ± 18.7	.2238

Abbreviations: BL, baseline; BMI, body mass index; FFI-R, Foot Function Index–Revised; PF, plantar fasciitis; VAS, visual analog scale.

^aData are presented as n (%), mean ± standard deviation, or median (minimum, maximum).

used to analyze interindividual differences in intraindividual changes over time, was utilized to assess efficacy measures while controlling for possible covariates. The LMM assessed the impact of treatment group on VAS for pain and FFI-R scores over time, across baseline, 1-month, 2-month, and 3-month visits, while controlling for demographic variables, which consisted of body mass index (BMI), age, and gender as fixed effects and study site as a random effect. The LMM utilized restricted maximum likelihood estimation (REML) whereas compound symmetry was selected for specifying the covariance structure.

Results

Study Outcomes

The primary efficacy endpoint was change in VAS score for pain between baseline and the 3-month follow-up visit. At baseline, VAS scores were similar for treatment and control subjects ($P = .8347$). At the 3-month follow-up visit, the mean VAS scores in the treatment group were 76% lower compared with a 45% reduction in mean VAS scores for controls, which equated to a 54-point drop in the treatment group vs a 32-point drop in the control group ($P < .0001$) (Table 3). Overall, at the 3-month study visit, 60 (82.2%) of

subjects in the treatment group, and 34 (47.2%) of subjects in the control group reported at least a 50% reduction in VAS score from baseline ($P < .0001$).

A linear mixed model (LMM) was used to control for possible covariates influencing VAS scores and treatment outcome. Similar to a regression model, the LMM calculates a linear relationship between explanatory variables and the dependent variable (VAS pain) for repeated visits. Age and BMI were categorized into 4 levels each based on (1) minimum–quartile 1; (2) quartile 1–median; (3) median–quartile 3; and (4) quartile 3–maximum levels. Results of the LMM model are presented in Table 4. Treatment group was a significant factor in predicting VAS pain scores while controlling for all other variables within the model ($P = .002$). Study visit, which is indicative of changes occurring over time, was also a significant factor in predicting VAS pain scores in general when controlling for other factors in the model ($P < .0001$). Additional covariates examined in the LMM included demographics associated with plantar fasciitis: age, gender, and BMI. When controlling for other factors in the model, gender was found to have a significant impact on VAS scores ($P = .0165$). In general, women reported higher VAS scores than men. Although there was a disparity in mean age between the treatment and control groups, output from the LMM

Table 3. Primary Study Outcome.

	VAS Baseline	VAS 3-mo	Paired Difference ^a (Baseline–3-mo)
Treatment (n=73)			
Mean ± SD	71.2 ± 13.0	17.1 ± 23.6	54.1 ± 24.9
95% CI	68.1, 74.2	11.6, 22.6	48.3, 59.9
Control (n=72)			
Mean ± SD	70.8 ± 11.6	38.8 ± 31.2	31.9 ± 30.4
95% CI	68.0, 73.5	31.5, 46.2	24.8, 39.1
Two-sample <i>t</i> test on paired differences			<.0001

Abbreviations: CI, confidence interval; SD, standard deviation; VAS, visual analog scale.

^aDifference in VAS pain score between baseline and 3 months. Two-sample *t* test on paired differences.

Table 4. Results of a Linear Mixed Model (LMM) Analysis Used to Control for Possible Covariates Influencing VAS Pain Scores and Primary Treatment Outcome.

Type III Test of Fixed Effects ^a	F Value	P Value
Treatment (micronized dHACM or placebo)	9.7	.002
Study visit (BL, 4-wk, 8-wk, 3-mo)	188.9	<.0001
Age	0.4	.7685
Gender	5.8	.0165
BMI	1.8	.1396
Treatment × Visit ^b	9.7	<.0001

Abbreviations: BL, baseline; BMI, body mass index; dHACM, dehydrated human amnion/chorion membrane.

^aAge and BMI each transformed into categorical variables at 4 levels based on Q1, median, and Q3 values.

^bUsing linear mixed model between BL and 3-month endpoints (4 visits in total); 145 subjects.

indicates that when controlling for other variables including treatment, visit, gender, and BMI, age was not a significant factor in predicting VAS pain scores ($P = .7685$), nor was BMI ($P = .1396$). Of note, the interaction between treatment group and visit was statistically significant ($P < .0001$), indicating that as visits progressed over time from baseline to 3 months, there was a significant difference in the reduction of pain scores between micronized dHACM and control groups. In other words, the trajectory of pain scores was significantly lower for micronized dHACM-treated patients over time starting at baseline and progressing to the 3-month visit. After adjusting for covariates in the LMM, the least squares adjusted means at the 3-month time point between micronized dHACM treatment and controls are significantly different ($P < .0001$), with micronized dHACM generating a significantly lower VAS pain score of 17.0 versus 38.3.

The secondary study endpoint was change in FFI-R score between baseline and 3 months. At 3 months, subjects who received micronized dHACM injection had a mean reduction of 60% in FFI-R score compared to baseline, whereas subjects who received the saline placebo had a mean reduction of 40% in FFI-R score at 3 months compared with baseline, which equated to a 36-point drop in

the treatment group and a 22-point drop in the control group ($P = .0004$). Although FFI-R scores were similar between the groups at baseline ($P = .2238$), subjects receiving micronized dHACM injection had a significantly greater mean difference between baseline and 3-month FFI-R scores compared with those receiving placebo (Table 5). The LMM analysis (Table 6) showed that when controlling for all factors in the model, visit, BMI, and gender were significant at explaining the variance in FFI-R scores overall ($P < .0001$, .0216, and .0244, respectively). FFI-R scores were lower as visits progressed and higher with increased BMI and female gender. FFI-R scores were not influenced by age ($P = .3169$). The interaction between treatment group and visit was statistically significant ($P = .0002$), indicating that from baseline to 3 months, as visits progressed over time, there was a significant difference in the improvement of function as determined by FFI-R scores between micronized dHACM and control groups. After adjusting for covariates in the LMM, least squares adjusted means at the 3-month time point between micronized dHACM treatment and controls were significantly different ($P = .0286$), with micronized dHACM generating a significantly lower FFI-R score of 24.1 versus 32.4.

Table 5. Secondary Outcome.^a

	FFI-R Baseline	FFI-R 3-mo	Paired Difference (Baseline–3-mo) ^b
Treatment (n=73)			
Mean ± SD	59.5 ± 21.3	23.7 ± 23.6	35.7 ± 22.6
95% CI	54.5, 64.5	18.2, 29.3	30.5, 41.0
Control (n=72)			
Mean ± SD	55.4 ± 18.7	33.2 ± 26.2	22.2 ± 22.0
95% CI	51.0, 59.8	27.0, 39.4	17.1, 27.4
Two-sample t test on paired differences			<.0004

Abbreviations: CI, confidence interval; FFI-R, Foot Function Index–Revised; SD, standard deviation.

^aData presented as mean ± standard deviation, 95% CI, as indicated.

^bDifference in FFI-R score between baseline and 3-month scores. Two-sample t test on paired differences.

Table 6. Results of a Linear Mixed Model (LMM) Analysis Used to Control for Possible Covariates Influencing FFI-R Score and Secondary Treatment Outcome.

Type III Test of Fixed Effects ^a	F Value	P Value
Treatment (micronized dHACM or placebo)	0.1	.8152
Study visit (BL, 4-wk, 8-wk, 3-mo)	138.2	<.0001
Age	1.2	.3169
Gender	5.1	.0244
BMI	3.3	.0216
Treatment × Visit ^b	6.6	.0002

Abbreviations: BL, baseline; BMI, body mass index; dHACM, dehydrated human amnion/chorion membrane; FFI-R, Foot Function Index–Revised.

^aAge and BMI each transformed into categorical variables at 4 levels based on Q1, median, and Q3 values.

^bUsing linear mixed model between BL and 3-month endpoints (4 visits in total); 145 subjects.

Safety/Adverse Events

All untoward medical occurrences during the course of the study, whether or not considered to be treatment or study related, were recorded as adverse events per the Medical Dictionary for Regulatory Activities (MedRA) coding guidelines used by regulatory authorities in the pharmaceutical industry during the regulatory process. During the study period, 30 subjects in the treatment group and 39 subjects in the control group experienced 71 and 98 adverse events, respectively. Based on MedDRA categories, the 5 most frequent adverse events occurring in study subjects, which were not believed to be treatment related, included musculoskeletal and connective tissue disorders (43); injury, poisoning, and procedural complications (15); infections and infestations (12); nervous system disorders (13); and skin and subcutaneous tissue disorders (8). Any medical occurrence that resulted in death, was life-threatening, required hospitalization, or resulted in persistent or significant disability, was considered a serious adverse event. Four serious adverse events occurred, 1 in the treatment group and 3 in the control group. These serious adverse events were unlikely to be related to the study and included a groin abscess and methicillin-resistant *Staphylococcus aureus*

(MRSA) infection, deep vein thrombosis and saddle pulmonary embolism, a medial meniscus tear and degenerative changes, and difficult urination. Finally, there were 3 adverse events that were considered possibly related to the micronized dHACM product; however, the Clinical Events Committee determined these events were anticipated, normal events associated with the product. These adverse events included 2 cases of postinjection pain at the injection site and 1 case of postinjection itching.

Discussion

Treatments for plantar fasciitis that can interrupt the process of inflammation and degeneration before long-term damage has occurred are desirable from both clinical and financial perspectives. Generally, when treating plantar fasciitis, the primary goals for both patient and clinician are pain relief and functional improvement. Our purpose was to evaluate the safety and efficacy of micronized dHACM injection as a treatment for plantar fasciitis. The results of this multicenter randomized controlled, single-blind study provide Level I evidence as to the efficacy of micronized dHACM injection over placebo injection in reducing pain associated with plantar fasciitis and improving function.

Subjects receiving 1 micronized dHACM injection had a significantly greater reduction in VAS scores for pain between baseline and 3 months postinjection than those subjects receiving placebo injection. Subjects receiving micronized dHACM also had a significantly greater improvement in function at the 3-month assessment compared with those receiving placebo. To evaluate product safety, all untoward medical occurrences were thoroughly documented as adverse events during the study period, even if the investigator believed the event was not considered to be treatment or study related. These adverse events were further evaluated by a Clinical Events Committee. There were no unanticipated adverse events attributed to injection of the micronized dHACM product.

Our findings are not unprecedented and support the conclusions of a previous study that examined the feasibility of injecting micronized dHACM as a treatment for plantar fasciitis.²⁰ In the previous single-center, randomized controlled trial including 45 subjects diagnosed with refractory plantar fasciitis, 30 received treatment with micronized dHACM. Patients receiving micronized dHACM injection had significantly greater improvement in both physical and mental scores compared to controls after 8 weeks (all $P \leq .002$). No adverse events related to treatment were observed in any study subjects. Zelen²⁰ concluded that micronized dHACM allograft injection is an effective treatment for patients with chronic plantar fasciitis and may reduce costs by decreasing the need for repeat office visits or costly operative interventions. The present study provides further evidence to support the safety and efficacy of micronized dHACM injection as a treatment for plantar fasciitis.

Human amniotic membrane is a reproductive tissue composed of amnion and chorion layers. Amniotic membrane in its native form has inherent properties that enhance the healing process. These properties include being immunoprivileged, modulating inflammation and reducing scar tissue formation.¹⁴ It is also recognized that amniotic membrane is a reservoir of multiple growth factors involved with tissue growth and regeneration.¹⁴ For these reasons amniotic membrane presents remarkable therapeutic potential for wound healing, tissue repair, and regenerative therapy.^{12,15,18}

The PURION processed dHACM allografts, composed of both amnion and chorion layers of the amniotic membrane, have been shown to contain important biological molecules including collagen, connective tissue, cytokines, and growth factors that work to modulate inflammation and promote healing.⁸⁻¹¹ These growth factors include EGF, TGF- β , and FGF, which are known to stimulate epithelial cell migration and proliferation, and PDGF A and B, which stimulate many metabolic processes, including general protein and collagen synthesis, collagenase activity, and chemotaxis of fibroblasts and of smooth muscle cells.⁸⁻¹¹ Results from both in vitro and in vivo experiments have

established that dHACM contains one or more soluble factors capable of stimulating mesenchymal stem cell migration and recruitment into the area of implantation.¹⁰ Clinicians are increasingly examining therapeutic strategies to augment intrinsic or operative repairs of bone, tendon, and ligaments. Biologic treatments aim to provide mechanical durability or augment the biologic healing potential. Such treatments may use scaffolds, genes, growth factors, and cell delivery. PURION processed dHACM products deliver human extracellular matrix components, essential growth factors, and specialized mediating cytokines all of which may regulate and enhance the healing process.⁸⁻¹¹

Strength of the present study lies in its randomized, multicenter design, providing Level I evidence as to efficacy of micronized dHACM injection for treatment of plantar fasciitis. The 3-month assessment allowed for better evaluation of safety and efficacy outcomes over a longer period of time than the prior 8-week study.²⁰ While we currently only report 3-month outcomes, subjects continue to be followed through 12 months, and these results will be reported in a subsequent manuscript. Our results are limited as the comparative group received placebo injection; thus, we cannot speak to the effectiveness of micronized dHACM allograft versus, or as an addition to, other advanced therapies. As study subjects received only 1 treatment, we do not know if additional injections would further improve efficacy.

In 2007, the annual economic burden in direct costs related to ambulatory care visits, physical therapy, medications, exercise counseling/education, for treatment of plantar fasciitis was estimated to be between \$192 and \$376 million.¹⁹ Physician and inpatient charges of operative intervention for chronic plantar fasciitis range up to approximately \$10000 per case.¹⁹ Injectable treatments such as micronized dHACM are variable in cost, depending on dose, product distribution method, and frequency of treatment, and for these reasons we did not attempt to perform a cost analysis at this time with only 3-month outcomes. If long-term results continue to support efficacy of 1 micronized dHACM injection for reduction of pain and improved function, it stands to reason that the product would prove cost-effective through a reduction in direct costs such as those outlined above, especially those related to treatments that may require multiple or repeated injections, and reduced indirect costs related to quality-of-life factors.

Although treatment group subjects experienced significantly greater improvement in both pain and function during the study period, subjects in the control group reported a reduction in pain and improved function over time as well. This is not unusual in that symptoms of plantar fasciitis often may reduce over time as supported by our statistical analysis. We also must acknowledge that blinding of subjects as to treatment received may have resulted in a placebo effect. All patients were instructed on off-loading, night splinting, and orthotics; thus, we are unable to

comment on how these standard interventions may have impacted study results in either the treatment or control group.

In conclusion, the results of the present study provide Level I evidence regarding the safety and efficacy of micronized dHACM injection as a treatment for plantar fasciitis. Treatment with micronized dHACM resulted in a statistically significant and clinically relevant reduction in pain and improved function.

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Editor's Note

The authors are to be commended for performing a high-quality prospective, randomized trial. They did find a 76% decrease in VAS pain score at 3 months in the dHACM group vs control and a 60% decrease in Foot Function Index score in the treatment group vs 40% decrease in the control group. It is unfortunate that they have only reported their 3-month outcomes despite seeing the patients at 6 and 12 months after enrollment. It is unknown whether the beneficial effects of the treatment persist without this information, but the results, although encouraging, are preliminary at best. Also, no information about the cost of this injection, which is always important with new treatment modalities especially in our current health care environment, is given. They mentioned the economic burden of this disease but did not give any type of cost estimate. One could also argue that enrollment in the study after only 30 days of conservative treatment was not a long enough period of conservative treatment; however, because many practitioners will give a steroid injection after 30 days of failed conservative treatment, I believe this was a reasonable time period.

Declaration of Conflicting Interests

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References

- Andres BM, Murrell GAC. Treatment of tendinopathy: what works, what does not, and what is on the horizon. *Clin Orthop Relat Res*. 2008;466(7):1539-1554.
- Budiman-Mak E, Conrad KJ, Mazza J, Stuck RM. A review of the Foot Function Index and the Foot Function Index—Revised. *J Foot Ankle Res*. 2013;6:5.
- Budiman-Mak E, Conrad K, Stuck R, Matters M. Theoretical model and Rasch analysis to develop a revised Foot Function Index. *Foot Ankle Int*. 2006;27(7):519-527.
- Cornwall MW, McPoil TG. Plantar fasciitis: etiology and treatment. *J Orthop Sports Phys Ther*. 1999;29(12):756-760.
- DiGiovanni BF, Nawoczenski DA, Malay DP, et al. Plantar fascia-specific stretching exercise improves outcomes in patients with chronic plantar fasciitis. A prospective clinical trial with two-year follow-up. *J Bone Joint Surg Am*. 2006;88(8):1775-1781.
- Goldin M, Malanga GA. Tendinopathy: a review of the pathophysiology and evidence for treatment. *Phys Sportsmed*. 2013;41(3):36-49.
- Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: visual analog scale for pain (VAS Pain), numeric rating scale for pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res*. 2011;63(suppl 11):S240-S252.
- Koob TJ, Lim JJ, Massee M, Zabek N, Denoziere G. Properties of dehydrated human amnion/chorion composite grafts: implications for wound repair and soft tissue regeneration. *J Biomed Mater Res B Appl Biomater*. 2014;102(6):1353-1362.
- Koob TJ, Lim JJ, Massee M, et al. Angiogenic properties of dehydrated human amnion/chorion allografts: therapeutic potential for soft tissue repair and regeneration. *Vasc Cell*. 2014;6:10.
- Koob TJ, Rennert R, Zabek N, et al. Biological properties of dehydrated human amnion/chorion composite graft: implications for chronic wound healing. *Int Wound J*. 2013;10(5):493-500.
- Maan ZN, Rennert RC, Koob TJ, et al. Cell recruitment by amnion chorion grafts promotes neovascularization. *J Surg Res*. 2015;193(2):953-962.
- Manuelpillai U, Moodley Y, Borlongan CV, Parolini O. Amniotic membrane and amniotic cells: potential therapeutic tools to combat tissue inflammation and fibrosis? *Placenta*. 2011;32(suppl 4):S320-S325.
- Margo KL. ACP Journal Club. Review: corticosteroids improve short-term outcomes but worsen longer-term outcomes in some types of tendinopathy. *Ann Intern Med*. 2011;154(4):JC2-JC5.
- Niknejad H, Peirovi H, Jorjani M, et al. Properties of the amniotic membrane for potential use in tissue engineering. *Eur Cell Mater*. 2008;15:88-99.
- Parolini O, Solomon A, Evangelista M, Soncini M. Human term placenta as a therapeutic agent: from the first clinical applications to future perspectives. In: Berven E, ed. *Human Placenta: Structure and Development*. Hauppauge, NY: Nova Science; 2010:1-48.
- Riddle DL, Schappert SM. Volume of ambulatory care visits and patterns of care for patients diagnosed with plantar

- fasciitis: a national study of medical doctors. *Foot Ankle Int.* 2004;25(5):303-310.
17. Thomas JL, Christensen JC, Kravitz SR, et al. The diagnosis and treatment of heel pain: a clinical practice guideline revision 2010. *J Foot Ankle Surg.* 2010;49(3)(suppl):S1-S19.
 18. Toda A, Okabe M, Yoshida T, Nikaido T. The potential of amniotic membrane/amnion-derived cells for regeneration of various tissues. *J Pharmacol Sci.* 2007;105(3):215-228.
 19. Tong KB, Furia J. Economic burden of plantar fasciitis treatment in the United States. *Am J Orthop.* 2010;39(5):227-231.
 20. Zelen CM, Poka A, Andrews J. Prospective, randomized, blinded, comparative study of injectable micronized dehydrated amniotic/chorionic membrane allograft for plantar fasciitis—a feasibility study. *Foot Ankle Int.* 2013;34(10):1332-1339.