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Initial phase I safety of retrovirally transduced human chondrocytes expressing transforming growth factor-beta-1 in degenerative arthritis patients

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Abstract

Background aims. TissueGene-C (TG-C) represents a cell-mediated gene therapy for localized delivery of allogeneic chondrocytes expressing transforming growth factor (TGF)-β1 directly to the damaged knee joint. Untransduced human chondrocytes (hChonJ cells) have also been incorporated into the TG-C product at a 3:1 ratio with TGF-β1-expressing chondrocytes (hChonJb#7) in order to help fill in the defect and as target cells for the actions of the expressed TGF-β1. *Methods*. A phase I dose-escalating clinical trial was performed to evaluate the safety and biologic activity of TG-C in patients with advanced osteoarthritis of the knee joint (full thickness cartilage defect) that was refractory to existing non-operative therapies. Following a single intra-articular injection into the joint space of the damaged knee, patients were monitored for safety, and an evaluation was performed to assess the pharmacokinetics and biologic activity of TG-C. *Results*. There were no treatment-related serious adverse events. Swelling, effusion and minor localized reactions such as warming sensation or itching were observed in a dose-dependent manner at the injection site. Knee evaluation scores seemed to indicate a dose-dependent trend toward efficacy; however, patient numbers were not sufficient to determine statistical significance. *Conclusions.* Overall, there were no significant safety issues related to the administration of TG-C, with only some minor injection site reactions observed. Additionally, knee scoring analyzes indicated a possibility that TG-C may contribute to improvement of arthritic symptoms. More study is warranted to evaluate further the safety and determine the potential efficacy of TG-C.

Key Words: *cell-mediated therapy, degenerative arthritis, phase I clinical study, transforming growth factor-beta-1*

Introduction

The Arthritis Foundation estimates that osteoarthritis (OA) currently affects more than 25 million Americans, and a World Health Organization (WHO) study claims that world-wide 40% of people over the age of 70 suffer from OA (1). This study also reported that 80% of patients with OA have a certain limitation of movement, while 25% of them cannot perform the major daily activities of life, further emphasizing the severity of the world's most prevalent articular disease (1). As the average age of the population gets older, and with the drastic increase in the percentage of people currently exceeding their ideal body mass index (BMI), it is estimated that the incidence of OA of the knee will increase sharply over the next several years.

Manifestations of OA include inflammation and the breakdown and eventual loss of the cartilage of the joints. Among the more than 100 different types of arthritic conditions, OA is the most common. It usually affects hands, feet, spine and large weight-bearing joints, such as the hips and knees. The primary pathogenesis of the disease is degeneration of the hyaline articular cartilage, which becomes deformed, fibrillated and eventually excavated during the course of the disease (2). If degenerated articular cartilage could be regenerated, most patients would be able to function better without debilitating pain.

Regarding application to numerous areas of orthopedics, several cellular signal transduction pathways are being considered as suitable candidates for the treatment of orthopedic diseases. For example, bone morphogenic proteins (BMP) have been identified as effective stimulators of bone formation (3–5). Analogously, transforming growth factor-β proteins (TGF-β) have been reported to induce osteogenesis

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and chondrogenesis (6,7). Among the TGF-β, TGF-β1 is known to be the most important factor in the biologic process of cartilage formation. TGF-β1 plays crucial roles in tissue regeneration, cell differentiation and extracellular matrix protein synthesis (6). Studies have suggested that TGF-β1 stimulates proteoglycan synthesis in chondrocytes (8,9) and the growth of articular chondrocytes (10–12). In addition to its stimulatory action on chondrocytes, TGF-β has been shown to possess anti-inflammatory and immune suppressive properties (13). This has led to recent reports on the therapeutic value of TGF-β proteins in the orthopedic field, such as in the treatment of OA (14–17). However, widespread clinical applications of this protein have been limited because of its short-term effects as a result of a short half-life. Therefore, a new method for the long-term and effective delivery of TGF-β1 is required for the treatment of OA.

TissueGene-C (TG-C) is a cell-mediated gene therapy for the regeneration of cartilage tissue. TG-C is a 3:1 mixture of normal allogeneic human chondrocytes (hChonJ) and irradiated allogeneic human chondrocytes that express TGF-β1 (designated hChonJb#7) (Figure 1). We have identified a proprietary technology to deliver TGF-β1 to degenerative joints in a minimally invasive manner that does not require surgery (18). Human chondrocytes were transfected with a viral vector containing the human TGF-β1 gene. The transduced human chondrocytes, when injected into the damaged knee joints of rabbits and dogs, have exhibited sustained TGF-β1 release and proliferation of regenerative cartilage (19). Uninfected chondrocytes are included as additional cells for filling the defect site. These cells also serve as additional target cells for TGF-β1 expressed from transfected cells because TGF-β1 has a paracrine mode of action (20).

We report the results of a phase I safety study conducted in 12 patients with severe OA of the knee joint. In general, the aim of this study was to assess the feasibility, from a safety perspective, of utilizing allogeneic cells for tissue regeneration and to determine whether there are any unforeseen risks associated with the use of allogeneic human chondrocytes expressing TGF-β1.

The primary objective of this study was to evaluate the safety and biologic activity of intra-articularly administered TG-C as evidenced by observation of the injected joint for the incidence and severity of any

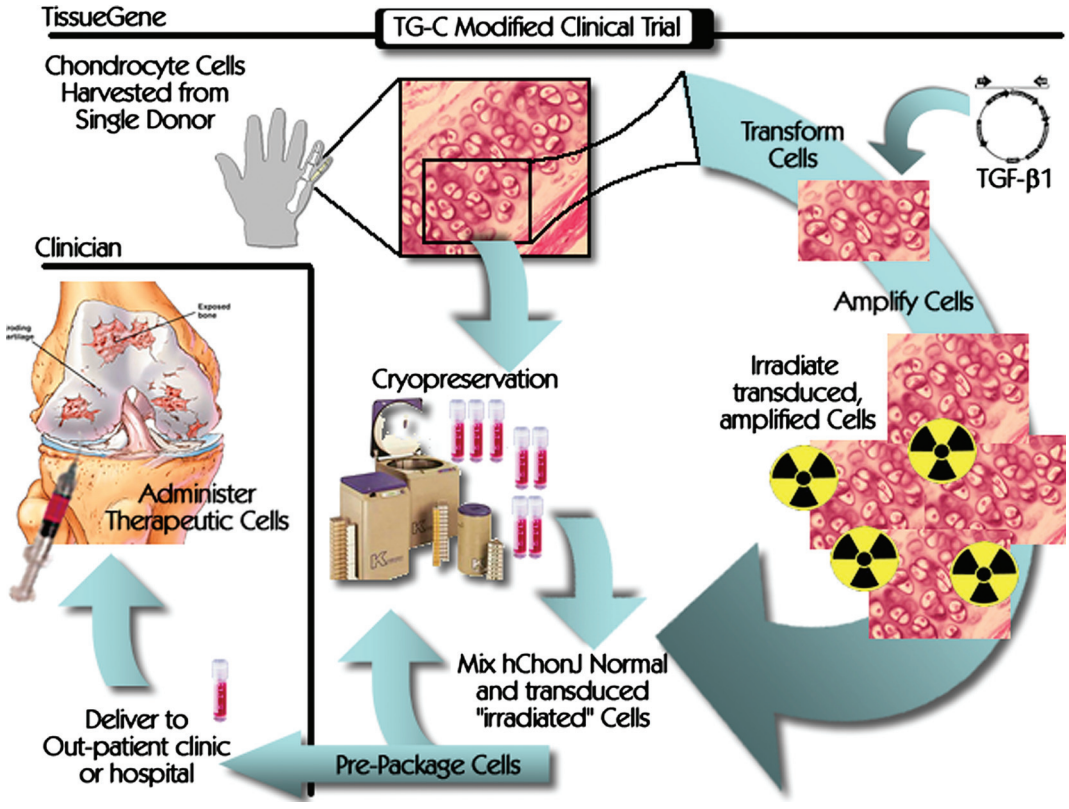

Figure 1. Production scheme of TG-C. The cells used to create the cell banks for human chondrocytes were derived from a human donor. The transduced cell line (hChonJb#7) was isolated according to the limiting-dilution method. The cryopreserved cells were thawed and washed, and the hChonJb#7 cells were irradiated prior to mixing at a 3:1 ratio (hChonJ:hChonJb#7) at the planned dose. Prepared doses are injected into the joint.

adverse events, and the changes in findings of physical examination and laboratory tests. The secondary objectives of this study were to evaluate the dose–response of the hChonJb#7 cells in forming cartilage, as determined by magnetic resonance imaging (MRI), and to evaluate the biologic activity of TG-C on joint pain, range of motion and function.

Methods

Overall study design and patient population

A single-center, open-label, dose-escalation study was conducted to evaluate the dose–response of three dose levels of TG-C in 12 adult patients. The patients had severe OA of the knee that has been refractory to previous medical and physical treatments. The diagnosis of OA of the knee for this study was based on characteristic radiographic changes in the knee joint using the grading system introduced by Kellgren & Lawrence (21). The knees with Kellgren & Lawrence grade 4 were included in the trial. Patients with inflammatory joint disease, significant medical illness or ongoing infectious disease, or who had recent intra-articular injection or anti-inflammatory medication, were excluded from this study. Other detailed inclusion and exclusion criteria are listed in Table I. All patients participating in this study provided written informed consent prior to being enrolled. The study protocol was approved by the institutional review board at Samsung Medical Center.

Dose schedule

Patients received one of three doses of TG-C: 3×10^6 cells, 1×10^7 cells or 3×10^7 cells. Four patients were enrolled and treated with the lowest dose level first, and the dose of cells was increased to the next dose level following agreement of the Independent Data Monitoring Committee to proceed after review of 1 month's worth of safety data, including serum TGF-β1 levels after each dose level treatment was finished.

Treatment

TG-C was supplied in separate vials containing hChonJ and hChonJb#7. Prior to dosing, the hChonJb#7 cells were washed with Dulbecco's modified Eagle medium (DMEM) and resuspended in DMEM. The resuspended hChonJb#7 cells were irradiated with 15 Gy radiation. The hChonJ cells were also washed with DMEM and resuspended in DMEM. These two cells were then mixed at a 3:1 ratio (hChonJ:hChonJb#7) and the final mixture was loaded into a syringe for injection. All these procedures were performed in a class 1000 operating room. Prior to the beginning of the clinical study, the preparation procedures were validated. For each dose, a Gram stain was performed on the final prepared dose for immediate evidence of sterility. At the same time, an aliquot of the final preparation was sent for sterility and endotoxin testing. After the validation process had been completed successfully, enrollment in the clinical trial was initiated. The formulated doses were prepared in the same class 1000 operating room with the same method approved for administration in the clinical trial. Prior to TG-C administration, each patient's knee joint was aspirated to remove synovial fluid and to make sure the injection was in the joint space. Prior to dose administration, the cells were mixed by gently inverting the syringe several times. TG-C was administered by a single intra-articular injection via

Table I. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Aged 18 years or older, providing written informed consent • In good general health, as determined by physical examination, blood and urine laboratory testing results, and a BMI between 18.5 and 45.5. • Diagnosed as OA of the knee refractory to existing therapies • Radiographically confirmed defect size >2 cm^2 • Severe OA (grade 4) confirmed by radiographic criteria of Kellgren & Lawrence • Symptomatic pain for more than 4 consecutive months of intensity >4 on a 10-point scale	• Patients with abnormal laboratory blood and/or urine screening results • Patients taking anti-inflammatory medications within 14 days prior to dosing • Patients with a history of drug abuse or a positive drug/alcohol urine test at time of screening • Women who are pregnant or breastfeeding • Patients who had received injections to the target knee within 2 months prior to treatment • Patients with systemic rheumatic or inflammatory disease of the knee or chondrocalcinosis, hemochromatosis, inflammatory arthritis, necrosis of the femoral condyle, arthropathy of the knee associated with juxta-articular Paget's disease of the femur or tibia, ochronosis, hemophilic arthropathy, infectious arthritis, Charcot's knee joint, villonodular synovitis and synovial chondromatosis • Patients with ongoing infectious disease, including Human Immunodeficiency Virus (HIV) and hepatitis • Patients with clinically significant cardiovascular, renal, hepatic, endocrine disease, cancer or type I diabetes • Patients participating in a study of an experimental drug or medical device within 30 days of study entry

a 21-gauge needle to the damaged joint area as follows. As the patient lay supine with the knee straight, the aspiration was performed from the superolateral portal. To avoid shearing of the cells, the injection was performed slowly. Each patient was required to stay on a bed in such a manner that the lesion site remained in a dependent position for 2 h after TG-C administration. During the 2-h observation period (post-dosing), the patient's blood pressure, pulse and temperature were measured every 15 min for the first hour, followed by every 30 min for the second hour. After 2 h post-dosing, the patients were allowed to carry out all normal activities of daily living, including mild sports activities.

Evaluation schedule

After being screened for study enrollment, patients discontinued any anti-inflammatory medications prior to and until 72 h after TG-C administration. Patients were evaluated at baseline screening, immediately prior to dosing, for 2 h post-dosing (every 15 min for the first hour, followed by every 30 min for the second hour), then at days 7, 14, 21 and 28 post-dosing. Follow-up patient monitoring was performed at 3, 6, 9 and 12 months post-dosing. In addition to monitoring for adverse events, the following parameters were evaluated at each time-point.

Laboratory assessments for safety

The following hematologic parameters were measured: hemoglobin, hematocrit, platelet count, Red Blood Cell (RBC) and White Blood Cell (WBC) with differential, Prothrombin Time (PT) and International Normalized Ratio (INR), and Partial Thromboplastin Time (PTT). The serum chemistry tests included total protein, albumin, glucose, Blood Urea Nitrogen (BUN), creatinine, total bilirubin (direct, indirect and total), alkaline phosphatase, phosphorus, calcium, Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), sodium, potassium, chloride and bicarbonate. Urine analysis included pH, specific gravity, glucose, protein, ketones and microscopic analysis (WBC, RBC, epithelial cells, casts and crystals).

TG-C concentrations in the blood

Blood samples were collected at screening, baseline, 24 h post-dosing and at every scheduled visit. The samples collected from baseline until 12 months were analyzed for TGF-β1 expression by enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) for vector DNA. Additionally, at 9 and 12 months post-dosing, replication-competent retrovirus (RCR) testing was performed on peripheral blood mononuclear cells (PBMNC) using PCR to detect RCR-specific DNA sequences.

MRI

3.0 Tesla high-resolution MRI was performed in order to assess the extent and depth of the articular cartilage of the knee joint at baseline and at post-dosing 1, 3, 6 and 12 months. The articular cartilage status was assessed by the International Cartilage Repair Society (ICRS) grading system (22) at baseline to confirm the grade 4 (full-thickness) defect.

Clinical assessment

Physical examination of the target knee was performed at screening, baseline, 2 h post-dosing and at 7, 14, 21 and 28 days and 3, 6, 9 and 12 months. Knee joint pain was assessed using a 100-mm visual analog scale: patients were asked to evaluate their pain by drawing a mark on a 100-mm line, the distance from the start indicating the level of pain. The range of motion of the knee joint was measured by an orthopedic fellow while the patient was in a supine position and passively flexing the knee. The function of the knee joint was assessed using the clinical rating system of the American Knee Society (23). Additionally, study subjects completed the Western Ontario and MacMaster Universities' (WOMAC) OA index questionnaire for functional evaluation, focusing on the patients' activities in daily living. This questionnaire consists of three parts: pain, disability and joint stiffness.

Statistical analyzes

Because of the limited number of enrolled patients in this phase I trial, the sample size was not sufficient to power any statistical analyzes in this study.

Results

Adverse events

Serious adverse events related to the treatment were not seen following administration of TG-C at any of the dose levels. No dose-limiting toxicity was observed, and dosing proceeded to the highest planned dose level of 3×10^7 cells. The most commonly reported adverse event was effusion (fluid collection) in the joint (Table II).

At the low dose level of 3×10^6 cells, one patient noted a mild warming sensation and itching in the injected joint, which subsequently disappeared spontaneously. One of the other patients experienced grade 2 hydrarthrosis (joint fluid collection) that was possibly related to the treatment, which was treated and resolved with aspiration and anti-inflammatory medication. The

Table II. Summary of adverse events.

Group	Patient number (sex, age)	Safety: TGF-b1 ELISA/PCR	Safety: Laboratory results	Safety: Adverse events
Dose level 1, 3×10^6 cells	001 (M, 77)	Normal	Normal	2 days post-dosing: 3–4 h after dinner, patient complained of itching and warming sensation in the injection area. Sensation subsequently disappeared spontaneously in a few hours
	002 (F, 62)	Normal	Normal	No adverse events
	003 (F, 59)	Normal	Normal	Patient experienced grade 2 hydrarthrosis(joint fluid collection) of the injected joint from day 14 until day 18 post-dosing, which was probably related to TG-C treatment. Patient was treated with aspiration, Nonsteroidal Anti-inflammatory Drug (NSAID), acetaminophen and resolved
	004 (F, 73)	Normal	Normal	No adverse events
Dose level 2, 1×10^7 cells	006 (F, 53)	Normal	Normal	1 day post-dosing: patient complained of pain, swelling and warming sensation of the injected joint. Prescribed NSAID at 8 days post-dosing (medication for 38 days). The symptom had disappeared at 45 days post-dosing
	007 (F, 52)	Normal	Normal	Afternoon of the day of dosing: patient had headache and a warming sensation in the injected joint. Symptoms spontaneously disappeared in a few hours
	008 (M, 69)	Normal	Normal	4–5 h post-dosing: patient had pain in the injected joint, which disappeared spontaneously in a few hours. Pain of the injected joint at 23 days post-dosing. Prescribed NSAID and acetaminophen from day 24 to day 30 post-dosing (for 7 days). Symptom was resolved
	009 (M, 60)	Normal	Normal	At 22 days post-dosing, patient had swelling and effusion (fluid collection) of the injected joint after hiking. Prescribed Etololac 600 mg (once a day) from day 22 to day 28 post-dosing. Symptoms were resolved
Dose level 3, 3×10^7 cells	010 (F, 71)	Normal	Normal	For 7 days after injection, patient felt stiffness and discomfort of knee. The symptoms disappeared without any treatment
	011 (M, 65)	Normal	Normal	From 1 day post-dosing, patient had swelling and dull pain. Hydroarthrosis and warmth was observed at the joint. Prescribed Acetaminophen 650 mg (3 times/day, for days 5–35 post-dosing), Celecoxib 200 mg (once a day, for days 11–35 post-dosing). Symptoms disappeared by day 40 post-dosing
	012 (M, 55)	Normal	Normal	For 2 weeks after injection, patient had dull pain and swelling of the injected knee. The symptoms disappeared without any treatment
	013 (F, 62)	Normal	Normal	There was swelling and mild fever on the day of injection. Hydroarthrosis was observed. Treated with Acetaminophen 650 mg (3 times/day, from 1-day post-dosing), Celecoxib 200 mg (once a day, for days 7–30 post-dosing). Symptoms disappeared by day 30 post-dosing

M, male; F, female; age, years.

remaining two patients had no adverse events. At the middle dose level of 1×10^7 cells, two patients experienced pain (one with swelling and a warming sensation as well) in the injected joint, which was treated with anti-inflammatory medication. One of the other two patients experienced a headache and a warming sensation in the injected joint, which resolved spontaneously. The remaining patient experienced swelling and fluid collection in the injected joint after hiking, which was resolved with anti-inflammatory medication. Three patients from the high-dose group (3×10^7 cells) experienced swelling at the injection site. Two experienced grade 2 hydrarthrosis and a warming sensation of the injected knee. Other effects observed included pain, discomfort and pyrexia (Table II). There were no adverse events observed in the laboratory parameters for safety evaluation.

TG-C concentrations in the blood

ELISA analysis of blood samples for TGF-β1 showed levels within the normal range (18 289–63 416 pg/mL) for all patients at all dose levels at every time-point. PCR analysis detected no vector DNA in the blood of any patient at any time-point. No RCR were detected in any patient at any time-point.

MRI

No significant differences were noted when evaluating MRI, according to the ICRS grading system, between baseline and 6 months post-dosing, with all patients remaining at grade 4. However, visual analysis of the MRI indicated limited effects noticeable in the middle- and high-dose patients. The appearance of small amounts of regenerated cartilage was seen in one patient at the grade 4 lesion site (Figures 2 and 3).

Knee Society Clinical Rating System

The Knee Society Clinical Rating System (KSCRS) knee score evaluates pain, range of motion and joint stability, with a maximum possible score of 100, with higher scores indicating better results (23). Ten of the 12 patients showed an increase in their KSCRS score from baseline to 6 months. After 12 months there were noticeable trends in improvement in both pain (in the mid- and high-dose groups; Figure 4a) and range of motion (in all three dose groups; Figure 4b) scores. Accordingly, there was a corresponding improvement in overall KSCRS score after 12 months for the mid- and high-dose groups (Figure 4c). The change in KSCRS score demonstrated that clinical symptom improvement was observed from 1 month post-dosing. The improvement lasted for up to 1 year post-dosing.

WOMAC OA index

Seven of the 12 patients showed an improvement in their WOMAC score from baseline to 6 months. In general, a decrease in WOMAC score is indicative of symptomatic improvement. Patients receiving the low and middle dose levels showed an improvement in the WOMAC stiffness score (Figure 5a) after 12 months. Although there was some early (after day 21) improvement in overall WOMAC scoring with the low and middle dose levels, there was no clear trend in the WOMAC score after 12 months (Figure 5b).

Visual analog pain scale

There was a marked improvement (>40%) in pain score for patients treated with the high dose, for up to 3 months (Figure 6).

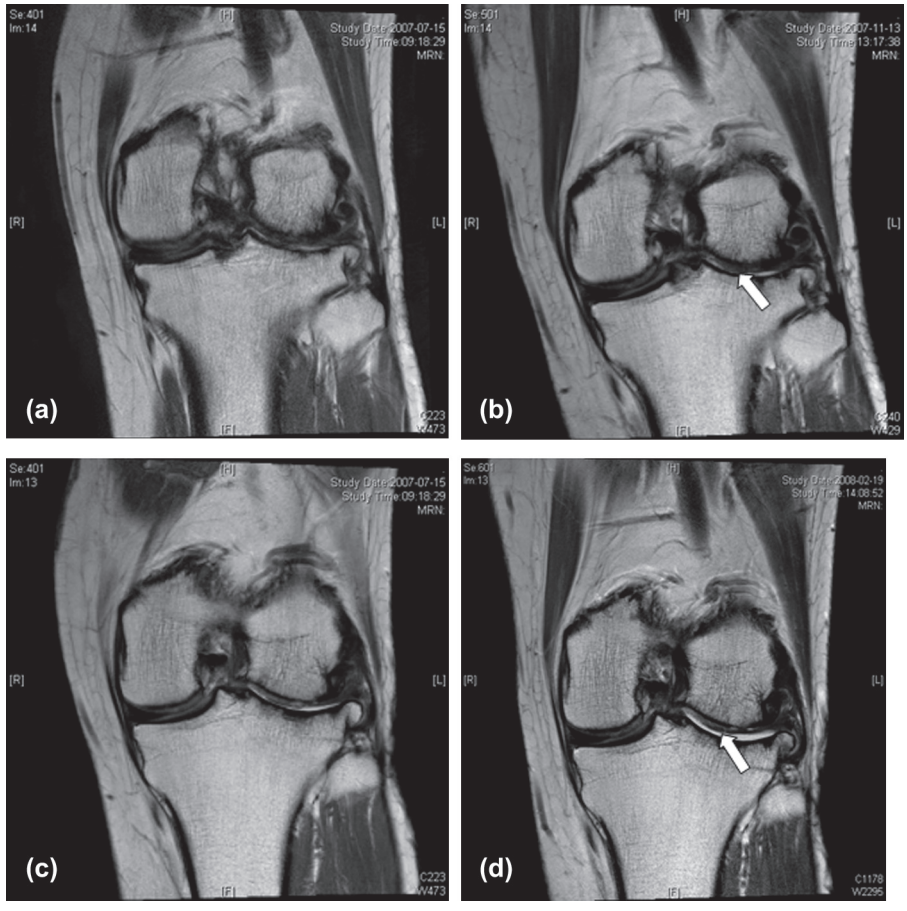

Figure 2. Proton-density coronal magnetic resonance image for patient 007 at baseline (a, c), 3 months (b) and 6 months (d). The appearance of subtle cartilage regeneration is seen in (b) and (d) at the weight-bearing portion of the lateral femoral condyle, as indicated with the arrow.

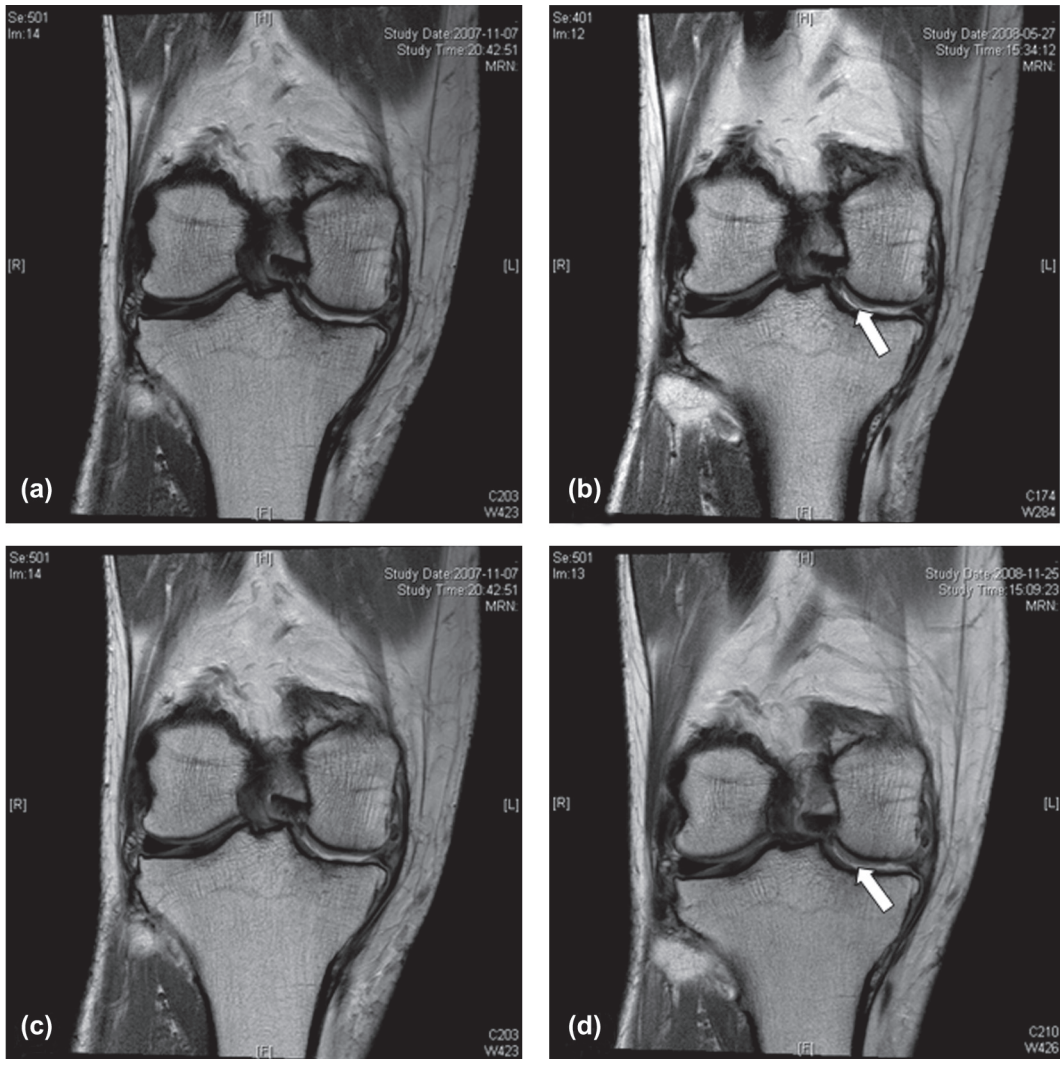

Figure 3. Proton-density coronal magnetic resonance image for patient 011 at baseline (a, c), 6 months (b) and 12 months (d). The appearance of cartilage regeneration is seen in (b) and (d), especially around the periphery of the grade 4 lesion site at the medial femoral condyle, as indicated with the arrow.

Overall efficacy analysis

As described above, trends were observed in the KSCRS, WOMAC and visual analog pain (VAS) scale that seemed to indicate symptomatic improvement. We noted, however, that there was a significant fluctuation in the range of these scores, which was probably because of the limited sample size that did not allow for statistical powering or analysis of the results, or 'smoothing' of the curves in the figures of the various scores.

Discussion

OA is the most frequently encountered orthopedic disease associated with cartilage damage, and is known to impact 1 in 7 people. Almost all joints in the body, such as the knees, hips, shoulders and hands, are susceptible to cartilage damage. Current methods for treating OA include pharmacologic treatments, physical therapy and surgery. The primary goal of these treatments is to reduce the symptomatic pain associated with the arthritis. However, these treatments do not result in physiologic or structural regeneration of the damaged joint.

Currently Carticel™ is approved for articular cartilage regeneration using transplantation of autologous cartilage cells that were expanded in culture (24,25). However, this procedure entails two operations and requires a lengthy recovery time. A cell-mediated cytokine gene therapy approach for cartilage regeneration does not require an operation or a lengthy rehabilitation time, whereas autologous cell-based therapy (24,25) and cytokine protein-based therapy involve at least one operation and a substantial rehabilitation time (5). These autologous

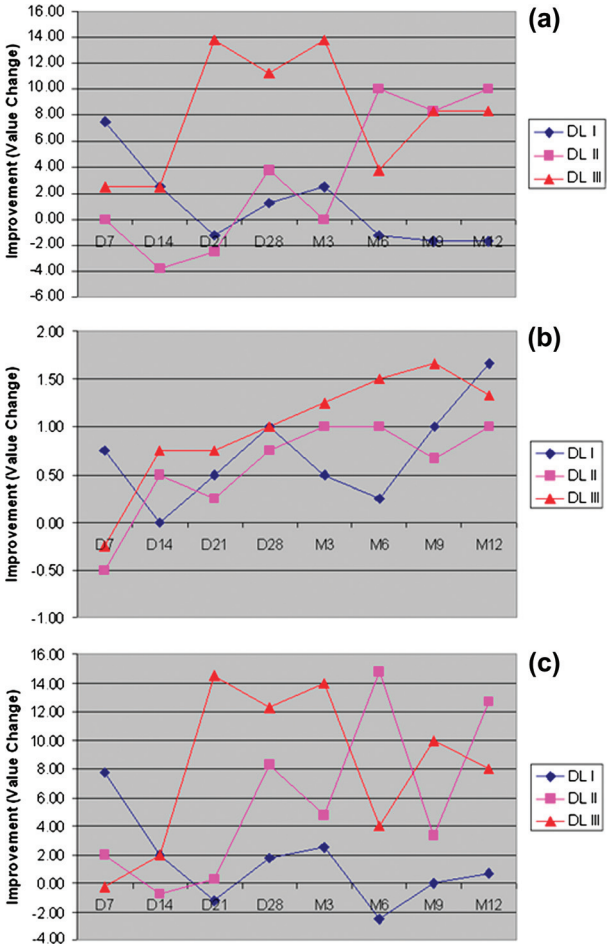

Figure 4. The average change in score (positive mean improvement) in KSCRS (a) pain score, (b) range of motion score and (c) overall score from baseline until 12 months post-dosing (M12). Improvements in KSCRS pain and range of motion scores for dose levels 2 and 3 could be seen with a corresponding improvement in overall score.

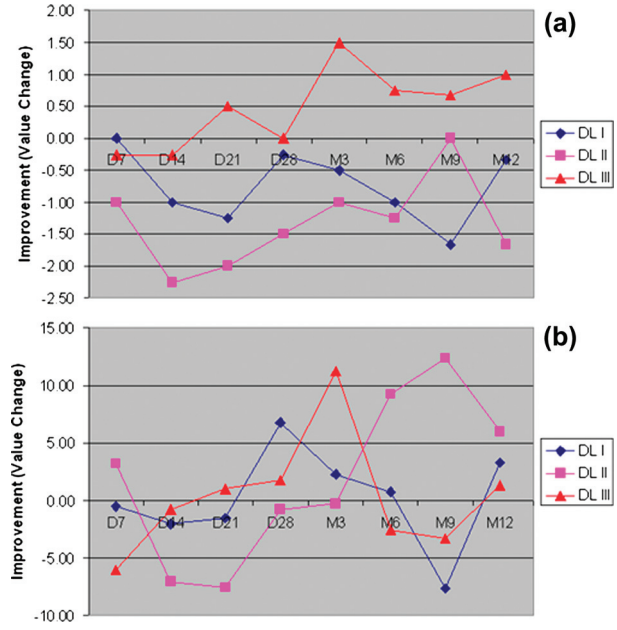

Figure 5. The average change in score (positive mean improvement) in WOMAC (a) stiffness score and (b) overall score from baseline until 12 months (M12). On average, patients receiving dose levels 1 and 2 showed improvement early on (by day 21) but there was no clear trend in WOMAC scores after 12 months.

chondrocytes have a limited capacity to regenerate hyaline cartilage. Accordingly, products such as Carticel are not indicated for cartilage damage associated with generalized OA (Carticel™ Package Insert 2007). Therefore, cell-mediated TGF-β1 gene therapy may be a clinically useful and efficient therapy for treating orthopedic diseases with hyaline cartilage damage.

The clinical trial described here represents the first in-human treatment of allogeneic human chondrocytes genetically modified to express TGF-β1. The primary goal of this phase I study was to establish initial proof of safety for this novel treatment. The results from this study indicate that TG-C is well-tolerated at all dose levels, with transient injection site reactions, such as joint fluid collection, as the primary adverse events.

As a safety measure, the transduced cells containing the TGF-β1 transgene were irradiated prior to dosing to render them replication incompetent. This allows the cells to express TGF-β1 for up to 2 weeks (data not shown), which can then act on the normal human chondrocytes that are also included as part of the TG-C product, while ensuring that there is no prolonged or excessive TGF-β1 expression, and that the gene-modified cells do not persist *in vivo*. The results of the TGF-β1 ELISA testing, PCR for vector DNA and replication-competent virus testing confirmed that there was no increase in systemic TGF-β1 levels and that the transduced cells did not enter the systemic circulation or introduce replication-competent virus.

Although the primary purpose of this study was safety, some endpoints to assess the potential biologic activity of TG-C were included. Of particular interest were the changes seen in patients' knees in the magnetic resonance images. There were some findings of possible cartilage regeneration in some of the high-dose patients. The results from all three scoring systems, KSCRS, WOMAC and VAS, showed early improvements. However, long-term (12-month) trends in scoring were not clearly discernable. It should be noted that, because of the limited enrollment in this trial, there was not sufficient sample size to power a statistical analysis. As this study has provided initial proof of safety in humans for this novel gene-modified cellular therapy, further study is warranted with larger numbers of patients to evaluate fully the potential efficacy of TG-C.

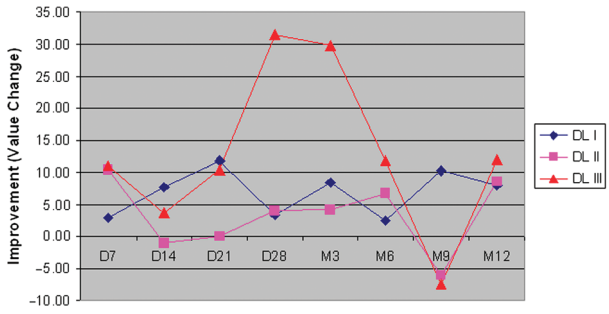

Figure 6. The average change in score (positive mean improvement) in VAS on pain score from baseline until 12 months (M12). On average, patients showed a decrease in pain with all three dose levels, with a marked improvement with dose level 3 at 3 months with a regression at 6 months.

To this end, there are several methods under consideration for providing evidence of cartilage regeneration and efficacy in the treatment of OA. The evaluation of patients will continue to include standard clinical measurements such as WOMAC, KSCRS, knee injury and OA outcome score (KOOS) and VAS. Future patients may also be evaluated for the International Knee Documentation Committee (IKDC) knee score, Cincinnati Knee Score, Lysholm index and Outcome Measure in Arthritis Clinical Trials–OA Research Society (OMERACT-AOARSI) responder index. To visualize regeneration further, alternate MRI methodology may be employed in the future, including 3-dimensional (3-D) MRI and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), which will allow an assessment of the change from baseline in proteoglycan content. Furthermore, because the expression of TGF-β1 is limited because of the terminal life span of the transduced cells from irradiation, it may be necessary to assess whether a multiple dosing regimen would provide additional benefit.

In summary, these initial results show limited localized adverse events and suggest there may be a trend towards a dose-dependent improvement in patient symptoms. Based on the results of this clinical study, additional clinical testing is warranted in a larger patient population to determine further the safety, efficacy and optimal dose of TG-C.

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