The Safety and Efficacy of a Novel Cell-Based Gene Therapy for Knee Osteoarthritis

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ABSTRACT

A promising new gene technology has been developed for the treatment of osteoarthritis, utilizing transduced human cells expressing transforming growth factor-β1. The safety and efficacy of this treatment modality has been demonstrated in laboratory studies, as well as Phase I, II, and current Phase III human clinical trials. Due to a misidentification error, there have been concerns that this cell-based gene therapy is based on a different cell than the one that was initially approved. However, its safety profile has been demonstrated by over 10 years of data revealing no evidence of tumorigenicity or other long-term safety concerns. In all studies to date, there have been no treatment-related serious adverse events. Although the nomenclature of one component of the drug product has changed, the product itself has not. In this review, we will present the technology, history of use (animal and clinical studies), development, efficacy, and, despite the recent misidentification error, the overall safety of this treatment modality.

INTRODUCTION

Nonoperative treatment modalities for knee osteoarthritis currently include physical therapy, nonsteroidal anti-inflammatory medications (NSAIDs), and intraarticular corticosteroid and hyaluronic acid injections. While these measures may provide pain relief for some patients, they do not reverse or slow the progression of the disease. A promising new gene technology has been developed for the treatment of osteoarthritis, utilizing what was thought to be a 3:1 mixture of allogeneic chondrocytes and transduced human chondrocytes expressing transforming growth factor-β1 (TGF-β1).[1-4] It was then found that the mixture did contain 75% chondrocytes, but the group of cells forming TGF-β1 were in fact irradiated transduced GP2-293 cells and not chondrocytes. As a result, there have been concerns that this gene cell therapy is based on a different cell than the one that was initially approved. However, the problem was simply a misidentification of the transduced cells. The drug has been unchanged (except for dosage levels) throughout all phases of clinical testing. The product used in all studies (*in vitro,* animal and Phase I, II, and current Phase III human clinical trials) was uniformly derived from the same source. Fortunately, data from these investigations have demonstrated no evidence of tumorigenicity or other short- or long-term safety concerns.[3-9] In addition, there is no published evidence of mutagenesis from *in vitro* studies or tumorigenesis in humans attributable to the administration of stably transfected GP2-293 cells used in other applications. Therefore, we believe that this promising new drug can continue to be used in patients with knee osteoarthritis.

NOVEL TECHNOLOGY

The novel technology introduced by Kolon TissueGene, Inc. (Rockville, Maryland) transduces allogeneic human cells with a retroviral vector, genetically engineering them to express TGF-β1 that stimulates cartilage regeneration. TissueGene-C (TG-C) is a 3:1 mixture of normal allogeneic human chondrocytes and irradiated allogeneic human cells that express TGF-β1. Normal, unmodified chondrocytes are included in addition to the transfected cells on the basis that they: (1) provide additional cells for the filling of cartilage defects, and (2) provide additional cells for the TGF-β1 expressed on the genetically engineered cells. Additionally, *in vitro* studies have established that the transduced human cells have the ability to adhere to host cartilage and sustain production of TGF-β1.[1] The actions of these cells that express TGF-β1 are possibly due to the paracrine properties of TGF-β1.

To understand the role of TGF-β1, one must know that cartilage development is a complex balance of anabolic and catabolic activity, and that TGF-β1 is one of the most important factors for maintaining this homeostasis.[10,11] This growth factor is known to play a vital role in tissue regeneration, cell differentiation, and synthesis of extracellular matrix proteins.[12] In addition, TGF-β1 has been shown to stimulate proteoglycan synthesis in chondrocytes and to promote the growth of articular chondrocytes.[13-17] Furthermore, anti-inflammatory and immuno-modulatory effects of TGF-β1 have been demonstrated.[18] While the TGF-β1 protein alone does not induce cartilage formation, human chondrocytes engineered to express a retroviral vector encoding TGF- β1 have been found to stimulate chondrogenesis when injected intradermally in the mouse model.[19] Moreover, chondrocyte proliferation in damaged areas of articular cartilage has been observed following intraarticular administration of genetically modified chondrocytes that produce TGF- β1.[6,8]

Table I
Laboratory assesments in Phase I clinical trial

Blood	Serum	Urine
Hemoglobin	Sodium	Specific gravity
Platelet Count	Potassium	pH
Red blood cell (RBC) count	Chloride	Glucose
White blood cell (WBC) count, with differential	Bicarbonate	Protein
	Calcium	Ketones
Prothrombin time	Phosphorus	Microscopic analysis (WBC, RBC, epithelial cells, casts, and crystals)
International normalized ratio	Glucose	
Parthial thromboplastin time	Creatinine	
	Blood urea nitrogen	
	Total protein	
	Albumin	
	Bilirubin (total, direct and indirect)	
	Alkaline phosphatase	

HISTORY OF USE

Animal studies

The feasibility of TG-C as a regenerative cartilage treatment modality has been demonstrated in several animal studies. Over 15 years ago, Song et al.[9] compared the efficacy of cartilage regeneration with TGF-β1-producing human cells to that of human chondrocytes (hChonJ) alone when injected intradermally into nude mice. The mice were injected with either TGF-β1-producing cells, chondrocytes alone, or a mixture of chondrocytes and TGF-β1-producing cells. They reported that the mixed cells, as well as the TGF-β1-producing cells, induced cartilage formation, whereas, the chondrocytes alone did not.

To further elucidate the role of these cells in cartilage regeneration, these same authors surgically produced partial thickness cartilage defects in the medial femoral condyle of a rabbit knee joint. The defects were treated with a mixture of TGF-β1-producing cells and chondrocytes (n=5), TGF-β1-producing cells alone (n=5), or chondrocytes alone (n=5). Six weeks following injection, chondral defects treated with TGF-β1-producing cells were found to be filled with regenerative hyaline-like cartilage as evidenced by histological analysis. Conversely, chondrocytes alone did not fill the cartilage defects in most cases.

The mechanism by which TG-C regenerates cartilage was further clarified by Yoon et al.[20] Using immunohistochemistry techniques, the authors

Table II
Summary of adverse events in Phase I clinical trial

Group	Patient number (sex, age)	TGF-β1 ELISA/PCR	Laboratory results	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

demonstrated the ability of modified chondrocytes in TG-C to attach to damaged cartilage cells and to produce type II collagen-glycosaminoglycan matrices via continuous secretion of TGF-β1.

In summary, the positive effects on cartilage in the above-mentioned studies prompted its further testing for safety and efficacy in human trials, which will be elaborated on in the next section.

Clinical studies

The initial Phase I human safety study of TG-C was conducted in South Korea by Ha et al.[6] in 2012. This was a single-center, open-label study that investigated the dose-response relationships of TG-C. Twelve adult patients with severe knee osteoarthritis (Kellgren Lawrence grade 4) refractory to non-operative measures were included. Patients received one of three TG-C dose levels: 3×10^6, 1×10^7 , or 3×10^7 cells. They were evaluated at baseline screening, immediately prior to dosing, for a two-hour period after dosing, and on post-injection days seven, 14, 21, and 28. In addition, monitoring continued at approximately three, six, nine, and 12 months post-injection. Evaluation parameters included several laboratory assessments (Table I), TG-C blood concentrations, 3.0 Tesla MRI analyses, and physical examinations. Additionally, patients were followed closely to monitor for adverse events. The authors observed minor adverse events in the hours to weeks following the injection (Table II). However, subjects experienced no serious adverse events or laboratory/blood index abnormalities at any dose-level. At six months follow up, Knee Society Clinical Rating System (KSCRS) scores were improved in 10 of 12 patients and Western Ontario and McMaster osteoarthritis (WOMAC) score was improved in seven of 12 patients.

Ha et al.[3] conducted a Phase IIa clinical trial and evaluated the safety and efficacy of TG-C in 27 adults who had International Cartilage Repair Society (ICRS) grade 4 knee osteoarthritis. Patients were randomized to receive TG-C doses of 6×10^6 (group 1) or 1.8×10^7 cells (group 2) at a 1:1 ratio. Evaluations at two, four, 12, and 24 weeks post-injection included the International Knee Documentation Committee (IKDC) score, the WOMAC index and the pain assessment by the visual analog scale (VAS). At 12 and 24 weeks, there were significant improvements in all outcome measures ($p<0.05$). Once again, there were no treatment-related serious adverse events, prompting further clinical studies.

Next, Lee et al.[4] conducted the Phase IIb clinical trial by evaluating a total of 54 patients in a placebo-controlled randomized trial with a single injection of TG-C treatment (1.8×10^7 TG-C cells, n=27) or placebo (saline, n=27). The authors compared IKDC, VAS, WOMAC, and Knee Injury and Osteoarthritis Outcome Scores (KOOS) between groups at 24 weeks follow up. The treatment group exhibited a significantly greater improvement in mean IKDC score than the placebo group ($p=0.03$). Improvements in all other parameters were noted in the treatment group; however, they did not differ significantly from the improvement observed in controls. A low rate of injection site-related adverse events was observed, all of which resolved or were improving by the end of the study. One patient in this study experienced an anaphylactic reaction but was discharged the following day after a full recovery. Allergy testing was performed on this patient which revealed a severe hypersensitivity anaphylaxis to CS-10, a cryopreservation medium. Once again, after completion of this study, it was felt that TG-C was safe to proceed with further human studies.

In Phase III clinical testing, Cho et al.[5] evaluated 156 patients who had knee osteoarthritis and were treated with TG-C (n=78) or were controls (saline, n=78). The primary outcomes

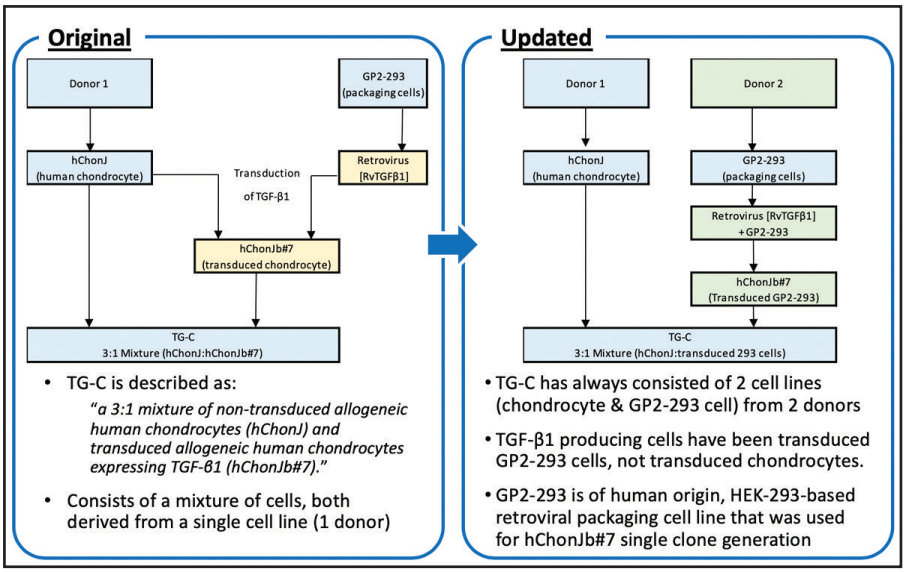

Figure 1. Updated drug description.

of interest were IKDC and VAS scores at 52 weeks. Results of the study indicated that intraarticular administration of TG-C significantly improved IKDC and VAS scores one year after injection. TG-C was not associated with any serious adverse events at up to one year following administration. This study reiterated that TG-C may be an efficacious and safe treatment modality for patients with knee osteoarthritis, and it prompted clinical studies in the United States.

Lee et al.[7] carried out the Phase II clinical trial in the United States, the results of which were recently published. A total of 102 patients were 2:1 randomized to treatment (TG-C, n=67) or placebo (saline, n=35). The primary outcomes of interest were IKDC and VAS scores at baseline and 12, 52, 72, and 104 weeks post-injection. Patient-reported adverse events (severe and non-severe) were also reported, as well as results of magnetic resonance imaging (MRI) at three-, six- and 12-month timepoints. There were significant improvements in IKDC scores in patients injected with TG-C, when compared with patients injected with the placebo at week 12 (p=0.034), week 52 (p=0.01), week 72 (p=0.003), week 104 (p=0.008), and overall (p=0.01). No severe adverse events in the TG-C group were reported. Common minor adverse events, including arthralgias, and joint inflammations, as well as joint effusions, occurred at similar rates in both cohorts. MRI analysis at 12 months demonstrated that compared to controls, subjects in the TG-C group had less progression of cartilage disease (RR: 0.7; 95% CI: 0.5–1.1; p=0.077) and less progression of infrapatellar fat pad synovitis and effusion-synovitis (RR: 0.5; 95% CI: 0.2–1.2; p=0.115). Importantly, the safety profile of TG-C two years following administration was demonstrated in this study.

In summary, clinical testing of TG-C in Korea and the United States has demonstrated its clinical efficacy. In addition, MRI findings in patients who underwent treatment with TG-C indicate that it may help slow the progression of osteoarthritis and potentially delay or prevent total knee arthroplasty. Most importantly, the lack of severe adverse events and only minor transient adverse events related to TC-G treatment warrant further long-term investigation of this novel, non-operative treatment method. It is encouraging that the product used for all these years has a great safety profile and certainly has a favorable risk-benefit profile.

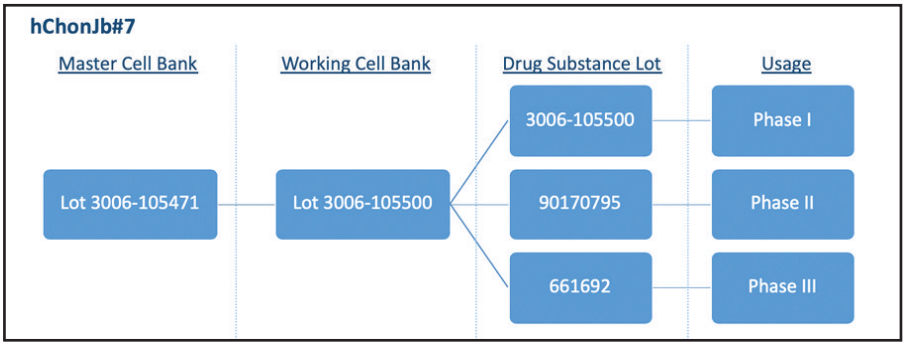

Figure 2. Product consistency.

Identification Error

Recently, genetic analyses (karyology and DNA fingerprinting) indicated that the transduced cells used in TG-C are made up of irradiated, transduced GP2-293 cells—not transduced chondrocytes as originally thought. Consequently, all dosing was immediately suspended as a precautionary measure until an internal review was completed. It is important to note that the drug product used in the completed Phase I, II, and current Phase III clinical trials were uniformly derived from the same source. Therefore, the current information on the drug's safety profile and efficacy in the published literature as summarized above, remains pertinent and accurate.

Originally, TG-C was described as a mixture of cells both derived from a single cell line (one donor) and consisting of "a 3:1 mixture of non-transduced allogeneic human chondrocytes (hChonJ) and transduced allogeneic human chondrocytes expressing TGF-β1 (hChonJb#7)." Extensive research to accurately characterize TG-C revealed that TG-C has always consisted of two cell lines (chondrocytes and GP2-293 cells) from two donors and that TGF-β1 producing cells have always been transduced GP2-293 cells, not transduced chondrocytes. Please see Figure 1 for a schematic description of the drug product before and after discovery of the identification error. Importantly, TG-C has been unchanged throughout all phases of clinical testing. A single master cell bank and working cell bank was used to generate hChonJb#7's for all clinical studies. Figure 2 illustrates that the clinical trial material used in Phase I, Phase II, and the current Phase III clinical trials were derived from the same source (Master Cell Banks and Working Cell Banks). Thus, all the clinical safety data accumulated to date are derived using the same drug product; TG-C.

Description of GP2-293 cells

GP2-293 is a human-derived cell line

that originated from human embryonic kidney (HEK) cells. They have been used widely in genetic and biotechnology research for many years to deliver genes into other types of cells.[21-25] As a result, the transduced cells can stably express the protein encoded by the delivered gene. Prior to distribution, they underwent staining for alkaline phosphatase. Confirming the absence of alkaline phosphatase expression ensures that only replication-incompetent retrovirus is produced.

In 1999, Biard et al.[26] attempted to characterize the biological role of a bacterial protein on the proliferative activity of human-derived tumor cells. The protein under investigation (Kin17) was transfected in three tumorigenic cells (HeLa, H1299, and HCT116) and in immortalized GP2-293 cells. It was found that in contrast to HeLa, HCT116, and H1299 cells, HEK 293 cells are non-tumorigenic when injected into nude mice. In fact, it has been reported in another *in vitro* study, that HEK-293 cells have a poor ability to spontaneously produce multinucleated cell lines.[27]

Also in 1999, Lohr et al.[28] conducted an open-label, Phase I/II study to assess the feasibility and safety of encapsulated human GP2-293 cells stably transduced to express CYP2B1. The authors hypothesized that the CYP2B1 expressed by the transduced cells would locally metabolize the chemotherapeutic prodrug into its active metabolite and aid in the treatment of pancreatic adenocarcinoma. A total of 51 patients underwent treatment with this experimental therapy. In four patients, the tumor regressed after treatment and in 10 others, it remained stable throughout the study period. Median survival was doubled in the treatment group compared to historic controls, and one-year survival rate was improved by a magnitude of three. No treatment-related serious adverse events occurred in any patient. The favorable outcomes and lack of treatment-related serious adverse events demonstrated in this study give reason to believe that transduced GP2-293 cell-mediated gene therapy is a feasible, safe treatment modality even when administered systemically. Table III provides an outline of the cell ratios, dosages, and product names throughout the history of use of TG-C.

In summary, immortalized GP2-293 cells have been studied in many laboratory, animal, and human studies. These studies have demonstrated that these cells may be safe, non-tumorigenic, and efficacious for the treatment of many disease processes.

Table III
History of use

Study	Ratio Normal chondrocytes : Transduced cells	Dose Number of cells	Product Name
Animal			
Song et al. 2005[23]	1:1 5:1 Transduced cells alone	6×10^5	hChon-TGF-β1
Noh et al. 2010[19]	3:1	1.8×10^5 1.8×10^6 9×10^6 3×10^7	TissueGene-C
Yoon et al. 2015[28]	3:1	2×10^6	TissueGene-C
Human			
Ha et al. 2012[9] Phase I, Korea	3:1	3×10^6 1×10^7 3×10^7	TissueGene-C
Ha et al. 2015[8] Phase IIa, Korea	3:1	6×10^6 1.8×10^7	TissueGene-C
Lee et al. 2015[13] Phase IIb, Korea	3:1	1.8×10^7	TissueGene-C
Cho et al. 2016[4] Phase III, Korea	3:1	1.8×10^7	Invossa
Lee et al. 2019[11] Phase II, United States	3:1	3×10^7	TissueGene-C

A summary of cell ratios, dosages, and product names throughout the history of use of TG-C.

FURTHER SAFETY CONSIDERATIONS

The safety profile of intra-articular TG-C administration has thus been demonstrated by 11 years of data revealing no evidence of tumorigenicity or other long-term safety concerns.[3-7] In all studies to date, there have been no treatment-related serious adverse events (Table IV). Moreover, most treatment-related adverse events were mild or moderate. In summary, over 250 patients have been treated in seven Phase I-III studies with minimal treatment-related adverse events, and no treatment-related serious adverse events. In addition to long-term studies providing clinical evidence that intraarticular administration of TG-C poses little risk, its safety profile is supported by three key points:

(1) The knee joint space is relatively avascular, and, therefore, systemic circulation of TG-C is unlikely. This notion is reinforced by a 60-day biodistribution study of 80 immune-competent rats that underwent intraarticular injection of TG-C (n=70) or placebo (n=10) (internal data). Tissue from 11 sources (knee joint, blood, bone marrow, brain, heart, kidney, liver, lung, ovary/testis, pancreas, and spleen) was collected and analyzed via quantitative polymerase chain reaction (qPCR) for TGF-β1 on days 0, 1, 3, 7 and 14. The hChonJb#7 cells were observed at the knee administration site on day 3, but they

Table IV
Clinical safety overview from US clinical studies

	Phase I (TGC-03-01)				Phase II (TGC09201)		Phase III (TGC12301)	LTS
	TG-C Dose Level 1 (N=3)	TG-C Dose Level 2 (N=3)	TG-C Dose Level 3 (N=3)	Placebo (N=3)	TG-C (N=67)	Placebo (N=35)	Blinded (N=11)	TG-C (N=38)
≥1 Treatment-Related AE	1 (33.3%)	1 (33.3%)	2 (66.7%)	0 (0.0%)	45 (67.2%)	10 (28.6%)	2 (18.2%)	1 (2.6%)
≥1 Treatment-Related SAE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: Subjects who have the same treatment-related AE more than once are counted only once for the Preferred Term. Subjects who have more than one treatment-related AE within a System Organ Class are counted only once in that System Organ Class. A treatment-related AE is defined as an AE with a relationship of unlikely, possible, probable, or definite. **AE,** Adverse event; **LTS,** Long-term study; **SAE;** Serious adverse event

were undetectable on day 7. All tissue sources other than the knee were void of hChonJb#7 cells on days 1, 3, 7, and 14. Furthermore, biodistribution studies of immunodeficient mice, rabbits, and female goats have shown that TG-C does not persist at detectable concentrations.[8]

(2) Subcutaneous injections of the irradiated hChonJb#7 cells expressing TGF-β1 were not tumorigenic in nude mice. Song et al.[9] injected hChonJb#7 cells intradermally in 10 immuno-deficient (athymic nude) mice. While all mice developed lesions at the injection site, they were likely an inflammatory response to TGF-β1. All lesions shrank over time and eventually disappeared. Further analysis revealed no evidence of neoplastic lesions at the site of injection or in any of the other organs.

(3) As a safety measure, hChonJb#7 cells are irradiated with 60 Gy during manufacturing to render them replication-incompetent. Although 60 Gy is a low-dose irradiation and poses little concerns for mutagenesis, it is sufficient to render the hChonJb#7 cells incapable of replication. In fact, a previous study revealed that 15 Gy were sufficient to successfully arrest the replicative ability of hChonJb#7 cells,[9] as evidenced by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The *in vitro* data also revealed that hChonJb#7 cells only express TGF-β1 for up to two weeks after irradiation (Fig. 3). With the foregoing data, we believe that TG-C as a gene-modified cell therapy for knee osteoarthritis is safe for some or all of the following reasons:

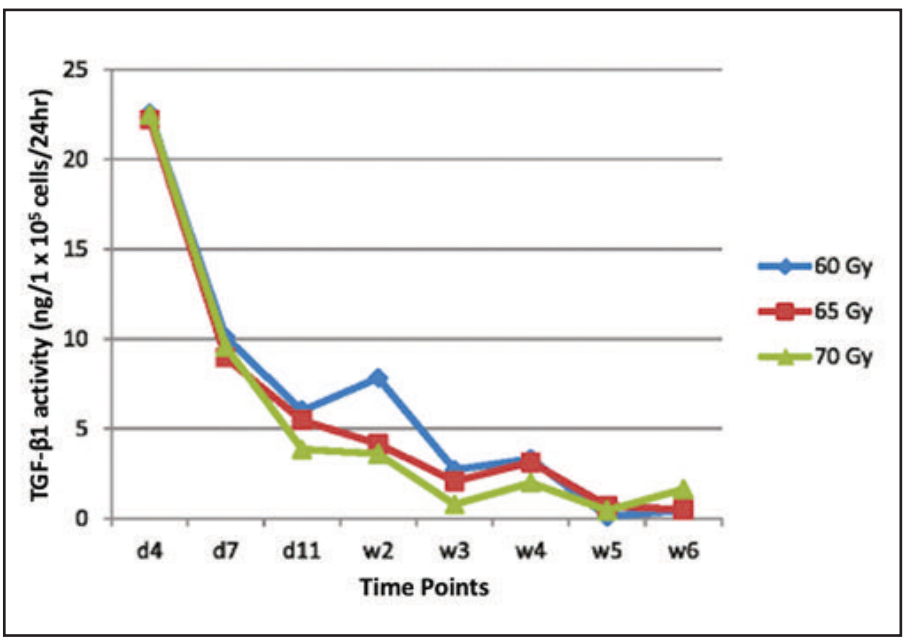

Figure 3. TGF-β1 expression following irradiation.

Reasons for safety

1. The same cell line has been used for the last 15 years.
2. As a safety measure, hChonJb#7 cells are irradiated with 60 Gy during manufacturing to render them replication-incompetent.
3. Subcutaneous injection of the irradiated hChonJb#7 cells expressing TGF-β1 was not tumorigenic in nude mice.
4. The misidentified cells (GP2-293) have been used in multiple animal studies showing no evidence of tumorigenicity or adverse events.
5. The knee joint space is relatively avascular, and, therefore, systemic circulation of TG-C is unlikely.
6. The cells were never changed throughout all phases of clinical testing.
7. TissueGene has utilized this product in five different clinical studies with over 350 patients, similarly demonstrating no adverse effects.

CONCLUSION

The safety profile of intraarticular TG-C administration has been demonstrated by over 10 years of data revealing no evidence of tumorigenicity or other long-term safety concerns. In all studies to date, there have been no treatment-related serious adverse events, and most treatment-related adverse events were mild in severity. Although nomenclature of the transduced component of the TG-C product has changed, the product itself has not. Therefore, the authors of the current review believe that the recent identification error has no impact on TG-C quality, the manufacturing process, safety, or efficacy. We look forward to the continued use and investigation of this potential disease modifying antirheumatic drug for the treatment of knee osteoarthritis. STI

AUTHORS' DISCLOSURES

Dr. Mont is a consultant for, or has received institutional or research support from, the following companies: Sage Products, TissueGene, OnGoing Care Solutions, DJO Global, Microport, Orthosensor, National Institutes of Health, Stryker, Johnson & Johnson, Pacira Pharmaceuticals, Merz, and US Medical Innovations. He is on the editorial/governing board of the American Journal of Orthopedics, Journal of Arthroplasty, Journal of Knee Surgery, and Surgical Technology International. He is a board or committee member of AAOS.

All other authors have no conflicts of interest to disclose.

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