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Case Series

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Ex Vivo Culture-Expanded Autologous Bone Marrow-Derived Mesenchymal Stem Cells (aBM-MSC) for Treatment of Chronic Achilles Tendon Rupture: A Prospective Series

Robert SOLER-RICH MD MS[1], Gil RODAS MD MS PhD[2], Rafael ARRIAZA MD PhD[3,4], Miguel A. SAAVEDRA-GARCÍA[4], Xavier ALOMAR MD MS[5], Alejandra JIMÉNEZ BSN[1], Francesc MALAGELADA MD FEBOT PhD[7*], Veronica GARCÍA PhD[6], Lluís OROZCO MD MS PhD[1]

Abstract

Background: Management of chronic Achilles tendon rupture (ATR) typically involves demanding surgery, frequently with the use of grafts, and requires prolonged rehabilitation.

Purpose: This study aims at trialing a novel non-invasive treatment method Autologous Bone Marrow-Derived Mesenchymal Stem Cells (aBM-MSC)

Study Design: Case series

Methods: Six patients with magnetic resonance imaging (MRI) confirmed symptomatic partial or total chronic ATR were treated with percutaneous intratendinous injection of expanded 20x10e6 aBM-MSCs. Cells were injected percutaneously, under sonographic control, in the damaged tendon area.

Results: Six patients were followed up for a minimum of 24 months. aBM-MSC treatment was safe and well tolerated. MRI showed maximum regeneration gradient of Achilles tendon tissue in all patients by the last visit. Patients reported significantly reduced pain [median scores: VAS (-8.5), VAS sport (-9.7), and improved VISA-A (86.5)]. All patients returned to their pre-injury daily activities immediately and to recreational sports activities by four months post-injection.

Conclusions: Percutaneous intratendinous injection of 20x10e6 cultured aBM-MSCs is effective, feasible and safe and should be considered a promising option in the personalized treatment of chronic ATR.

Clinical Relevance: A new development in the treatment of ATR that overcomes the current difficulties in relation to surgical management such as increased risk of complications, limited weight bearing, immobilization and a faster return to sports.

Keywords: Regenerative medicine; Mesenchymal stem cells; Achilles tendon rupture; Tendinopathy

What is Known about the Subject: Surgery is the standard treatment to manage chronic ATR, with limited weight bearing and immobilization implications.

What this Study Adds to Existing Knowledge: A completely novel treatment option which is minimally invasive, effective and avoids devastating surgical risks and complications. Return to sports is accelerated significantly compared to the available surgical options.

Affiliation:

[1]Institut de Teràpia Regenerativa Tissular (ITRT), Centro Médico Teknon, Barcelona, Spain

[2]Medical Department, Barça Innovation Hub (FIFA Medical Center of Excellence), Futbol Club Barcelona, Barcelona, Spain

[3]Instituto Médico Arriaza y Asociados. A Coruña, Spain

[4]INCIDE Group. Physical Education and Sports School, Universidade da Coruña, A Coruña, Spain

[5]Department of Radiology, Clínica Creu Blanca, Barcelona (Spain)

[6]Unidad de Producción Celular (Citospin S.L), Instituto de Biología y Genética Molecular (UPC-IBGM), Universidad de Valladolid y Consejo Superior de Investigaciones Científicas (UVA-CSIC), Valladolid, Spain

[7]The Royal London Hospital, Barts Health NHS Trust, OneWelbeck Orthopaedics, Cromwell Hospital, London, United Kingdom

***Corresponding Author:**
Francesc Malagelada, The Royal London Hospital, Barts Health NHS Trust, OneWelbeck Orthopaedics, Cromwell Hospital, London, United Kingdom.

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Key Messages:

- Chronic and complex ruptures of the Achilles (complete and/or partial) are challenging injuries routinely leading to complex surgery and extensive recovery.
- The use of aBM-MSCs can treat this condition minimally invasively allowing a quick return to pre-injury daily activities and a return to sports expected by 4 months post-injection.
- This novel technique is set to enormously affect clinical practice and research, providing a new non-surgical treatment option and enhanced recovery.

Background

Achilles tendon rupture (ATR) is a common injury in professional and semi-professional athletes [1,2], as well as in recreational athletes [3-5]. If not treated, ATR affects the movement and function of the ankle by weakening foot plantar flexion, producing pain and inducing long-term functional limitations when walking, climbing, descending stairs, and playing sports [6].

Early diagnosis of acute ATR is essential to successfully restore tendon length and tension; however, 20–30% of patients are not diagnosed promptly and present with chronic ruptures [6]. Clinical management of chronic ATR requires complex surgery, as the tendon ends are often retracted and a graft may be necessary to bridge the gap [7,8]. These procedures are followed by long periods of rehabilitation and have a relatively high risk of complications [6,7].

Recently, mesenchymal stem cells (MSCs) and platelet-rich plasma (PRP) have been used for the management of musculoskeletal conditions, including tendon injuries [9,10]. Non-clinical studies have demonstrated the ability of bone marrow–derived and adipose-derived MSC extracts to regenerate, heal, and modulate inflammatory processes in injured tendons, restoring their histological and biomechanical features [11,12]. Our team recently demonstrated the safety and superiority of a local injection of 20×10^6 aBM-MSCs compared to PRP to reduce pain and regenerate tendon structure in patients with chronic patellar tendinopathy with a gap >3 mm (NCT03454737) [13-15]. Based on these findings, we hypothesized that the local injection of aBM-MSCs would also regenerate tendon structure in patients with chronic ATR, as well as improve pain and function.

In this prospective case series, the feasibility and the structural and clinical effects of a local aBM-MSC intratendinous injection with immediate post-injection mobilization in patients with chronic ATR was assessed.

Methods

Study Design and Patient Recruitment:

All consecutive patients presenting with symptomatic chronic ATR who were treated with an intratendinous injection of aBM-MSCs were included in the study. The study was performed under compassionate use authorization in accordance with the Spanish Agency of Medicines and Medical Devices (hereinafter AEMPS) as part of clinical trial NCT03454737, within the scope of an exemption license in Advanced Medical Therapies to treat chronic tendinopathy in a Spanish healthcare institution. All patients presented with chronic ATR diagnosed by clinical examination, ultrasound imaging, and confirmed by MRI. Patients presented with pain, which was treated with regular NSAID and analgesics intake, functional limitation and impaired walking ability which required the use of one or two crutches, and had no metabolic or musculoskeletal pathologies which could have interfered with the harvest or administration of aBM-MSCs. All patients signed a written informed consent form.

Patients were confirmed negative for human immunodeficiency virus (HIV) 1/2 (Elecsys HIV Combi PT; *Roche Diagnostics*, Mannheim, Germany), hepatitis C (Elecsys Anti-HCV II; *Roche Diagnostics*, Mannheim, Germany), B (Elecsys HBsAg II; *Roche Diagnostics*, Mannheim, Germany), and syphilis (Elecsys syphilis total Ab; *Roche Diagnostics*, Mannheim, Germany). All procedures were performed by Orthopedic surgeons and Sports Medicine physicians involved in clinical trial NCT03454737 [1,16], in compliance with the principles of the World Medical Association's Declaration of Helsinki [17] and the Spanish Ministry of Health regulation on advanced medical therapies [18]. All patients were clinically monitored and followed-up at ITRT.

STROBE checklist was followed in the preparation of the manuscript [19] and the recommendations from Murray et al. on the minimum requirements for studies evaluating the effect of MSC treatments in orthopaedics were followed (Annex 1) [20].

Therapeutic Intervention:

ITRT's aBM-MSC manufacturing and administration processes have been reported in detail in past clinical trials published in the literature [1,16]. In summary:

aBM-MSC Manufacturing and Characteristics:

Patients were sedated with midazolam and positioned prone. Local anesthesia (20 mL of 1% (v/v) lidocaine diluted with saline) was applied to both posterior iliac crests. Autologous bone marrow (BM) stromal cells were obtained by aspiration from the posterior iliac crest. All BM samples collected were processed within 24 hours under Good Manufacturing Practices (GMP) in an authorized cell production facility. The mononuclear fraction was isolated, cultured in a 175 cm^2 tissue culture flask with cell culture

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medium, and incubated at 37°C with 10% CO_2 until the adherent cells reached 80% confluence. After two cell culture passages [22 (±2) total days], aBM-MSCs were obtained. The obtained cells demonstrated >98% viability, suitable flow cytometric immunophenotypic profiles (CD14–, CD34–, CD45–, HLA-DR–, CD105+, CD166+, CD73+, CD90+), and were negative for adventitious microbial agents (BacT/ALERT System, Biomerieux, Spain) and mycoplasma (PCR, Eur. Ph.2.6.7), in compliance with the procedure authorized (PEI 10-34) by the Spanish Medical Association, and in accordance with the International Society for Cellular Therapy's criteria for MSCs [21]. aBM-MSCs were resuspended in Ringer's lactate solution with 0.2% human albumin and 5 mM glucose and delivered in two Luer-Lok syringes: one containing $10(\pm1) \times 10^6$ aBM-MSCs in 2 mL of total solution and the other one containing $10(\pm1) \times 10^6$ aBM-MSCs in 4 mL of total solution. The final aBM-MSC medicinal product was stable for eight hours at 4–12ºC. The remaining cells obtained were then cryopreserved.

aBM-MSC Administration at the Outpatient Clinic:

Patients were sedated with midazolam and propofol and positioned prone. All patients received a total dose of $20(\pm2) \times 10^6$ aBM-MSCs administered through three ultrasound-guided injections in a single treatment session: 2 mL containing 10×10^6 cells were administered inside the tendon, 2 mL containing 5×10^6 cells were injected into the medial peritendinous area, and 2 mL containing 5×10^6 cells were injected into the lateral peritendinous area. After aBM-MSC injection, patients were allowed to stand up without immobilization, walking aids, or protection of the treated lower limb. All patients underwent standard progressive rehabilitation, based on progressive strength exercise, starting with isometrics and aiming towards eccentric exercise. Patients did not receive additional or concomitant standard ATR treatment during follow-up.

Collection of Data and Follow-Up Assessment:

Demographic, clinical, and structural tendon characteristics (through imaging modalities) were collected at baseline and 1, 2, 3, 6, 12, and 24 months after aBM-MSC injection, as follows:

Demographic and Clinical Characteristics:

Demographic and clinical characteristics collected included age, gender, body mass index (BMI), time between injury and aBM-MSC injection (Table 1), physical and serum biochemical parameters, type of Achilles tendon injury (partial/complete rupture), VAS pain score, and the Spanish version of VISA-A [4].

Imaging:

Ultrasound (Aplio 500 TUS-500 5.0 Platinum Series, Canon Medical Systems, Otawara-shi, Tochigi, Japan) and MRI (Vantage Galan 3Teslas, Canon Medical, Otawara-shi, Tochigi, Japan) were used to assess tendon structure, Kager fat pad status, peritendon status, presence/absence of neovascularization, intrasubstance appearance, tendon thickness, echogenicity, and presence/absence of calcifications.

MRI scans were obtained and analyzed by an independent radiologist. The images were weighted and scored as follows: (1) for muscle-tendon body rupture (out of a total of 300): absence of tendon edema (0 to 100 points), granulation tissue formation (0 to 100 points), and collagen fiber formation (0 to 100 points); for insertional tendon rupture (out of a total of 500 points): absence of tendon edema (0–100 points), granulation tissue formation (0–100 points), collagen fiber formation (0–100 points), absence of peritendon edema (0–100 points), absence of geodes (0–50 points), and absence of edema in Kager's fat (0–50 points). The degree of structural restoration was calculated as the average percentage of the total scores during each visit.

Outcomes and Follow-Up Assessment:

The primary outcome consisted of structural changes in the treated tendon upon imaging at 12 and 24 months after aBM-MSC injection. Secondary outcomes assessed were pain reduction and functional status (measured by VAS and VISA-A scores, at 12 and 24 months), serious adverse events reported, and re-ruptures during the follow-up period.

Statistical Analysis:

Considering study design and feasibility, it was elected to recruit a small number of patients. Descriptive statistics and non-parametric tests were performed (Friedman test for paired samples). Quantitative variables are expressed as the median value (interquartile range), and changes in pre-treatment and post-treatment measures are expressed as the median value (interquartile range) of the differences.

Results

Six consecutive Caucasian patients (all males) diagnosed with chronic ATR were treated at ITRT in Barcelona (Spain) with aBM-MSCs between September 2018 and July 2020 (treatment administration as described in point 2.2 of the Methods section) and prospectively followed for a minimum of 24 months. On presentation, all patients reported Achilles tendon pain, tenderness on palpation, and insufficiency to walk on tiptoes, run and jump. Diagnosis of chronic partial or total ATR was confirmed for all patients on ultrasound and MRI, as described. Median patient age on presentation was 67 (46 – 85) years. Median BMI was 24 (21.6 – 38.9). Median daily life visual analog scale (VAS), sport VAS, and Victorian Institute Sport Assessment (VISA-A) scores were 8.5 (6.9 - 9.8), 10.0 (10.0 - 10.0), and 12 (6.3 – 17.8), respectively. Median time elapsed since ATR was 39 (12 – 120) months.

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Table 1: Patient demographic and clinical characteristics at baseline.

CASE	Gender	Ethnicity	Age (Years)	BMI	Achilles Rupture	Time Since Injury (Mo.)
CASE 1	Male	Caucasian	46	24.5	Partial	24
CASE 2	Male	Caucasian	70	38.9	Partial	48
CASE 3	Male	Caucasian	52	26.6	Partial	30
CASE 4	Male	Caucasian	64	23.5	Partial	60
CASE 5	Male	Caucasian	85	22.5	Complete	12
CASE 6	Male	Caucasian	72	21.6	Complete	120

BMI: Body Mass Index; **Mo.:** Month

Four patients presented with a partial rupture (median percentage of tendon tissue: 46.0 (42,8 – 46.2) %), and the other two patients presented with a complete rupture (lesion gaps of 18 and 20 mm, respectively).

All patients had undergone conservative or surgical treatment at other institutions. Case 3 had developed a post-surgical infection and abscess formation. Table 1 presents detailed clinical information of each case at baseline.

By the end of the study period, all six patients achieved complete regeneration of the Achilles tendon (median regeneration rate of 96.3 (95.0 – 100) at month 12, and all patients achieved a 100% regeneration rate at month 24 of follow-up). All patients returned to their daily activities the day after their treatment session and reported clinically significant pain relief by three months since the index intervention. Their daily life VAS and sport VAS scores were reduced to zero by the last visit (median score reduction was -8.5 (-10, -6.5) points for VAS and -9.7 (-10.0, -8.6) points for sport VAS), and their VISA-A score had increased markedly by the last visit (median VISA-A score difference was 86.5 (68.0 – 94.0) points). All patients returned to their recreational sports activities by a median of 4.0 months (Table 2).

MRI showed a reduction in hyperintense signals on T2-weighted, spin-echo, and fat-saturated sagittal and coronal images of the Achilles tendon, with signs of collagen fiber formation, and reduction in tendon edema and granular tissue. Case 1 (46 years old,), Case 2 (70 years old, Figure 1), and Case 3 (52 years old, Figure 2) – all initially diagnosed with partial chronic ATR – exhibited homogeneous tendon fibers/fascicles crossing the original gap at 12 months. Case 4 (64 years old) – initially diagnosed with partial chronic insertional ATR at the calcaneus level– showed clear continuity of tendon tissue fibers at insertion, absence of peritendinous and Kager's fat edema at 12 months, and complete tendon regeneration at 24 months. Finally, Case 5 (85 years old, Figure 3) and Case 6 (72 years old, Figure 4) - diagnosed initially with complete chronic ATR – showed tendon tissue regeneration completely bridging the gap at 12 and 24 months, respectively. Ectopic signs of calcification were not observed in the follow-up MRIs of any patient.

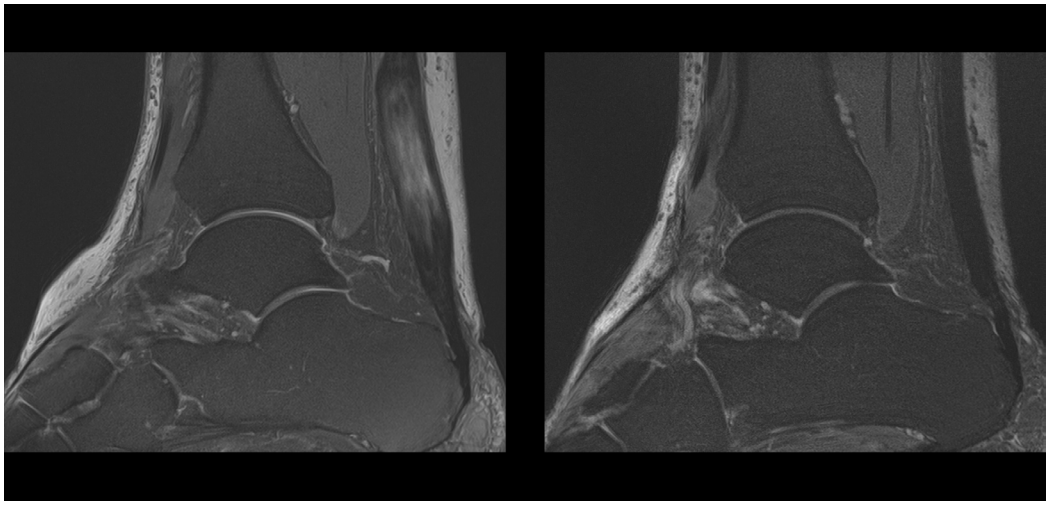

Figure 1 (Case 2): A 70-year-old patient with a four-year history of chronic partial rupture of the Achilles tendon insertion in the left ankle, who failed prior conservative treatment. A) T2-weighted magnetic resonance imaging (MRI) before local autologous bone marrow mesenchymal stem cell (aBM-MSC; 20 × 10^6 cells) injection. Presence of tissue 46.0%. B) T2-weighted MRI at 12 months post-aBM-MSC injection. Almost complete tissue regeneration of chronic partial Achilles tendon rupture (96%) was achieved. No adverse events. The patient resumed hiking after four months.

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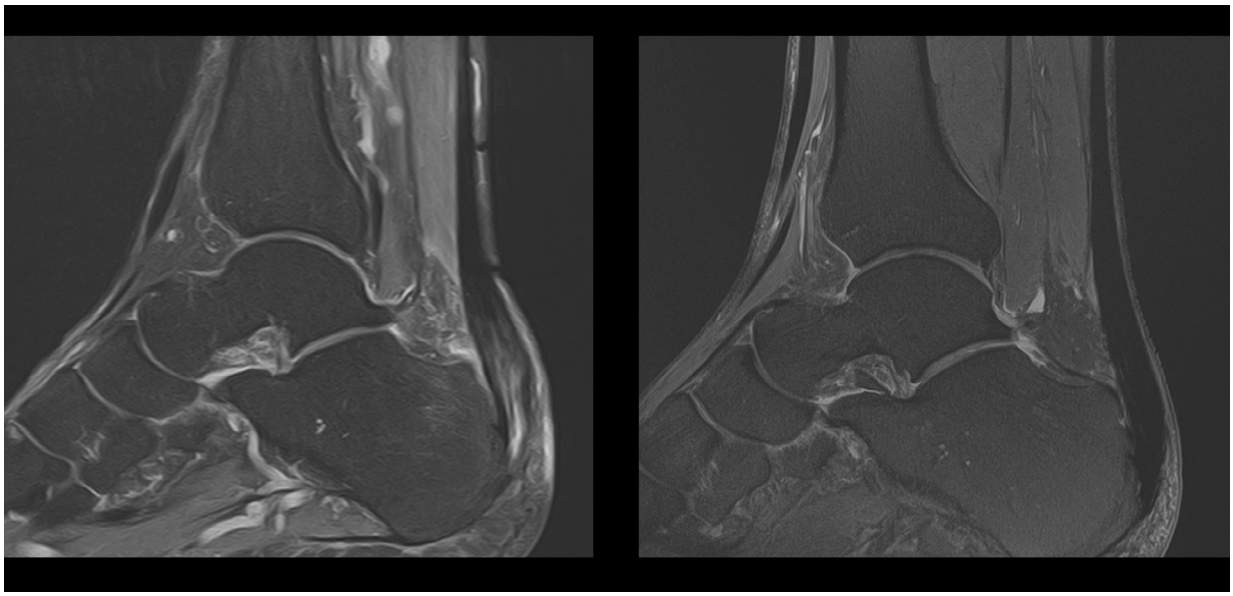

Figure 2 (Case 3): A 52-year-old patient with a surgical infection and a 2.5-year history of chronic partial rupture of the Achilles tendon in the left ankle. The patient had previously undergone debridement, removal of the surgical material, and endovenous antibiotic treatment. Six months later, the patient received aBM-MSC treatment. A) T2-weighted magnetic resonance imaging (MRI) before local autologous bone marrow mesenchymal stem cell (aBM-MSC; 20×10^6 cells) injection. Presence of tissue 33.3%. B) T2-weighted MRI at 12 months post-aBM-MSC injection. Complete regeneration of chronic partial Achilles tendon rupture (100%) was achieved. No adverse events. The patient resumed padel tennis after four months.

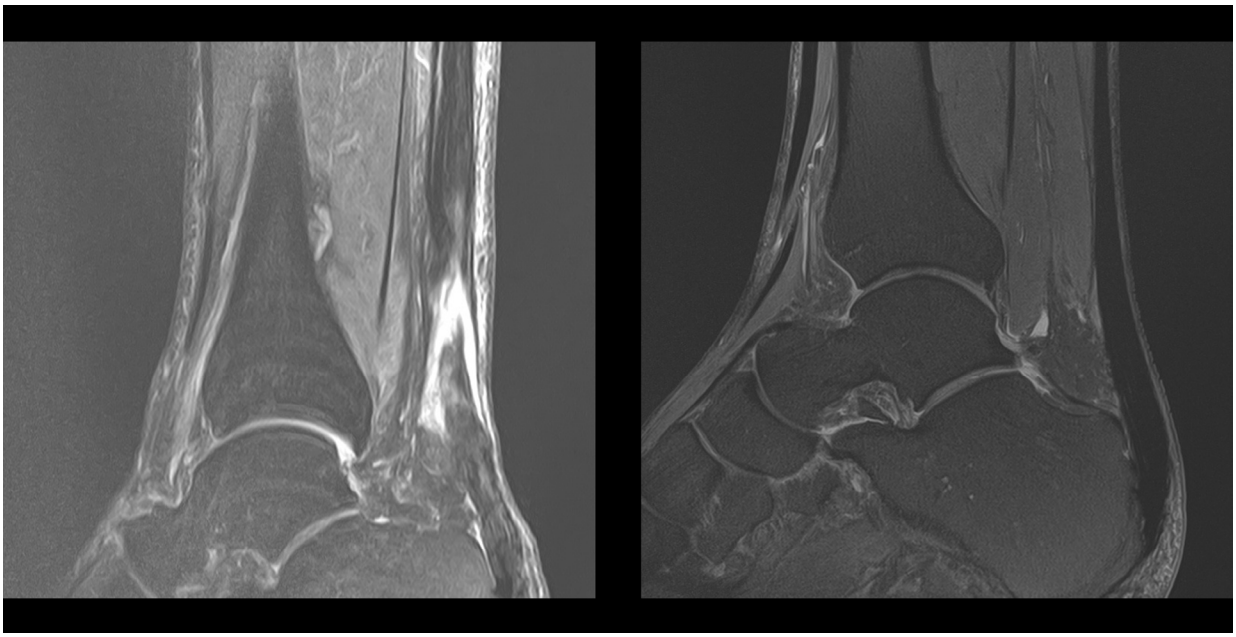

Figure 3 (Case 5): A 72-year-old patient with a 10-year history of chronic complete Achilles tendon rupture in the right ankle and failed conservative treatment. A) T2-weighted magnetic resonance imaging (MRI) before local autologous bone marrow mesenchymal stem cell (aBM-MSC; 20×10^6 cells) injection. Lesion gap (18 mm). Absence of tissue. B) T2-weighted MRI post-aBM-MSC injection. Appearance of progressive T2-weighted hypointense fibrous tissue and reduction of lesion gap to complete regeneration of chronic Achilles tendon rupture. Tissue regeneration: B1 (86.6%, month 8), B2 (95%, month 14), and B3 (100%, month 24). No adverse events. The patient progressively went back to playing double's tennis after four months.

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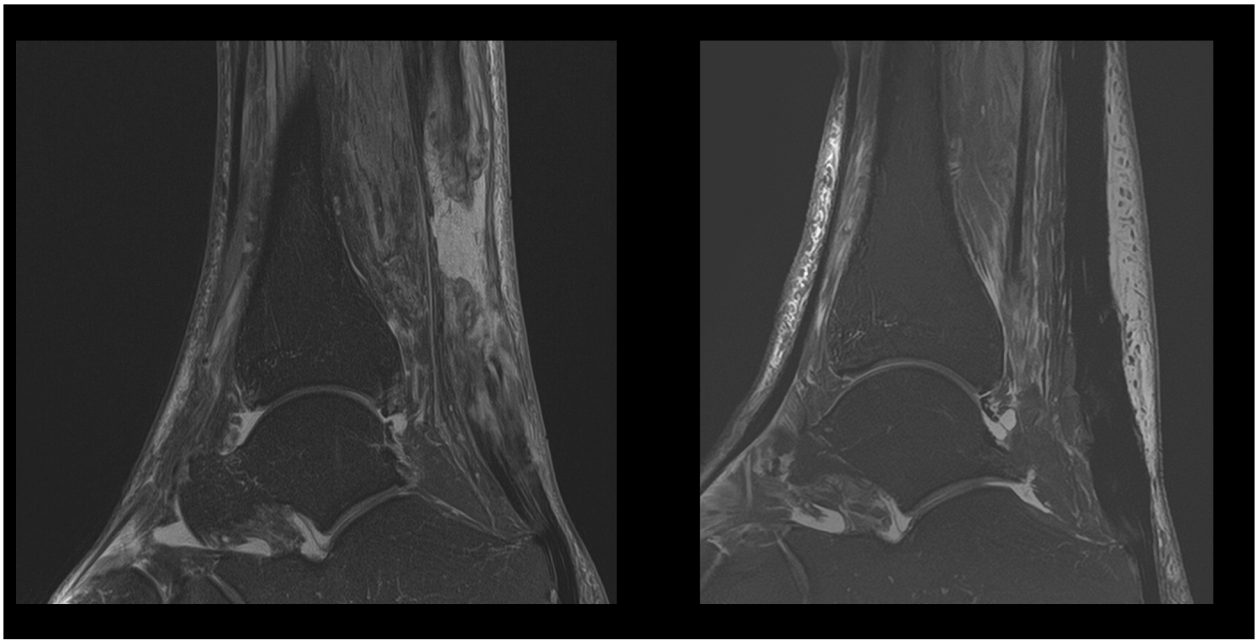

Figure 4 (Case 6): An 85-year-old patient with one year of complete chronic Achilles tendon rupture in the left ankle and failed conservative treatment. A) T2-weighted magnetic resonance imaging (MRI) before local autologous bone marrow mesenchymal stem cell (aBM-MSC; 20 × 10^6 cells) injection. Lesion gap (20 mm). Absence of tissue. B) T2-weighted MRI at twelve months post-aBM-MSC injection. Post-rupture changes in the middle third with regenerative hypertrophy of the entire tendon and presence of extensive areas of remarkably active granulation tissue of longitudinal disposition without retraction of ends were observed. Almost complete tissue regeneration of chronic Achilles tendon rupture (95%) was achieved. No adverse events. The patient resumed playing tennis after four months.

Table 2: Response to aBM-MSC treatment at baseline, 12, and 24 months.

Case	Tissue Regeneration (%)				VAS Dayli Life (Score)				VAS Sport (Score)				VISA-A (Score)				Return to Sport	
	M 0	M 12	M 24	Dif.	M 0	M 12	M 24	Dif.	M 0	M 12	M 24	Dif.	M 0	M 12	M 24	Dif.	M	Sport Activity
1	46.6	.	100	53.4	6.5	0	0	-6.5	10	.	0	-10	32	98	100	68	3	Triathlon
2	46	96.3	100	54	8	0	0	-8	9.8	0	0	-9.8	18	100	100	82	4	Hiking
3	33.3	100	100	66,7	10	0	0	-10	10	1.4	0	-8.6	6	100	100	94	4	Padel Tennis
4	46	98	100	54	10	1	0	-10	10	2	0	-10	6	97	100	94	5	Nordic Walking
5	0	95	100	100	9	0	0	-9	10	1.2	0	-8.8	7	97	100	90	4	Tennis Double's
6	0	95	100	100	6.5	0	0	-6.5	10	4.5	0.5	-9.5	17	95	100	83	4	Tennis
	Sig. Friedman test			0.003*	Sig. Friedman test			0.001*	Sig. Friedman test			0.003*	Sig. Friedman test			0.001*		

aBM-MSC: Ex vivo culture-expanded autologous bone marrow mesenchymal stem cells. **M:** Months. **Dif.:** Score value difference between baseline (M.0. and last visit (M.12 or M.24). **M.0:** Baseline (pre aBM-MSC injection); **M.12.:** 12 months post aBM-MSC injection; M.24: 24 months post aBM-MSC injection; **VAS:** Visual Analog Scale questionnaire; **VISA-A:** Victorian Institute of Sport Assessment; **(.)** Missing data; *Statistical significance.

All patients tolerated local administration of 20 × 10^6 aBM-MSCs into the Achilles tendon without complications. Adverse events/serious adverse events were not observed or reported during follow-up. By the end of the follow-up period, all patients reported that they were satisfied or very satisfied with the results of their treatment.

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Discussion

Our main finding is that local injection of a single dose of 20 × 10^6 aBM-MSCs regenerated tendon (or tendon-like) tissue in chronic ATR and improved tendon function without ankle immobilization in all six patients described in this case series. All patients experienced pain relief, were able to resume their daily activities immediately, and returned to their recreational activities after four months. aBM-MSC treatment was safe and well tolerated, as it has been previously reported in patients with chronic patellar tendinopathy with a gap [13,14].

Surgery is the standard treatment to manage chronic ATR, with a large variety of procedures reported in the literature, including direct end-to-end tendon sutures and allografts [7]. Surgical treatment implies limited weight bearing, with immobilization protocols ranging from two to six weeks [6]. Recently, Xu et al. [22], showed that two weeks is the optimal duration of ankle immobilization after open surgery for acute ATR, but there are no similar studies for chronic ATR, most probably due to the many different surgical procedures used by different authors. A recent systematic review on the surgical management of 1.046 chronic ATR patients reported a post-intervention complication rate of 15.8%, which included infections (5.8%), wound dehiscence (3.10%), re-ruptures (0.85%), and deep vein thrombosis [7]. After surgery, most patients recover functionally for daily activities; however, in some patients, deficits in ankle plantar flexion strength limit their return to sport activities [23-25].

Non-surgical treatment of chronic ATR, although less frequent compared to surgery, is an option for patients in which surgery is contraindicated, but logically, pain and functional deficits will remain unchanged [5,22]. Differently, in acute ATR, Winson et al., reported beneficial outcomes of the non-surgical Swansea Morriston Achilles Rupture Treatment Protocol (SMART), especially in young patients presenting within 12 weeks of acute ATR and with a gap size between the tendon stumps <45 mm. Emphasizing the minimally invasive nature of the aBM-MSC treatment outlined in this case series, it's crucial to note that post-injection all patients remained mobile without immobilization or walking aids, except for pain control and compensation of functional deficits, as they did before the procedure, which should help to reduce the complications found even with the non-surgical treatment of acute ATR, due to the initial immobilization required, which include even cases of fatal pulmonary embolism [24]. Importantly, there were no instances of re-ruptures throughout the 24-month follow-up period. As no surgical incision is required, there is minimal risk of infections and wound healing complications. Early mobilization likewise minimizes the occurrence of deep vein thrombosis. Finally, all patients experienced early structural and functional recovery.

To our best knowledge, no other previous clinical research in the literature has investigated the clinical safety and efficacy of aBM-MSC therapy in patients presenting with chronic ATR [10,26]. Previous clinical studies have demonstrated the regenerative and anti-inflammatory potential of MSC extracts in Achilles tendon injuries. Stein et al. combined the open Krackow technique with direct injection of bone marrow aspirate concentrate into the repair site of patients with acute ATR. After rehabilitation and limitations to bearing weight, as well as with a splint at 20° of equinus, followed by a controlled ankle movement boot at 20° of plantar flexion, patients reported pain relief and returned to daily activity after 3.4 ± 1.8 months and to sports after 5.9 ± 1.8 months. No serious adverse events were reported after 29 months of follow-up. Only one patient developed superficial wound dehiscence without infection. A randomized trial showed better results with a single injection of autologous adipose tissue stromal vascular fraction (SVF) containing adipocyte-derived MSCs compared to PRP for chronic non-insertional Achilles tendinopathy [27]. Patients experienced pain relief and recovered functionally within 15 days, although the authors did not observe signs of regeneration on MRI. Recently, Iuso et al. also reported positive functional gains in a single patient treated for ATR with a minimally invasive injection of SVF [28].

Several non-clinical studies have shown the ability of MSCs to secrete growth factors, proangiogenic factors, cytokines, and chemokines that modulate granulation tissue formation and wound healing by reducing scarring through paracrine signaling [9,29,30]. Transforming growth factor beta and bone morphogenetic protein 2 are involved in cell differentiation into tenocytes and regeneration of the fiber matrix [31]. BM-MSC extracts and SVF aspirates contain small amounts of MSCs (0.001-0.01%) [32] and progenitors (0.5-0.6%) [30]. In the cases presented in our series, the aBM-MSCs in a controlled environment allowed extensive cell proliferation while maintaining the particular characteristics of MSCs. Although it is unclear what the optimal number of MSCs injected into the impaired Achilles tendon should be, we theorize that the higher dose injected in the cases presented, as compared to the number of viable MSC present in bone marrow aspirate concentrate or in autologous adipose tissue stromal vascular fraction might facilitate the adaptive responses of exogenous aBM-MSCs, favoring faster regeneration and healing. However, it is unclear how long the injected MSCs act in the tendon. Some *in vivo* non-clinical studies have shown a lifespan of between 10 and 30 days for exogenous MSCs [3]. Further studies should clarify the lifespan of exogenous aBM-MSCs and their paracrine action on endogenous MSCs in the tendon niche to provide long-term regeneration.

We acknowledge the limitations of this case series,

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including the nature of the study's design and the small size and gender representation of the population, which restricts the amount of evidence provided. We highlight that our patients represent a small case series treated with aBM-MSCs within the scope of a hospital exemption to treat patients with chronic Achilles tendon tears based on the positive findings of clinical trial NCT03454737 and, as such, without a control group [13,15]. Our patients were consecutively included in the series. All but one were males who played recreational sports, likely because Achilles tendon injuries in recreational sports are three times more common in males than in females [3]. Professional and semi-professional athletes were not represented in this case series because of the small sample size, but they were not excluded intentionally. Nevertheless, in the 35 studies found by Azam et al. [33] in their systematic revision of the treatment of chronic ATR in 2023 [34-36] only 23 included more than eleven cases, which underlines the difficulty of gathering large number of patients and places our study within a logical range for a completely new approach in the treatment of severe tendon injuries.

Our findings are promising and warrant further investigation. Future research could develop along three lines: (i) conducting dose-efficacy clinical trials with a larger and more varied sample of patients, aiming to define the optimal dose and effect; (ii) investigating biocompatible markers that provide a more reliable analysis of the exogenous aBM-MSC lifespan in the tendon without altering cell migration and viability; and (iii) performing pharmacodynamic and pharmacokinetic studies on the local injection of MSC-based medicines.

Conclusions

Intratendinous injection of a single dose of $20(\pm2) \times 10^6$ *ex vivo* culture-expanded aBM-MSC under good manufacturing practices in combination with a standard rehabilitation protocol was clinically safe and efficacious in regenerating tendon in patients presenting with chronic ATR, thus avoiding surgery. This case series suggests that intratendinous aBM-MSC therapy should be considered a promising option for the personalized treatment of chronic ATR. Randomized clinical trials are warranted, in order to assess the clinical utility of aBM-MSC therapy in the treatment of chronic ATR on a large clinical scale.

Investigation performed at:

Institut de Teràpia Regenerativa Tissular (ITRT), Centro Médico Teknon, Barcelona (Spain).

Disclosure statement:

"We declare that we have no conflicts of interest in the authorship or publication of this contribution".

Ethics statement: This study was performed under compassionate use authorization in accordance with the Spanish Agency of Medicines and Medical Devices as part of clinical trial NCT03454737, within the scope of an exemption license in Advanced Medical Therapies to treat chronic tendinopathy in a Spanish healthcare institution.

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