Journal of Equine Veterinary Science 34 (2014) 1357–1360

Contents lists available at ScienceDirect

Journal of Equine Veterinary Science

journal homepage: www.j-evs.com

Short Communication

Long-Term Follow-up of Superficial Digital Flexor Tendonitis Treated by a Single Intralesional Injection of a ReGeneraTing Agent in 51 Horses

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ARTICLE INFO

Article history:
Received 2 June 2014
Received in revised form 16 September 2014
Accepted 28 September 2014
Available online 2 October 2014

Keywords:
Horse
Tendonitis
Regenerative medicine
Matrix therapy
Regenerating agent

ABSTRACT

ReGeneraTing Agents (RGTA) are nanopolysaccharides engineered to mimic heparan sulfates and have been shown to stimulate tissue repair and healing (skin, cornea, gingival, and muscle) in several animal models of injury and in human medicine. A preliminary study, monocentric and uncontrolled, was conducted to evaluate the efficacy of a dedicated RGTA (named Equitend) in improving the healing quality of the injured tendon after a single and ultrasound-guided intralesional injection. Improvement of ultrasonographic appearance of tendinous or ligamentous lesion was documented at least over 4 months in Equitend-treated horses and was further supported by another study on superficial digital flexor tendonitis, in 51 horses (16 French Standardbred trotters (ST), 13 Thoroughbreds (TB), and 22 eventers). Long-term follow-up of these horses showed high rates of return to racing, with 95% of eventers, 87.5% of French ST, and 77% of TB. The mean duration before the first race or competition was 6.6 and 7.4 months for ST and eventers, respectively. The group of 16 treated ST was then compared with a matched control group, showing that the Equitend-treated group was able to return to a higher level of earning after lesion (74% vs. 15% in the control group). Furthermore, the Equitend-treated group was back in racing 2.4 months earlier than the control group.

1. Introduction

Pathogenesis, prevalence, and management of tendonitis in horses have now been studied largely [1–4], mostly in Thoroughbreds (TB) and on the superficial digital flexor tendon (SDFT) [3–5]. Recent researches focused on the development of matrix and/or cellular therapies aiming at improving the healing quality and functional capacity of the tendon after injury [6,7].

Efficacy of ReGeneraTing Agents (RGTA) on tissue repair was demonstrated in several experimental animal models of injury and in human medicine [8–10]. ReGeneraTing Agents are nanopolysaccharides engineered to mimic heparan sulfate (HS), a subset of glycosaminoglycans, obtained by substitution of dextran by sulfate and carboxymethyl groups. Heparan sulfates are key elements of the matrix architecture, bridging and protecting matrix

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http://dx.doi.org/10.1016/j.jevs.2014.09.014

proteins, as well as storing, protecting, and positioning in the extracellular compartment heparin-binding cytokines, chemokines, and growth factors. After injury, HS are readily destroyed by enzymes. ReGeneraTing Agents are resistant to enzymes and once injected in the lesion could thus replace HS at heparan-binding sites available on the matrix proteins. They promote tissue regeneration by protecting both structural proteins and endogenous factors of cellular communication involved in the natural process of tissue regeneration. Therefore, RGTA allow the reconstruction of the extracellular matrix scaffold and growth factors repositioning in the cellular microenvironment [8,11].

The objective of this preliminary study was to evaluate the efficacy of a specific RGTA, different from others RGTA by the presence of additional acetate groups (Equitend, Regenmove BV, Holland) designed for the intralesional treatment of tendonitis, before starting an experimental trial. The specific objective of this article was to present the effects of a single injection of Equitend on the long-term prognosis of superficial digital flexor (SDF) tendonitis evaluated by performance criteria assessment during the follow-up of the treated racehorses (TB and trotters) and eventers.

2. Materials and Methods

2.1. Population

A monocentric preliminary study was conducted at Center of Imaging and Research on Equine Locomotor Injuries (CIRALE, Normandy, France) to evaluate the effect of a single intralesional injection of Equitend on tendon healing. Fifty-one racehorses and eventers presented with acute or chronic SDF tendonitis were included with consent of their owner: 13 TB, 16 French Standardbred trotters (ST), and 22 eventers. Only racehorses and eventers were included to have a better access to objective performance criteria and to obtain a more accurate comparison between populations and with literature data.

On the TB population, five were flat racing and eight were steeplechasers. Half of the lesions included in this population were primary lesion and half were reinjury. In contrary, the lesions of the ST and eventers were mainly primary.

The 16 treated ST were also individually matched with 16 control ST that had suffered an SDF tendonitis diagnosed and/or followed at CIRALE and that did not receive any other treatment than progressive rehabilitation program and corrective shoeing (wide toe and narrow branches). Individual matching was based on the severity of the lesion (echogenicity, architecture, cross-sectional area, and longitudinal extend), sex, and age.

2.2. Diagnosis and Short-Term Follow-up

All horses underwent a complete ultrasonographic examination of both metacarpal tendon areas, using a 7.5-MHz linear probe (Alpha-10 Prosound or 5500; Aloka). Diagnosis of SDFT injury was based on clinical examination and identification of ultrasonographic findings. Severity of the lesion was assessed evaluating the echogenicity grade, extend, and architecture on transverse and longitudinal ultrasound scans. Clinical and ultrasonographic examinations were scheduled 1 month (M1), 2 months (M2), and 4 months (M4) after the initial treatment (D0).

2.3. Treatment

Intralesional ultrasonographic-guided injection of 1-mL Equitend solution was performed using a multifrequency (5–10 MHz) microconvex probe (Alpha-10 Prosound or 5500; Aloka) covered by a sterile glove. After aseptic preparation of the tendon region, the affected limb was held in flexion and the SDFT lesion was imaged on a transverse section using a palmar approach. A 0.5 × 16-mm needle was introduced laterally in the ultrasound beam and 1 mL of Equitend was injected in two or three points depending on the proximodistal extend of the lesion. After injection, the limb was bandaged immediately.

2.4. Long-Term Follow-up

Racing or sport data were obtained for each horse from Web sites: “Fédération Française d’Equitation” (ffecompet.ffe.com), “France Galop” (france-galop.com), and the “Cheval Français” (cheval-francais.fr). The duration before the first race or competition was calculated; the number of races and/or competitions and the earnings per start for each horse were obtained.

In the matched ST groups (treated and control), racing criteria were compared over a 24-month period follow-up.

To assess the associations between the racing criteria and treatment (vs. control), racing criteria have been dichotomized according values that were close to the median value. Crude and multivariate logistic regression models have been used to quantify the associations with treatment by providing odds ratios (OR); OR were estimated by the maximum-likelihood estimation method, and the chi-square score statistics was used for testing the null hypothesis. One separate multivariate model was performed adjusting for “earnings per start before.”

Table 1
Results of long-term follow-up in the three populations presented with a tendonitis of the superficial digital flexor tendon and treated by a single intralesional injection of Equitend.

Population	Number of Horses Included	Number of Horses Back in Race/Competition (%)	Mean Duration Before the First Race/Competition (month ± SD)	Number of Reinjury (%)	Mean Duration Before Reinjury (mo)
Eventers	22	21 (95.5)	7.4 ± 3.7	2 (9)	6.5
Thoroughbreds	13	10 (77)	15.0 ± 4.4	3 (23)	8
French Standardbred trotters	16	14 (87.5)	6.6 ± 3.1	2 (12.5)	4.5

Table 2
Comparison of the 16 Standardbred trotters (ST) treated by a single intralesional injection of Equitend with 16 matched control ST: follow-up of racing criteria over 24 months after lesion.

Group of treatment	Number of Horses	Number of Horses Back in Race (%)	Mean Earnings/ Start Before (12 mo)	Mean Earnings/ Start After (24 mo)	Ratio Before/ After (%)	Number of Races Before (12 mo)	Number of Races After (24 mo)	Mean Duration Before the First Race (mo)
Treated group	16	14 (87.5)	1,281	944	74	12.7	10	6.6
Control group	16	14 (87.5)	5,106	780	15	12.7	13.8	9

Statistical analyses were carried out with SAS (version 9.3; SAS Institute, Cary, NC).

3. Results

In the population of eventers, in which half performed at the international level (11 horses in Concours Complet International [CCI]), 95.5% of horses went back to competition at a good level. The only horse that was not able to resume competition presented a total rupture of the SDFT. The mean duration before the first competition was 7.4 months (8 months for CCI horses; Table 1). On average, eventers competed in 23.2 events (19.4 events for CCI horses) and were maintained at a good level of competition during 17 months after lesion. Half of eventers included in the study were still in competition 2 years after injury.

Ten TB (77%) went back to racing in a mean duration of 15.0 months. Thoroughbreds with primary lesion showed a better rate of return to racing (86% vs. 77% after reinjury), without significant difference on the duration before the first race. Moreover, steeplechasers (eight of 13) showed a better rate of return to racing (88% vs. 60% in flat racehorses), with four horses being able to race more than three times after injury.

Fourteen over 16 ST went back to race (87.5%) in a mean duration of 6.6 months. The same rate of return to racing was found in the matched control group (Table 2), but the mean duration before the first race was shorter in the treated group (6.6 vs. 9 months). Thirteen treated ST (81.3%) versus eight matched ST (50%) went back to racing within 8 months (result of borderline significance: OR, 3.7; 95% confidence interval [CI], 0.8–15.8; $P = .08$). Comparing

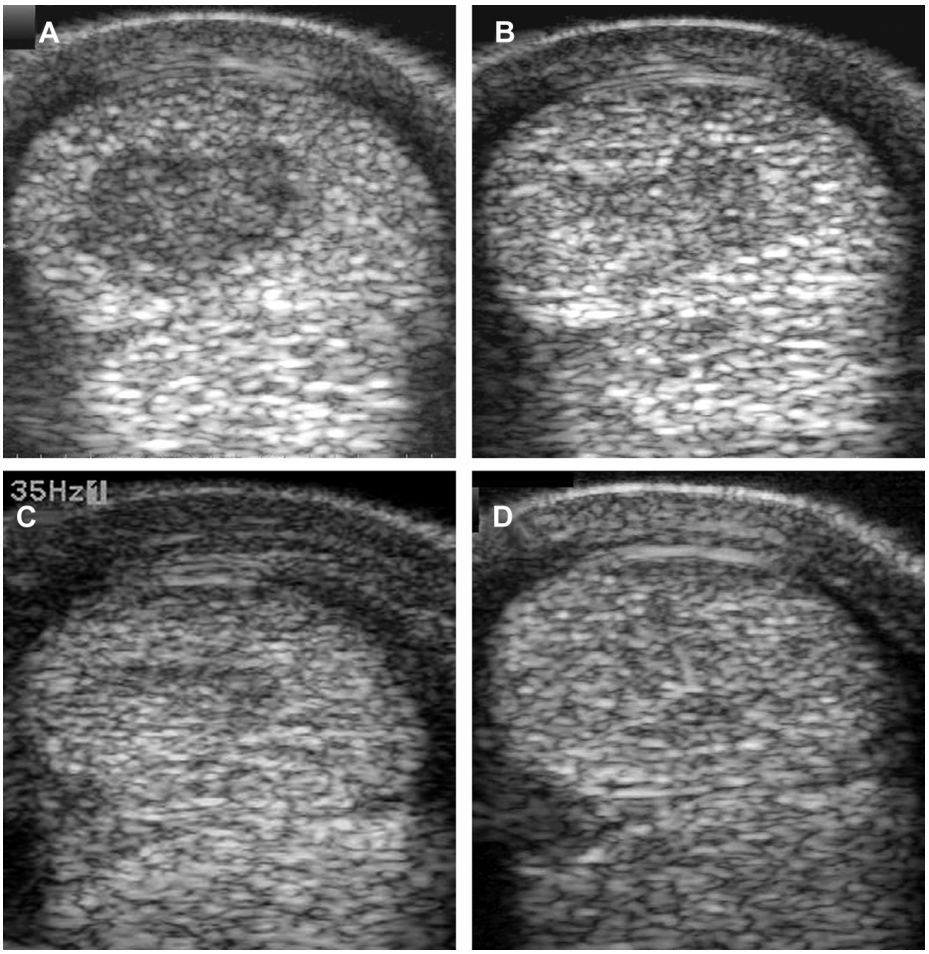

Fig. 1. Ultrasonographic follow-up of a recent tendonitis of the superficial digital flexor tendon (SDFT) on a flat racing Thoroughbred, treated by a single intralesional injection of 1 mL of Equitend. Transverse ultrasound scans of the SDFT on the day of treatment (D0-A) and one month (M1-B), 2 months (M2-C), and 4 months (M4-D) after treatment. Note the rapid improvement of the echogenicity of the core lesion.

the ratio of earnings per start before/after injury, a better return to the level of earnings was found for the treated group (74%), whereas the level of earnings markedly decreased in the control group (15%). After adjustment on the level of earnings before lesion, the number of horses earning more than €1,000 per start after injury was superior in the treated group (50%) than in the control group (18.8%) (result of borderline significance: OR, 4.0; 95% CI, 0.7–24.6; $P = .13$).

4. Discussion and Conclusions

Most research on tendonitis in horses are focusing presently on the development and evaluation of treatments that could improve the functional properties of the healed tendon [6,7,12,13]. Previous studies have reported the clinical use of intratendinous therapies to enhance the healing quality and therefore to decrease the risk of reinjury, particularly stem cells therapy [6,7,13].

The objective of the preliminary study was to evaluate the effects of a RGTA product (Equitend) on the tendon healing capacity, before starting an experimental trial. Therefore, the study has inherent limitations of a preliminary trial, especially the variety of the cases included in terms of severity and disciplines and the subsequent constitution of small groups, which impairs statistical analysis. Yet, some clear differences have been identified, and originality comes from the comparison of treated ST with a matched control group with differences close to significance in mean duration before the first race and earnings per start after injury.

Intralesional injection of Equitend proved to be a simple procedure with ultrasound guidance and was well tolerated. No local reaction was reported after injection, and no worsening of the injury was observed clinically or ultrasonographically during the follow-up period. Tendonitis of the SDFT treated by a single intralesional injection of Equitend presented a satisfactory ultrasonographic evolution (over 4 months after injection), showing a quick improvement in the echogenicity score of the tendon lesion starting as soon as M1 (Fig. 1). Nevertheless ultrasonographic appearance of the lesion is not the key criteria for evaluating the efficacy of tendon treatment [5].

To date, the major interest of this study is the long-term follow-up for more than 2 years for all included horses. Latest publications on the interest of intratendinous treatments (stem cell or platelet-rich plasma) describe rates of return to racing between 80% and 98% in TB [5,6] and 82% in Standardbreds [14]. The percentage of horses back in competition and/or race is superior in the population of eventers (95.5%) and ST (87.5%) in this study. Although results are slightly lower in TB (77%), the percentage of horses back in race is still superior to conservative treatment (71%) or pasture rest (25%) [13]. Lower results in the TB population can be partly explained by the nature and severity of lesions included, which were severe or chronic with half of reinjury. It would be worth pursuing the analysis on a more homogeneous group of TB, with only acute lesions. The reinjury rate is equivalent to previous reports [6] for TB (23%) and slightly lower in eventers (9%) and ST (12.5%).

Comparison of long-term follow-up of racing criteria of the treated ST group with a matched control group showed clear differences with shorter duration before the first race and a better level of earnings per start after injury for the treated group.

Regenerative therapy has become over the years a promising therapeutic approach, and these encouraging results obtained with Equitend treatment have led to ongoing experimental and clinical trials on a homogeneous population, blindly, versus placebo.

Acknowledgments

All OTR3 employees (K.K.) hold some shares of the Company. D.B. as founder and patent owner is a significant shareholder. V.C., A.G.D., D.C., S.J., L.B., N.C.D., J.M.D., and L.D. disclose no conflict of interest.

References

[1] Crevier-Denoix N, Collobert C, Pourcelot P, Denoix J-M, Sanaa M, Geiger D, Bernard N, Ribot X, Bortolussi C, Bousseau B. Mechanical properties of pathological equine superficial digital flexor tendons. Equine Vet J Suppl 1997;23:23–6.
[2] Denoix J-M. Les lésions du tendon fléchisseur superficiel du doigt—aspects échographiques et cliniques. Prat Vet Equine 1995; 27:197–215.
[3] Dyson SJ. Medical management of superficial digital flexor tendonitis: a comparative study in 219 horses (1992-2000). Equine Vet J 2004;32:415–9.
[4] Goodship AE, Birch HL, Wilson AM. The pathobiology and repair of tendon and ligament injury. Vet Clin North Am Pract 1994;10: 323–49.
[5] O'Meara B, Bladon B, Parkin TDH, Fraser B, Lischer CJ. An investigation of the relationship between race performance and superficial digital flexor tendonitis in the Thoroughbred racehorse. Equine Vet J 2010;42:322–6.
[6] Godwin EE, Young NJ, Dudhia J, Beamish IC, Smith RK. Implantation of bone marrow-derived mesenchymal stem cells demonstrates improved outcome in horses with overstrain injury of the superficial digital flexor tendon. Equine Vet J 2012; 44:25–32.
[7] Smith RK. Mesenchymal stem cell therapy for equine tendinopathy. Disabil Rehabil 2008;30:1752–8.
[8] Barritault D, Caruelle J-P. Regenerating agents (RGTAs): a new therapeutic approach. Ann Pharm Fr 2006;64:135–44.
[9] Desgranges P, Louissaint T, Allaire E, Godeau B, Kichenin K, Becquemin J-P, Barritault D. First clinical pilot study of matrix protection therapy in vascular disease with regenerating agent technology. J Wound Technol 2011;13:44–8.
[10] Khammari-Chebbi CK, Kichenin K, Amar N, Nourry H, Warnet J-M, Barritault D, Baudouin C. Pilot study of a new matrix therapy agent (RGTA OTR4120) in treatment-resistant corneal ulcers and corneal dystrophy. J Fr Ophtalmol 2008;31(5):465–71.
[11] Groah SL, Libin A, Spungen M, Nguyen K-L, Woods E, Nabili M, Ramella-Roman J, Barritault D. Regenerating matrix-based therapy for chronic wound healing: a prospective within-subject pilot study. Int Wound J 2011;8(1):85–95.
[12] Ferris DD, Kisiday JD, McIlwraith CW, Hague BA, Major MD, Schneider RK, Zubrod CJ, Watkins JJ, Kawack CE, Goodrich IR. Clinical follow-up of horses treated with bone marrow-derived mesenchymal stem cells for musculoskeletal lesions. In: Proceedings of the Annual Convention of the American Association of Equine Practitioners; 2009; Las Vegas, Nevada; 55, p 59–60.
[13] Gillis CL. Rehabilitation of tendon and ligament injuries. In: Proceedings of the Annual Convention of the American Association of Equine Practitioners; 1997; 43: p 306–9.
[14] Hogan PM, Bramlage LR. Transection of the accessory ligament of the superficial digital flexor tendon for treatment of tendinitis: long term results in 61 standardbred racehorses (1985-1992). Equine Vet J 1995;27:221–6.