CASE REPORT

Case Report: Efficacy of dobesilate in insertional Achilles tendinopathy [version 1; peer review: 1 approved, 1 not approved]

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Abstract

Achilles tendinopathy is an overuse syndrome, common among runners, with sometimes considerable negative impact on their performance, overall health, and well-being. Our report shows that local injection of an aqueous solution of the diethylammonium salt of dobesilate, an inhibitor of fibroblast growth factor with significant anti-angiogenic and anti-inflammatory effects, is effective in reducing vascular density and pain in insertional Achilles tendinopathy.

Keywords

Achilles tendinopathy , neovascularization , inflammation , fibroblast growth factor , dobesilate

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Approval Status

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Any reports and responses or comments on the article can be found at the end of the article.

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Case description

A 37-year-old healthy Caucasian male runner presented with a 3 month history of chronic pain and swelling on top of his left heel. There was no history of direct trauma to his left heel. He experienced a constant dull pain when walking. He had to discontinue sport because of the severity of his pain. At the beginning of symptomatology, the patient initiated sporadic treatments with over-the-counter analgesic and anti-inflammatory drugs. One week before presentation, following recommendations of his physician, the patient initiated, unsuccessfully, a treatment with paracetamol (1g twice a day) and ibuprofen (400mg three times per day). At presentation heel pain was rated as 6 out of 10 on the visual analogue scale (VAS). Colour doppler ultrasound examination at the insertional site of the left Achilles tendon revealed significant neovascularity, mainly at intratendinous mass (Figure 1). After discussing the various treatment options, the patient opted to try a dobesilate injection to the Achilles tendon and gave informed consent. Lidocaine was infiltrated into the skin overlying the Achilles tendon insertional junction. Dobesilate (2 ml of diethylammonium salt formulation; etamsylate, Dicynone®, Sanofi, France) was peritendinously

injected under ultrasound guidance into the Achilles tendon. The procedure was uneventful. The patient was advised to perform some gentle range of motion exercises the following day. He was back to his regular life the day after injection. At the 1 month follow-up visit, the patient reported a marked reduction of his pain, and the VAS was rated as 1. Colour doppler ultrasound scans revealed a significant reduction of tendon hypervascularity at the time (Figure 1). The patient was able to return to running and his previous level of sport without any restrictions. No adverse events were observed during treatment and the 2 month follow-up period.

Discussion

Tendinopathy is a common health problem affecting nearly 8% of middle and long distance runners under the age of 45. The consequences of this medical condition include pain, disability, early retirement from sport and work, mental distress and health care cost¹. The treatment of tendinopathies is a significant challenge for sport medicine physicians wishing to avoid surgery, since there is no obvious non-surgical options as efficacious therapeutic treatments².

Figure 1. Effect of dobesilate injection in insertional Achilles tendinopathy. Long-axis colour doppler ultrasound scans taken at three different planes before and after one month of treatment. Note the reduction of hypervascularity after treatment. The large vessels were persistently observed in real time ultrasonography examination. Achilles tendon mass was delimited by discontinuous line.

Inflammation and angiogenesis are two cardinal biological processes which cause tendinopathies³. Consequently, control of inflammation and neovascularization seem two obvious targets to develop new treatments for management of tendinopathies.

The anti-inflammatory treatments, by themselves, do not seem to achieve a significant success in the case of Achilles tendinopathies, in addition they seem less effective in patients with Achilles insertional tendinopathies than in those with mid-portion tendinopathies⁴.

Hypervascularity has been reported in human and animal Achilles tendinopathies, as well as in patellar disease, long head biceps tendons and in the rotator cuff^{5,6}. Furthermore, the tendon area of hypervascularization coincides with the most common localisation for tears^{5,6}. Healthy tendons are not painful, and have no detectable blood vessels, as assessed by ultrasonography⁹. However, pain is a common symptom which accompanies neovascularization in chronic Achilles tendinopathies. Furthermore, tendon neovascularization is accompanied with nerve in-growth facilitating pain transmission in Achilles tendinopathy¹⁰. Consequently, strategies to destroy neovessels (i.e. local application of sclerosing agents as polidocanol) cause pain amelioration^{11,12}, despite the associated side effects^{13,14}. Inhibiting angiogenesis in addition to inflammation seems, thus, a reasonable strategy for development of new therapies against Achilles tendinopathies^{4,7,8,15}.

Fibroblast growth factor (FGF) is nowadays considered a pro-inflammatory and pro-angiogenic protein^{16–18}. FGF can be inhibited with dobesilate¹⁹. This old drug, with a high safety profile²⁰ but with considerably vague pharmacological and therapeutic targets until its anti-FGF activities were described, has been shown, since this precise point in time, to relieve inflammation and prevents undesirable neovessel formation in many different pathological scenarios^{21–25}.

The data presented in this case report show that local administration of dobesilate seems also effective in reducing neovessel formation and inflammation in the case of insertional Achilles tendinopathies. Recently, it has been reported that FGF is a nociceptive modulator²⁶. Since target inhibition of FGF in tissues undergoing pathological angiogenesis is safe without significant off-target effects on non-diseased tissues²⁷, dobesilate seems an attractive drug for treating tendinopathies.

Large-scale therapeutic trials are obviously needed for more solidly establishing the efficacy of dobesilate in the treatment of Achilles tendinopathy. The results presented in this report seem a reasonable support for undertaking these trials.

Consent

Written informed consent for publication of the clinical details and images was obtained from the patient.

Author contributions

PC and GGG wrote the paper. TFJ and PG were the physicians responsible for the patient in this case report. All authors have participated in the concept and design/analysis and interpretation of data, drafting and revising the manuscript, and they have given final approval for the manuscript.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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This is an interesting article where the authors showed the efficacy of dobesilate for the treatment of Achilles tendinopathy.

Dobesilate is an inhibitor of Fibroblast Growth factors. Inhibition of FGF in this pathology reduced angiogenesis in the tendon and pain-related symptoms.

The report shows that it could be used safely in patients.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 02 November 2016

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Nicola Maffulli

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Thank you for having allowed me to review this manuscript. I am very concerned at the fact that

the authors try and generalise from one single case report.

1. There is little modern evidence that neovascularity is the *primum movens* of tendinopathy, and that it should be a therapeutic target.
2. The enrollment of the patient after such a short period of symptoms is questionable.
3. The follow up is much too short to be able to make recommendations.

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Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 29 Nov 2016

Pedro Cuevas, Universidad Alfonso X, Madrid, Spain

In summary, our report has been considered *not to be of an acceptable scientific standard* by the reviewer Nicola Maffulli. This blunt disqualifier statement is surprising. The report submitted to F1000 has been elaborated according the same scientific standards employed in the rest of our scientific papers, quoted thousands of times (according the statistics of the WOK), sometimes published in journals of the widest international diffusion. Keystone for the scientific disqualification seems an article published by the reviewer in 2012, in the journal "Knee Surg Sports Traumatol Arthrosc" (20:1891–1894), which has been quoted eleven times along these last four years, that defends that *detecting neovessels has no additional value for the diagnosis, no firmly confirmed prognostic value, and no proven relation with symptoms* in Achilles tendinopathy, a statement that seems contradictory with some studies quoted in the same article: *In (a series of) Swedish studies, the investigators were able to detect neovessels in 100 % of the symptomatic tendons [1, 26, 37, 38]..... other researchers, ... reported a percentage varying from 47 to 88 % [13, 41, 42, 54].*

Our report does not aim to engage in any sort of controversy about the relevance of neovascularization of the Achilles tendinopathy and whether it is a *primum movens* or not in such diseases, a discussion that still seem widely open, according to the results of bibliographical searches of recent publications. Accordingly, the report should not be judged from such a point of view. We, exclusively, intend to report the case of a tendinopathy the vascularization of which healed very efficiently, accompanied of a considerable relief of pain, after local treatment with an inhibitor of fibroblast growth factor (FGF), a main angiogenic and inflammatory protein. The treatment was applied after three months of unsuccessfully treated chronic pain and swelling on top of his left heel that made

the patient had to discontinue sport practices. This does not seem a questionable short period of symptoms, before the enrolment in the alternative treatment (point 2 of the reviewer considerations), taking into account the quite undesirable consequences of a prolonged inflammation and abnormal vascularization [Carmeliet, Nature 438 (2005) 932]. We did not try to report a long term healing process, but the fast disappearance of neovascularization and pain relief by inhibiting FGF, a treatment supported by a solid rationale. To this purpose a two-month follow up seems reasonable. A different question is if we had intended to report on a long-term cure. But this is the objective of a different-aimed observational study that we are carrying out at this moment (point 3 of the reviewer comments). The treatment was carried out, as detailedly described in the report, according to the requirements of a proper science, which, surprisingly, was straight on globally disqualified without pointing out at any major mistake in the followed procedure.

Competing Interests: We disclose any competing interests.

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