

## Case Report

# Dobesilate Injection in Mid-Portion of Achilles Tendinopathy with Chronic Pain: A Case Report

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## Abbreviations

FGF: Fibroblast Growth Factor; NO: Nitric Oxide; VAS: Visual Analogue Scale; VEGF: Endothelial Vascular Growth Factor

## Case Presentation

A 30-years old healthy Caucasian runner man presented with a 2 months history of chronic pain and swelling over the right mid-portion of his Achilles tendon, although he didn't reported any direct trauma. He referred a constant dull aching pain with walking, forcing to discontinue sport because of severity of his pain. Analgesic and anti-inflammatory drugs were initiated by the patient one week before presentation; however, his pain did not improve.

At presentation pain was rated as 5 out of 10 on Visual Analogue Scale (VAS). Colour Doppler ultrasound examination at the mid-portion of right Achilles tendon revealed significant neovascularity, formed by immature tortuous and dilated vessels, 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 signed an informed consent. Lidocaine was infiltrated into the skin overlying the mid-portion of Achilles tendon. Dobesilate (2ml of ammonium salt formulation; Etamsylate. Dicynone®. Sanofi France) was injected under ultrasound guidance into peritendinous Achilles tendon. The procedure was uneventful. After 15 minutes of Dobesilate injection colour doppler ultrasound scans revealed a significant reduction of tendon hypervascularity 1 (Figure 1). At 2 weeks follow-up visit, patient reported a marked reduction of his pain (VAS was rated as 1), and colour Doppler scans showed no, or few, remaining neovessels (Figure 1). Patient was able to return to running and his previous level of sport without any restrictions.

## Discussion

No studies have been performed to our knowledge to evaluate anti-angiogenic therapy in human Achilles tendinopathy. Considering the anti-angiogenic properties of Dobesilate [1], this study assesses the possible therapeutic effect of a local injection of Dobesilate in a patient with mid-portion Achilles tendinopathy. Our patient showed a good response to treatment suggesting that local administration of

## Abstract

Dobesilate injection performed in the peritendinous tissue of damaged mid-portion of Achilles tendon resulted in improved leg function, reduced pain and disappearance of pathologic neovascularization, after two weeks of treatment, and permitted patient to be back to his previous activity level.

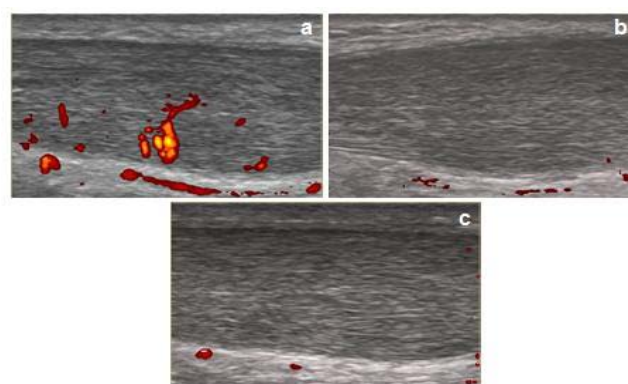
**Keywords:** Achilles tendinopathy; Dobesilate injection; Fibroblast growth factor; vascular endothelial growth factor

Dobesilate is of help in Achilles tendinopathies.

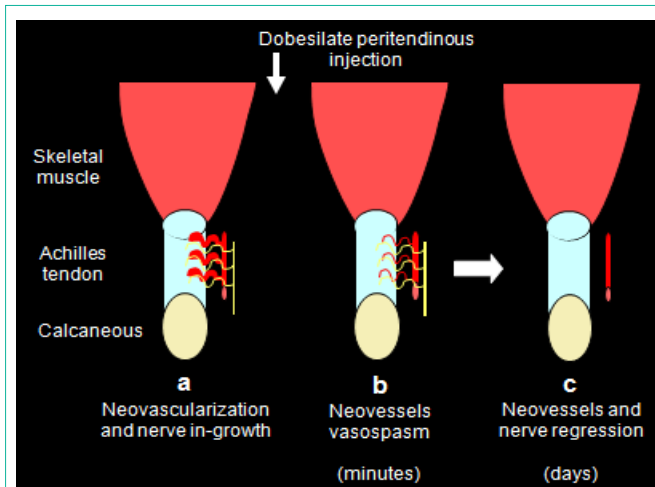
Symptoms of tendinopathy may include persistent pain, loss of range of motion, and dysfunction that can prevent a return to full activity. Furthermore, as a chronic connective disorder, tendon regeneration does not occur, resulting in a tissue structure that may incur further injury or rupture due to a failed healing repair response.

A number of options for the treatment of tendinopathies are ranging from rehabilitation protocols to injective treatment and surgery [2-4], but there is no efficient and safe treatment for this condition.

Neovascularization, the formation of new blood vessels from pre-existing one, has been identified in painful tendons from sport activity [5-7], which demonstrated a strong link between hypervascularity and tendon dysfunction caused by overuse. Hypervascularity which is a feature of chronic changes in tendon is one of the causes of pain due to parallel migration of vascular innervation [3,7,8] and can also contribute to the disorganization of the tendon tissue, which lead to increased metabolic demand and, consequently, increased hypervascularity [8].



**Figure 1:** Longitudinal colour doppler scans of mid-portion of Achilles tendon taken at baseline (a), at 15 minutes (b) and at 2 weeks (c) after dobessilate injection. Note the tortuous and dilated immature neovessels before treatment.



**Figure 2:** Simplified diagram of the proposed two-steps process implicated in dobesilate effectiveness in Achilles tendinopathy. FGF and VEGF signalling pathways promote vessel in-growth into tendon tissue and maintain vessel survival and patency (a). In a first minutes step dobesilate injection promotes neovessels spasm by elimination of FGF and VEGF vasorelaxation-dependent signals (b). Finally, dobesilate produced neovessels regression as consequence of neutralization of FGF and VEGF survival signals in vascular cells (c). Additionally, since FGF regulates pain and nerve invasion into the tendon, the inhibition of both processes by dobesilate can contribute to pain improvement in Achilles tendinopathy.

Since chronic tendon pathology appears to be a highly active process of ongoing angiogenesis, anti-angiogenic therapy could be a new approach for Achilles tendinopathy [8,10]. Angiogenesis is mediated by angiogenic factors as Fibroblast Growth Factor (FGF) and Vascular Endothelial Growth Factor (VEGF) which are highly expressed in degenerative Achilles tendons, whereas FGF and VEGF expression is nearly completely down regulated in healthy tendons [10-14]. It has been reported that neovessels are accompanied by small glutamate positive neural structures. This finding suggests that angiogenesis plays an important role in pain experienced during the degenerative tendon disease [7,13,14]. These findings are in accordance with clinical results showing that strategies to destroy neovessels (i.e. local administration of a sclerosing agent, polidocanol) produced pain improvement [14].

Recently, it has been reported that FGF is a nociceptive modulator [15,16]. Thus, the analgesic effect of Dobesilate injection in Achilles tendon may be related to inhibition of FGF-related nociception and also may be due to inhibition of nerve ingrowth that occurred in association to neovessels invasion during tendon angiogenesis.

FGF and VEGF are involved in several cellular signalling pathways that are important in regulation and maintenance of vasculature [17]. FGF signalling is critically required for maintenance of VEGF expression, and its inhibition has profound effects on VEGF-dependent biological processes [18]. A great amount of animal and clinical data showed that FGF and VEGF are required for function, maintenance and stability of blood vessels. Furthermore since FGF and VEGF can induce vessel relaxation through a nitric oxide (NO) pathway [19-25], the early consequence of inhibition of FGF and VEGF is thought to reduce NO synthesis promoting vasoconstriction.

Anti-angiogenic therapies targeting FGF and VEGF can cause

vessel disintegration and regression not only in many experimental setting, but also in human clinical trials [1,26-29].

Dobesilate is a dual antagonist of FGF and VEGF activities which inhibits some of their activities as such vessel relaxation and angiogenesis [19,27,29]. Thus Dobesilate may provoke spasm and destruction of neovessels in two consecutive steps. Since target inhibition of FGF in tissues undergoing pathological angiogenesis is safe without significant off-target effects on nondiseased tissues [30], dobesilate is an attractive drug for treating tendinopathies. A proposed mechanism of efficacy of dobesilate in Achilles tendinopathy is shown in (Figure 2).

Therapeutic modulation of neoangiogenesis by influencing the level of FGF and VEGF might be a promising target for new approaches in degenerative tendon diseases.

## Conclusion

Angiogenesis is associated with chronic overuse tendinopathies. We report here that local injection of Dobesilate, an antiangiogenic drug, in the mid-portion Achilles tendinopathy improved, as early after two weeks of treatment, leg function and pain concomitantly with a great decrease of tendon hypervascularity.

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