Antifibrotic medication using a combination of N-acetyl-L-cystein (NAC) and ACE inhibitors can prevent the recurrence of Dupuytren's disease

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SUMMARY

Dupuytren's disease is a progress fibromatosis of unknown origin first described in 1831. Nonoperative treatment options have been suggested involving radiation therapy, vitamin E, local injection therapy using calcium channel blockers, interferon, corticosteroids or collagenase. Transforming growth factor-beta1 (TGF-beta1) and its downstream Smad signalling system is well established as a key player during fibrogenesis. A number of in vitro experiments have been assessed the blockade of TGF-beta1 and TGF-beta 2. Clinically, a number of antifibrotic agents are available such as N-acetyl-L-cysteins (NAC) as well as angiotensin-converting enzyme (ACE) inhibitors or AT II antagonists. However, to date none of the well known substances has been tested clinically in fibromatosis such as Dupuytren's disease especially to prevent recurrences after surgical release.

Antifibrotic medication using a combination of N-acetyl-L-cystein (NAC) and ACE inhibitor can prevent the recurrence of Dupuytren's disease. Given the fact that recurrence rate in Dupuytren's disease is high and unpredictable after surgical release, an antifibrotic intervention might be worthwhile to consider in the clinical setting. Antifibrotic agents inhibit TGF-beta1, which play a key role in fibromatosis. Thus, antifibrotic medication might reduce the recurrence rate in fibromatosis such as Dupuytren's disease in a clinical significant way.

Introduction

Dupuytren's disease is a progress fibromatosis of unknown origin first described in 1831. While genetic factors have been discussed to be involved over decades, no conclusive multivariate risk factor analysis could support given risk factors. Recently, a specific genetic pattern has been identified in Dupuytren tissue with dysregulation of cytoskeleton development, and lipid and collagen metabolism [1].

Depending on the degree of the flexion contracture in Dupuytren's disease, no therapy at all for first degree cases without any contracture or surgical release are advocated for cases with advanced finger contracture. One major challenge in surgery for Dupuytren disease is the prevention of recurrence. Given the overall success rate of immediate surgical release by either selective or total fasciectomy, recurrence is not uncommon and unpredictable to date. Therefore, preventive measures after surgical release might be attractive to reduce the risk for Dupuytren recurrence. Post-operative splinting following surgical release has been studied using various study designs. However, to date the effect of post-operative static splinting is equivocal, as is the effect of patient adherence on outcome [2].

Nonoperative treatment options have been suggested involving radiation therapy, vitamin E, local injection therapy using calcium channel blockers, interferon, corticosteroids or collagenase [3]. However, none of them has been tested in higher level evidence based studies and therefore there is currently no recommendation at all to use any of these aforementioned agents in Dupuytren's disease.

Several different molecular processes related to Dupuytren's disease progression, including extra- and intra-cellular signalling, oxidative stress, cytoskeletal changes, and alterations in cellular metabolism have been studied [4]. In particular, autocrine regulation through ERBB-2 and IGF-1R receptors and the Akt signalling pathway have emerged as novel components of pro-survival signalling in Dupuytren's fibroblasts. In addition, transforming growth factor-beta1 (TGF-beta1) and its downstream Smad signalling system is well established as a key player during fibrogenesis.

However, to date none of the aforementioned pathways has been tried to be modified by medications in a clinical situation. Clinically, a number of antifibrotic agents are available such as N-acetyl-L-cysteins (NAC) as well as angiotensin-converting enzyme (ACE) inhibitors or AT II antagonists. However, to date none of...
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**Hypothesis**

Antifibrotic medication using a combination of N-acetyl-l-cysteine (NAC) and ACE inhibitor can prevent the recurrence of Dupuytren's disease. Given the fact that recurrence rate in Dupuytren's disease is high and unpredictable after surgical release, an antifibrotic intervention might be worthwhile to consider in the clinical setting. Antifibrotic agents inhibit TGF-beta1, which play a key role in fibromatosis. Thus, antifibrotic medication might reduce the recurrence rate in fibromatosis such as Dupuytren's disease in a clinical significant way.

**Evaluation of the hypothesis/idea**

TGF-beta1 is a key signalling component in fibromatosis. There is evidence accumulating that as the disease progresses, nodules develop into cords [5]. However, increased metabolic activity of fibroblasts derived from cords compared with nodule fibroblasts in patients with Dupuytren's disease has been noted [6]. TGF-beta has been described as a potent stimulator of collagen production for both, normal palmar fascia and Dupuytren's fascia [7,8].

A number of in vitro experiments have been assessed the blockade of TGF-beta1 and TGF-beta2. Tamoxifen, a synthetic nonsteroidal antiestrogen, is able to decrease TGF-beta2. Expression in Dupuytren affected fascia in cell cultures [9]. Zf9 is a transcription factor that increases TGF-beta1 expression in tissue. A case control study with 138 patients suffering Dupuytren's disease and 255 controls revealed a statistically significant difference in the genotype and allele frequencies between patients and controls for Zf9 gene polymorphism [10]. However, to date no clinical evidence has been published to modify either TGF-beta1 and/or TGF-beta2 albeit the aforementioned in vivo data in Dupuytren's disease.

**Current and potential future clinical applications of antifibrotic medications**

Besides the aforementioned Dupuytren’s disease, there are a number of seldom fibroproliferative diseases of the plantar fascia (Morbus Ledderhose), the penis (Morbus Peyronie) or the dorsal interphalangeal joints (knuckle pads), which might be treated in analogy to the Dupuytren’s disease.

Scar formation is another area where TGF-beta has been demonstrated to play a major role [11]. Hypertrophic scar fibroblasts have both intrinsic upregulation of connective tissue growth factor (CTGF) transcription and an exaggerated capacity for CTGF transcription in response to TGF-beta stimulation [12]. Abdominal adhesions have been used reduced using lisinopril in a rat model [13]. Experimental data suggest that TGF-beta antisenesce oligonucleotides are able to reduce capsular formation in a rat model in breast implants [14]. Blockade of TGF-beta by ACE inhibitor enalapril lowers the expression of fibrotic mediators, TGF-beta1, inflammatory markers, anti-ED1, anti-collagen III monoclonals, and the periprosthetic fibrosis process around rat mammary implants [15]. Combination therapy of potent TGF-beta inhibition and angiogenesis blockade results in an enhanced antifibrotic effect at least in glomerulonephritis [16].

As far as our primary hypothesis is concerned, combined medication of NAC and ACE inhibitors to reduce the risk of Dupuytren's disease recurrences after surgery has to be validated in a clinical setting. Testing our aforementioned hypothesis might be performed at best in a randomized-controlled, double-blinded trial. Outcome parameters have to be determined, since the course of Dupuytren's disease is often times unpredictable. Functional and subjective impairment derived from the disease might be one potential outcome parameter. As such, the validated DASH (disability arm shoulder hand) score has been applied in Dupuytren's disease with a mean DASH score of 15 (range 0–69) among the patients [17]. However, no correlation was found between the DASH score and the total flexion contracture, the number of the involved hands, fingers or joints, or the AMA (American Medical Association) impairment rating on the other hand.

Furthermore, the clinical degree of the Dupuytren's contracture has been used in several studies as a potential outcome parameter. Visual estimation of Dupuytren's contracture has been recently shown to correlate well with actual clinical goniometric measurements [18].

**Consequences of the hypothesis and discussion**

Our primary hypothesis is: antifibrotic medication using a combination of N-acetyl-l-cysteine (NAC) and ACE inhibitor can prevent the recurrence of Dupuytren's disease. Given the fact that recurrence rate in Dupuytren's disease is high and unpredictable after surgical release, an antifibrotic intervention might be worthwhile to consider in the clinical setting.

If randomized-controlled trials proof our hypothesis, these data might be extrapolated to by far less common fibroproliferative diseases such as plantar fibromatosis (Morbus Ledderhose), fibromatosis of the penis (Morbus Peyronie) or knuckle pads at the interphalangeal joints. Whether the combination of NAC and ACE inhibitors is superior to each of them has to be determined in the future. Furthermore, ACE inhibitors and AT II antagonists might be combined or not in this regard.

**Conflicts of interest statement**

None declared.

**References**


[12] Colwell AS, Phan TT, Kong W, Longaker MT, Lorenz PH. Hypertrophic scar fibroblasts have increased connective tissue growth factor expression after...


