Title

Pharmacotherapies in Dupuytren Disease: Current and Novel Strategies.

Journal

Journal of Hand Surgery (American Volume), 48(8)

Authors

Lambi, Alex
Popoff, Steven
Benhaim, Prosper
et al.

Publication Date

2023-08-01

DOI

10.1016/j.jhsa.2023.02.003

Peer reviewed

HHS Public Access

Author manuscript

J Hand Surg Am. Author manuscript; available in PMC 2024 August 01.

Published in final edited form as:

J Hand Surg Am. 2023 August ; 48(8): 810–821. doi:10.1016/j.jhsa.2023.02.003.

Pharmacotherapies in Dupuytren's Disease: Current & Novel Strategies

Alex G. Lambi, MD, PhD[1], **Steven N. Popoff, PhD**[2,3], **Prosper Benhaim, MD**[4], **Mary F. Barbe, PhD**[3,5]

[1]Department of Orthopedics and Rehabilitation, University of New Mexico School of Medicine, Albuquerque, NM

[2]Department of Orthopaedic Surgery, Lewis Katz School of Medicine at Temple University, Philadelphia, PA

[3]Department of Biomedical Education and Data Science, Lewis Katz School of Medicine at Temple University, Philadelphia, PA

[4]Department of Orthopaedic Surgery, University of California Los Angeles, Los Angeles, CA

[5]Center for Translational Medicine, Lewis Katz School of Medicine at Temple University, Philadelphia, PA

Abstract

Dupuytren's disease is a benign, progressive fibroproliferative disorder of the hands. To date, only one pharmacotherapy (clostridial collagenase) has been approved for use in Dupuytren's disease. There is a great need for additional non-operative methods that can be used to either avoid the risks of invasive treatments or help minimize recurrence rates following treatment. A number of non-operative modalities have been discussed in the past and continue to appear in discussions amongst hand surgeons, despite highly variable and often poor or no long-term clinical data. This article reviews many of the pharmacotherapies discussed in the treatment of Dupuytren's disease and novel therapies used in inflammation and fibrosis that offer potential treatment options.

Keywords

collagenase; Dupuytren's; fibrosis; myofibroblast; TGF-beta

Corresponding Author: Alex G. Lambi, MD, PhD, Department of Orthopedics & Rehabilitation, University of New Mexico School of Medicine, Address: UNM School of Medicine, MSC08 4720 1 UNM, Albuquerque, NM 87131, xelambi@gmail.com, Phone: (505) 272-2321.

Disclosure:

Dr. Benhaim is a speaker for Endo Pharmaceuticals. No benefits in any form have been received or will be received related directly or indirectly to the subject of this article. All remaining authors of this journal-based CME activity have no relevant conflicts of interest to disclose.

Introduction

Our understanding of the mechanisms behind fibroproliferative disorders continues to expand. As a result, newer potential pharmacotherapies in treating diseases such as idiopathic pulmonary fibrosis, scleroderma, Peyronie's disease, and Dupuytren's disease (DD) are being identified. There has also been renewed interest in repurposing medications already approved by the U.S. Food and Drug Administration (FDA) for the treatment of fibrotic disorders.[1–3] Despite this, the mainstay of treatment for Dupuytren's patients is largely surgical. The two most common non-surgical treatments are local collagenase injections, for enzymatic degradation, and local corticosteroid injections, to reduce inflammatory processes. There is a need for additional pharmacotherapeutic options that are directed towards halting early disease progression or following treatment to prevent recurrence.

The purpose of this article is to provide a summary of currently used and potential new pharmacotherapies in DD. A brief description of the pathophysiology, key signaling cascades, and natural history of the disease are included to set the stage for the need of additional non-surgical treatments. This paper covers many of the medications that have been considered for a repurposed use in DD over the years. Several newer monoclonal antibodies already in use are discussed for their potential antifibrotic and anti-inflammatory role.

Natural History

The typical patient presenting for symptomatic DD demonstrates contracture of the ulnar digits of the hand, with the long and ring fingers most often affected. Hueston's table-top test, considered positive when a patient can no longer place their hand and fingers flat on a table, can serve as an indication for intervention. Specific degrees of flexion contraction of 30° at the metacarpophalangeal (MCP) joint and 15° at the proximal interphalangeal (PIP) joint also serve as thresholds for provision of an intervention.[4] As contractures progress, impairment of hand function ensues, with 53° of MCP joint contracture and 77° of PIP joint contracture indicative of critical impairments in hand function.[5]

Current interventional strategies include fasciectomy, percutaneous needle fasciotomy (PNF), and enzymatic digestion. Fasciectomy techniques, including limited fasciectomy and dermatofasciectomy, remain the gold standard, since they have demonstrated high clinical efficacy and low recurrence rates.[4,6,7] However, due to their high complication rate as a consequence of their invasiveness, attention has been paid to minimally invasive techniques, such as PNF and enzymatic digestion.

Pathophysiology

DD is a benign fibroproliferative disorder that affects the palmar fascia of the hand and digits. Its clinical course can involve progressive and symptomatic contractures of the hand and digits, leading to decreased hand function and diminishing quality of life.[7] The natural history of DD can be divided into three histologic stages, as initially described by Luck.[8] Stage I, the proliferative phase, is classically characterized by nodule formation within the

palmar fascia as well as increased fibroblast activity. Myofibroblasts comprise the majority of cells in the nodule in this phase. Stage II, the involutional phase, is noted by marked nodular thickening and an increase in underlying type III collagen synthesis that becomes oriented along the lines of tension within the palm. Early joint contracture can be seen during this phase. Stage III, the residual phase, is characterized by a large disappearance of myofibroblasts and the replacement of type III collagen with type I collagen (Figure 1).[9]

Disease progression varies between individuals and can be influenced by established risk factors, such as alcohol intake, smoking, manual labor, diabetes, anticonvulsant drugs, metabolic factors, and genetic predisposition.[9–17] Despite significant research, the underlying genesis of DD has not been clearly elucidated. DD nodules are thought to originate from or near the palmar fascia via mechanisms that include trauma to the palmar fascia, altered immune responses, and/or the presence of oxygen free radicals.[7] Additionally, the amount and composition of subcutaneous palmar fat may play a role in the progression and recurrence of DD, as lower levels of subcutaneous fat tissue have been noted in individuals with DD.[18–20]

Although the specific mechanisms and triggers for DD development are still yet to be fully elucidated, it is well established that the cell type responsible for DD progression is the myofibroblast. Derived from fibroblasts, the myofibroblast is characterized by the co-expression of high levels of alpha-smooth muscle actin (alpha-SMA) and platelet derived growth factor (PDGF).[21] The clinical contractures seen in DD most likely occur on a cellular level through a contractile apparatus of the myofibroblast containing bundles of actin microfilaments and associated contractile proteins (e.g. non-muscle myosin). Intracellular actin bundles terminate on the myofibroblast surface in the fibronexus, an adhesion complex that incorporates transmembrane integrin proteins to link the actin with extracellular matrix proteins, such as fibronectin fibrils, and adjacent myofibroblasts.[22–26] Extensive research has been performed to better understand the modulators of fibroblasts and myofibroblasts in DD development. Transforming growth factor-β (TGF-β) signaling has been highlighted as critical in DD development.[27] Its specific role in myofibroblast function, DD progression, and potential in treatment is discussed below.

Transforming Growth Factor-β Signaling in Dupuytren's Disease Development

Transforming growth factor-β (TGF-β) has been implicated in DD development and progression. Three mammalian isoforms of TGF-β exist: TGF-β1, TGF-β2, and TGF-β3. All three isoforms have been identified in DD disease nodules, palmar fascia, and cord tissue.[28,29] TGF-β signaling is upregulated in DD and has been shown to be expressed in fibroblasts and myofibroblasts in all three histologic stages of DD progression.[28–31] In fibroblasts derived from either DD affected or unaffected tissues, TGF-β upregulates alpha-SMA expression and induces differentiation of a quiescent fibroblast to a contracting myofibroblast.[9,31–33] The addition of TGF-β in culture models leads to increased contracture of DD fibroblasts.[34] Furthermore, when TGF-β signaling is blocked in DD cells *in vitro*, a dose-dependent decrease in contractility with concomitant decreases in alpha-SMA and

Col1 gene expression and alpha-SMA protein level are seen.[32] Therefore, the ability to block the pro-fibrotic effects of TGF-β signaling in DD is an area ripe for research and clinical potential. Several therapeutic options discussed later in this article target the TGF-β pathway.

Challenges in Studying New Therapies in Dupuytren's Disease

To date no single, reliable animal model has been created to study the pathophysiology of DD or the disease response to therapeutics. As a result, researchers have had to rely on few ways to study potential efficacy of therapeutics. The first is through *in vitro* studies using fibroblasts isolated from Dupuytren's nodules or cords in comparison to fascia overlying the carpal tunnel or the transverse carpal ligament.[32] Key limitations to this approach include the fact that the palmar fascia overlying the carpal tunnel is rarely involved in DD, and the transverse carpal ligament never.[35] Furthermore, due to the paucity of cells isolated from tissue, many experiments expand their cell population through passage 5 prior to performing experiments. However, prior work has shown that by this passage the phenotypes and normal human dermal fibroblasts and mature myofibroblasts tend to converge.[36,37]

The other challenge in studying DD at the clinical level is our reliance on only clinical findings to measure therapeutic efficacy. A noninvasive test to measure the therapeutic effect on Dupuytren's tissues in real time is sorely needed. Imaging modalities for monitoring other fibrotic disorders, chiefly idiopathic pulmonary fibrosis, are well described.[38] Noninvasive tests that could be used to study DD are being investigated for other musculoskeletal fibroses. These include modalities such as nuclear magnetic resonance (NMR), to assess thickened tissue layers, and ultrasound shear-wave elastography (SWE), to assess tissue stiffness.[39]

Current Pharmacotherapies used in Dupuytren's Disease Treatment

Enzymatic Digestion with Collagenase

To date, the only approved pharmacologic therapy that has shown sustained efficacy in treating DD is clostridial collagenase. The underlying mechanism by which *Clostridium histolyticum* collagenases produce their effect is through degradation of the collagen found in DD contracture. In 2010, the U.S. Food and Drug Administration approved *C. histolyticum* for injectable use under the name Xiaflex (Auxilium Pharmaceuticals, Inc., Malvern, PA).[6,40,41] Xiaflex constitutes two purified collagenases (AUX-I and AUX-II) that preferentially degrade collagen types I and III found in DD cords, while sparing collagen types IV and VI that are predominant in vascular basement membranes and perineurium.[41] Treatment takes place over two stages, with the first including injection of the diseased DD cord and the second consisting of cord rupture via manual manipulation. Success has been seen in treatment of MCP and PIP joint contracture, with higher success rates seen in reducing contracture of MCP joints (to within 5° of full extension) than for PIP joints. However, limited data exists for the use of collagenase in early DD as the safety and efficacy data included in the original submission to the FDA for approval was for flexion deformities >20°, in either MCP or PIP joints.[42] Published recurrence rates following collagenase treatment vary widely, with the most cited rate as 35% when defined as a worsening of

previously treated contracture >20°.[43] With respect to recurrence rates, enzymatic treatment performs similarly to PNF when used in PIP joints and potentially outperforms PNF when used in MCP joints.[44]

Corticosteroid Administration

Corticosteroids, such as injectable triamcinolone, are a common treatment choice for patients with DD.[45–48] Corticosteroids have been shown to decrease rates of cell proliferation in DD nodules and in DD cells cultured *in vitro*,[49] as well as modify disease progression in patients.[46–48] Triamcinolone administration leads to inhibition of TGF-β1 expression and fibroblast apoptosis.[6] Triamcinolone has also been shown to potentiate the activity of collagenase *in vitro*[50] To our knowledge, no clinical studies have been performed examining the effect of triamcinolone as part of treatment with collagenase. It has been shown that short-term improvements in flexion deformity occur when triamcinolone injection is used in combination with needle aponeurotomy.[51] However, long-term studies are needed to examine whether these effects result in significant long-term recurrence reduction.

Repurposed Pharmacotherapies Proposed for Dupuytren's Disease (Table 1)

To date, several other pharmacotherapies have been proposed for off-label use in treating DD. None have demonstrated either decreased severity or recurrence in long-term clinical trials.[52] For the sake of understanding the rationale in their use they will be discussed here briefly.

Multiple classes of anti-inflammatory and anti-mitotic medications, in addition to corticosteroids, have been proposed for DD. The non-steroidal anti-inflammatory (NSAID) celecoxib is being investigated for a role in patients with high risk of recurrence (Van Nuffel, FESSH meeting), while naproxen may have a benefit in reducing post-operative swelling following fasciectomy in DD patients, although data thus far has been limited and not shown to effect a significant clinical difference.[53] Interferons, both gamma and alpha2b, have the ability to decrease mechanisms behind DD contracture *in vitro*.[54,55] A small pilot study demonstrated the potential to decrease the size of early DD nodules when injected intralesionally.[54] However, no further studies appear in the literature to expand this work. 5-Fluorouracil (5-FU) demonstrated inhibitory effects on Dupuytren's myofibroblasts *in vitro*,[56] but showed no beneficial clinical effect when used topically.[57] Systemic colchicine has been reported to improve the severity of penile contractures in Peyronie's disease, although without improving concomitant DD contractures.[58]

The anti-oxidants vitamin E and N-acetyl-L-cysteine (NAC) have been investigated for potential roles in DD owing to their ability to abrogate fibrogenesis *in vitro*.[59,60] Vitamin E supplementation was initially described in the 1940s as a potential substitute for surgical therapy in DD.[61] Its utility was refuted by subsequent studies as patients continued to progress despite supplementation.[62,63] NAC has been shown to play a potential role

in fibroblast maturation *in vitro*, although it has not been explored as a therapeutic in patients.[64]

Various anti-hypertensive and vasoactive medications have been described for DD. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists were proposed owing to their effect in decreasing fibrotic responses *in vitro* and in animal models.[65,66] More recently, Dupuytren's tissue has been shown to express angiotensin II receptors.[67] Calcium-channel blockers (e.g. verapamil) have been described owing to potential effects on myofibroblast-mediated contracture and potential to decrease scarring in burn patients.[68,69] Phosphodiesterase inhibitors (e.g., sildenafil) have been proposed as they improve fibrosis via plaque development in animal models with Peyronie's disease, another localized fibrotic process.[70–72] Nitric oxide donors (e.g., molsidomine) decrease lung fibrosis and Peyronie's disease progression in animal models, likely due to the inhibitory effect nitric oxide has on myofibroblast differentiation and function.[70,73–75] Neither phosphodiesterase inhibitors nor nitric oxide donors have been tested in models of DD.

The synthetic nonsteroidal antiestrogen, tamoxifen, modulates TGF-β production, signaling, and fibroblast contractility *in vitro*.[76–78] It also results in short-term improvements in DD patients undergoing limited fasciectomy. However, the gain is lost by two years after treatment and the side effect profile was poorly tolerated.[79] Recently, metformin was proposed as a potential treatment for DD due to its ability to prevent TGF-β-mediated induction of fibroblasts *in vitro*.[80,81] While these results were shown using fibroblasts isolated from DD patient samples, no clinical trials demonstrating an effect of metformin in DD have been performed.[82]

Currently Approved Therapies Targeting Inflammation and Fibrosis (Table 2)

Tumor Necrosis Factor (TNF) Inhibition

TNF is known to play a role in the development and maintenance of the myofibroblast phenotype in DD nodules. This has been demonstrated *in vitro* where the addition of TNF, but not other known pro-inflammatory cytokines (IL-6 and IL-1β), to fibroblasts from DD patient samples promoted their differentiation into myofibroblasts.[32] TNF blockade has been performed on DD cells *in vitro* using the FDA-approved anti-TNF agents, adalimumab and golimumab. Both agents effectively inhibit myofibroblast contraction.[32] These studies have since been corroborated in a proof-of-concept clinical trial. TNF blockade was performed by injection of adalimumab into DD nodules, followed by surgical excision and evaluation. Nodules demonstrated down regulation of the myofibroblast phenotype.[83,84] Most recently, adalimumab injection in early-stage DD resulted in nodule softening and size reduction at one year.[85] Further studies are necessary to assess the long-term utility of TNF blockade in the treatment of DD.

Nintedanib

Nintedanib is one of the two currently used treatments for idiopathic pulmonary fibrosis. Approved for use in the United States in 2014, and in Europe in 2015, Nintedanib is a tyrosine kinase inhibitor with known effects on signaling receptors involved in fibrogenesis, chiefly vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF).[86] Involvement of PDGF and FGF-mediated signaling has been shown in DD fibroblasts *in vitro*.[33,87] Stimulation of PDGF and FGF signaling pathways can be downstream of TGF-β signaling,[27] which as discussed earlier, plays a role in DD development. Yet, no studies examining the use of Nintedanib for DD have been performed to date. It could be a potential target in DD. However, since Nintedanib does not directly affect TGF-β-mediated fibrogenesis, it may ultimately have limited clinical utility.

Pirfenidone

Pirfenidone (PFD; 5-methyl-1-phenyl-2(1H)-pyridone) is the second most used treatment for idiopathic pulmonary fibrosis. Approved for use in Europe in 2011 and in United States in 2014, PFD has an inhibitory effect on TGF-β production and TGF-β-mediated fibroblast function and differentiation.[88,89] PFD has been tested in DD fibroblasts *in vitro* and shown to abrogate TGF-β effects including fibroblast proliferation, myofibroblast development, and matrix formation.[90,91] A PFD formulation that could be delivered locally in DD is currently in development.[92]

Tocilizumab & Rituximab

It is worth mentioning two additional therapies currently used in cancer and inflammation, and with proposed effects in fibrosis – tocilizumab and rituximab. Tocilizumab is a monoclonal antibody targeting the IL-6 receptor and preventing binding of IL-6. Although not currently approved for treatment of fibrosis, it has been suggested based on the known effect of IL-6 on myofibroblast development.[93] Despite the upregulation of IL-6 in cells from DD tissue, neither the addition of IL-6 nor its blockade has shown significant effects on DD cells *in vitro*.[32] Rituximab is a monoclonal antibody targeting the B-cell surface protein CD20, leading to downregulation of B-cell differentiation and antibody formation.[94] Its primary clinical applications include B-cell lymphomas, leukemias, and B-cell mediated autoimmune diseases.[95] While some have suggested a role for autoantibodies in DD,[96–98] a definitive link with CD20-positive cells has not been made.

Conclusion

Dupuytren's disease remains a challenging clinical entity to treat. While historically accepted and proven therapies such as fasciectomy procedures demonstrate good efficacy of treatment, their risk profile has led to a search for minimally invasive techniques. Enzymatic digestion and treatment with collagenase have become a staple in DD treatment for over a decade. Despite the addition and broad acceptance of this pharmacotherapy, there is a need of a primary (or adjuvant) therapy modality that can either stop progression in the 30-50% of patients in early stages at risk or prevent disease recurrence following treatment.

As fibroproliferation underscores the etiology of DD, it is important to take an antifibrogenic approach to finding new pharmacotherapies. This review highlights the pathophysiologic basis of the fibrotic response seen in DD, chiefly through TGF-β signaling. The two most utilized pharmacotherapies in DD today, collagenase for enzymatic digestion of diseased cords as well as corticosteroids for the anti-inflammatory effects, are described. For the sake of providing historical background, many of the medications that have been discussed in articles over years for a repurposed use in DD are covered. Lastly, the article presents several medications with current approval for anti-inflammatory or anti-fibrotic effects that either are being used or may be considered for use in DD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

All authors contributed to the preparation of the manuscript, including design and figure preparation. This work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Grant 5R01AR056019-13 to senior author (MFB). Figure 1 was created with BioRender.com.

Funding:

This work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Grant 5R01AR056019-13 to senior author (MFB).

References

1. Karatzas E, Kakouri AC, Kolios G, Delis A & Spyrou GM Fibrotic expression profile analysis reveals repurposed drugs with potential anti-fibrotic mode of action. PLoS One 16, e0249687, doi:10.1371/journal.pone.0249687 (2021). [PubMed: 33826640]
2. Rosenbloom J, Mendoza FA & Jimenez SA Strategies for anti-fibrotic therapies. Biochim Biophys Acta 1832, 1088–1103, doi:10.1016/j.bbadis.2012.12.007 (2013). [PubMed: 23266403]
3. Tai Y et al. Myofibroblasts: Function, Formation, and Scope of Molecular Therapies for Skin Fibrosis. Biomolecules 11, doi:10.3390/biom11081095 (2021).
4. Mella JR, Guo L & Hung V Dupuytren's Contracture: An Evidence Based Review. Ann Plast Surg 81, S97–S101, doi:10.1097/SAP.0000000000001607 (2018). [PubMed: 30161050]
5. Raymond A, Parry M & Amirfeyz R Critical Angles of Deformity in Dupuytren's Contracture of the Little and Ring Fingers. Hand Surg 20, 290–297, doi:10.1142/s0218810415500264 (2015). [PubMed: 26051771]
6. Denkler KA, Vaughn CJ, Dolan EL & Hansen SL Evidence-Based Medicine: Options for Dupuytren's Contracture: Incise, Excise, and Dissolve. Plast Reconstr Surg 139, 240e–255e, doi:10.1097/PRS.0000000000002857 (2017).
7. Shih B & Bayat A Scientific understanding and clinical management of Dupuytren disease. Nat Rev Rheumatol 6, 715–726, doi:10.1038/nrrheum.2010.180 (2010). [PubMed: 21060335]
8. Luck JV Dupuytren's contracture; a new concept of the pathogenesis correlated with surgical management. J Bone Joint Surg Am 41-A, 635–664 (1959). [PubMed: 13664703]
9. Zhang AY & Kargel JS The Basic Science of Dupuytren Disease. Hand Clin 34, 301–305, doi:10.1016/j.hcl.2018.03.001 (2018). [PubMed: 30012290]
10. Godtfredsen NS, Lucht H, Prescott E, Sorensen TI & Gronbaek M A prospective study linked both alcohol and tobacco to Dupuytren's disease. J Clin Epidemiol 57, 858–863, doi:10.1016/j.jclinepi.2003.11.015 (2004). [PubMed: 15485739]

11. Burke FD, Proud G, Lawson IJ, McGeoch KL & Miles JN An assessment of the effects of exposure to vibration, smoking, alcohol and diabetes on the prevalence of Dupuytren's disease in 97,537 miners. J Hand Surg Eur Vol 32, 400–406, doi:10.1016/J.JHSE.2005.02.002 (2007).
12. Burge P, Hoy G, Regan P & Milne R Smoking, alcohol and the risk of Dupuytren's contracture. J Bone Joint Surg Br 79, 206–210, doi:10.1302/0301-620x.79b2.6990 (1997). [PubMed: 9119843]
13. Liss GM & Stock SR Can Dupuytren's contracture be work-related?: review of the evidence. Am J Ind Med 29, 521–532, doi:10.1002/(SICI)1097-0274(199605)29:5<521::AID-AJIM12>3.0.CO;2-2 (1996). [PubMed: 8732927]
14. Gudmundsson KG, Arngrimsson R, Sigfusson N, Bjornsson A & Jonsson T Epidemiology of Dupuytren's disease: clinical, serological, and social assessment. The Reykjavik Study. J Clin Epidemiol 53, 291–296, doi:10.1016/s0895-4356(99)00145-6 (2000). [PubMed: 10760640]
15. Noble J, Heathcote JG & Cohen H Diabetes mellitus in the aetiology of Dupuytren's disease. J Bone Joint Surg Br 66, 322–325, doi:10.1302/0301-620X.66B3.6725338 (1984). [PubMed: 6725338]
16. Dibenedetti DB, Nguyen D, Zografos L, Ziemiecki R & Zhou X Prevalence, incidence, and treatments of Dupuytren's disease in the United States: results from a population-based study. Hand (N Y) 6, 149–158, doi:10.1007/s11552-010-9306-4 (2011). [PubMed: 21776198]
17. Rydberg M et al. Metabolic factors and the risk of Dupuytren's disease: data from 30,000 individuals followed for over 20 years. Sci Rep 11, 14669, doi:10.1038/s41598-021-94025-7 (2021). [PubMed: 34282190]
18. Rabinowitz JL, Ostermann L Jr., Bora FW & Staeffen J Lipid composition and de novo lipid biosynthesis of human palmar fat in Dupuytren's disease. Lipids 18, 371–374, doi:10.1007/BF02537234 (1983). [PubMed: 6877040]
19. Bergenudd H, Lindgarde F & Nilsson BE Prevalence of Dupuytren's contracture and its correlation with degenerative changes of the hands and feet and with criteria of general health. J Hand Surg Br 18, 254–257, doi:10.1016/0266-7681(93)90123-w (1993). [PubMed: 8501389]
20. Shih B, Brown JJ, Armstrong DJ, Lindau T & Bayat A Differential gene expression analysis of subcutaneous fat, fascia, and skin overlying a Dupuytren's disease nodule in comparison to control tissue. Hand (N Y) 4, 294–301, doi:10.1007/s11552-009-9164-0 (2009). [PubMed: 19184239]
21. Hinz B Formation and function of the myofibroblast during tissue repair. J Invest Dermatol 127, 526–537, doi:10.1038/sj.jid.5700613 (2007). [PubMed: 17299435]
22. Tomasek JJ, Schultz RJ & Haaksma CJ Extracellular matrix-cytoskeletal connections at the surface of the specialized contractile fibroblast (myofibroblast) in Dupuytren disease. J Bone Joint Surg Am 69, 1400–1407 (1987). [PubMed: 3440798]
23. Tomasek JJ, Gabbiani G, Hinz B, Chaponnier C & Brown RA Myofibroblasts and mechano-regulation of connective tissue remodelling. Nat Rev Mol Cell Biol 3, 349–363, doi:10.1038/nrm809 (2002). [PubMed: 11988769]
24. Singer II, Kawka DW, Kazazis DM & Clark RA In vivo co-distribution of fibronectin and actin fibers in granulation tissue: immunofluorescence and electron microscope studies of the fibronexus at the myofibroblast surface. J Cell Biol 98, 2091–2106, doi:10.1083/jcb.98.6.2091 (1984). [PubMed: 6373789]
25. Burridge K & Chrzanowska-Wodnicka M Focal adhesions, contractility, and signaling. Annu Rev Cell Dev Biol 12, 463–518, doi:10.1146/annurev.cellbio.12.1.463 (1996). [PubMed: 8970735]
26. Dugina V, Fontao L, Chaponnier C, Vasiliev J & Gabbiani G Focal adhesion features during myofibroblastic differentiation are controlled by intracellular and extracellular factors. J Cell Sci 114, 3285–3296, doi:10.1242/jcs.114.18.3285 (2001). [PubMed: 11591817]
27. Krause C & Kloen P Concurrent inhibition of TGF-beta and mitogen driven signaling cascades in Dupuytren's disease - non-surgical treatment strategies from a signaling point of view. Med Hypotheses 78, 385–388, doi:10.1016/j.mehy.2011.11.023 (2012). [PubMed: 22196988]
28. Berndt A et al. TGF beta and bFGF synthesis and localization in Dupuytren's disease (nodular palmar fibromatosis) relative to cellular activity, myofibroblast phenotype and oncofetal variants of fibronectin. Histochem J 27, 1014–1020 (1995). [PubMed: 8789403]

29. Baird KS, Crossan JF & Ralston SH Abnormal growth factor and cytokine expression in Dupuytren's contracture. J Clin Pathol 46, 425–428, doi:10.1136/jcp.46.5.425 (1993). [PubMed: 8320323]
30. Badalamente MA, Sampson SP, Hurst LC, Dowd A & Miyasaka K The role of transforming growth factor beta in Dupuytren's disease. J Hand Surg Am 21, 210–215, doi:10.1016/S0363-5023(96)80102-X (1996). [PubMed: 8683048]
31. Bisson MA, McGrouther DA, Mudera V & Grobbelaar AO The different characteristics of Dupuytren's disease fibroblasts derived from either nodule or cord: expression of alpha-smooth muscle actin and the response to stimulation by TGF-beta1. J Hand Surg Br 28, 351–356, doi:10.1016/s0266-7681(03)00135-9 (2003). [PubMed: 12849947]
32. Verjee LS et al. Unraveling the signaling pathways promoting fibrosis in Dupuytren's disease reveals TNF as a therapeutic target. Proc Natl Acad Sci U S A 110, E928–937, doi:10.1073/pnas.1301100110 (2013). [PubMed: 23431165]
33. Krause C, Kloen P & Ten Dijke P Elevated transforming growth factor beta and mitogen-activated protein kinase pathways mediate fibrotic traits of Dupuytren's disease fibroblasts. Fibrogenesis Tissue Repair 4, 14, doi:10.1186/1755-1536-4-14 (2011). [PubMed: 21711521]
34. Tse R, Howard J, Wu Y & Gan BS Enhanced Dupuytren's disease fibroblast populated collagen lattice contraction is independent of endogenous active TGF-beta2. BMC Musculoskelet Disord 5, 41, doi:10.1186/1471-2474-5-41 (2004). [PubMed: 15541177]
35. Satish L et al. Fibroblasts from phenotypically normal palmar fascia exhibit molecular profiles highly similar to fibroblasts from active disease in Dupuytren's Contracture. BMC Med Genomics 5, 15, doi:10.1186/1755-8794-5-15 (2012). [PubMed: 22559715]
36. Rehman S et al. Dupuytren's disease metabolite analyses reveals alterations following initial short-term fibroblast culturing. Mol Biosyst 8, 2274–2288, doi:10.1039/c2mb25173f (2012). [PubMed: 22772395]
37. Verjee LS, Midwood K, Davidson D, Eastwood M & Nanchahal J Post-transcriptional regulation of alpha-smooth muscle actin determines the contractile phenotype of Dupuytren's nodular cells. J Cell Physiol 224, 681–690, doi:10.1002/jcp.22167 (2010). [PubMed: 20432463]
38. Gotway MB, Freemer MM & King TE Jr. Challenges in pulmonary fibrosis. 1: Use of high resolution CT scanning of the lung for the evaluation of patients with idiopathic interstitial pneumonias. Thorax 62, 546–553, doi:10.1136/thx.2004.040022 (2007). [PubMed: 17536033]
39. Martins-Bach AB et al. Non-invasive assessment of skeletal muscle fibrosis in mice using nuclear magnetic resonance imaging and ultrasound shear wave elastography. Sci Rep 11, 284, doi:10.1038/s41598-020-78747-8 (2021). [PubMed: 33431931]
40. Murphy A et al. Minimally invasive options in Dupuytren's contracture: aponeurotomy, enzymes, stretching, and fat grafting. Plast Reconstr Surg 134, 822e–829e, doi:10.1097/PRS.0000000000000603 (2014).
41. Badalamente MA & Hurst LC Development of Collagenase Treatment for Dupuytren Disease. Hand Clin 34, 345–349, doi:10.1016/j.hcl.2018.03.004 (2018). [PubMed: 30012294]
42. Freshwater MF What were the adverse events for Dupuytren's patients treated with Xiaflex who had contractures less than 20 degrees ? Hand (N Y) 7, 348–349, doi:10.1007/s11552-012-9424-2 (2012). [PubMed: 23997748]
43. Scherman P, Jenmalm P & Dahlin LB Three-year recurrence of Dupuytren's contracture after needle fasciotomy and collagenase injection: a two-centre randomized controlled trial. J Hand Surg Eur Vol 43, 836–840, doi:10.1177/1753193418786947 (2018).
44. Skov ST, Bisgaard T, Sondergaard P & Lange J Injectable Collagenase Versus Percutaneous Needle Fasciotomy for Dupuytren Contracture in Proximal Interphalangeal Joints: A Randomized Controlled Trial. J Hand Surg Am 42, 321–328 e323, doi:10.1016/j.jhsa.2017.03.003 (2017). [PubMed: 28473158]
45. Ketchum LD The Rationale for Treating the Nodule in Dupuytren's Disease. Plast Reconstr Surg Glob Open 2, e278, doi:10.1097/GOX.0000000000000249 (2014). [PubMed: 25587512]
46. Zachariae L & Zachariae F Hydrocortisone acetate in the treatment of Dupuytren's contraction and allied conditions. Acta Chir Scand 109, 421–431 (1955). [PubMed: 13292033]

47. Ketchum LD & Donahue TK The injection of nodules of Dupuytren's disease with triamcinolone acetonide. J Hand Surg Am 25, 1157–1162, doi:10.1053/jhsu.2000.18493 (2000). [PubMed: 11119679]
48. Coste F & Weissenbach R [Treatment of Dupuytren's disease by local injections of hydrocortisone]. Rev Rhum Mal Osteoartic 20, 863–866 (1953). [PubMed: 13156289]
49. Meek RM, McLellan S, Reilly J & Crossan JF The effect of steroids on Dupuytren's disease: role of programmed cell death. J Hand Surg Br 27, 270–273, doi:10.1054/jhsb.2001.0742 (2002). [PubMed: 12074617]
50. Ketchum LD, Robinson DW & Masters FW The degradation of mature collagen: a laboratory study. Plast Reconstr Surg 40, 89–91, doi:10.1097/00006534-196707000-00016 (1967). [PubMed: 4290974]
51. McMillan C & Binhammer P Steroid injection and needle aponeurotomy for Dupuytren contracture: a randomized, controlled study. J Hand Surg Am 37, 1307–1312, doi:10.1016/j.jhsa.2012.04.026 (2012). [PubMed: 22633226]
52. Ball C, Izadi D, Verjee LS, Chan J & Nanchahal J Systematic review of non-surgical treatments for early dupuytren's disease. BMC Musculoskelet Disord 17, 345, doi:10.1186/s12891-016-1200-y (2016). [PubMed: 27526686]
53. Husby T, Haugstvedt JR, Fyllingen G & Skoglund LA Acute postoperative swelling after hand surgery: an exploratory, double-blind, randomised study with paracetamol, naproxen, and placebo. Scand J Plast Reconstr Surg Hand Surg 35, 91–98, doi:10.1080/02844310151032691 (2001). [PubMed: 11291357]
54. Pittet B et al. Effect of gamma-interferon on the clinical and biologic evolution of hypertrophic scars and Dupuytren's disease: an open pilot study. Plast Reconstr Surg 93, 1224–1235, doi:10.1097/00006534-199405000-00018 (1994). [PubMed: 8171142]
55. Sanders JL, Dodd C, Ghahary A, Scott PG & Tredget EE The effect of interferon-alpha2b on an in vitro model Dupuytren's contracture. J Hand Surg Am 24, 578–585, doi:10.1053/jhsu.1999.0578 (1999). [PubMed: 10357539]
56. Jemec B et al. The effect of 5-fluorouracil on Dupuytren fibroblast proliferation and differentiation. Chir Main 19, 15–22, doi:10.1016/s1297-3203(00)73455-x (2000). [PubMed: 10777424]
57. Bulstrode NW et al. A prospective randomised clinical trial of the intra-operative use of 5-fluorouracil on the outcome of dupuytren's disease. J Hand Surg Br 29, 18–21, doi:10.1016/j.jhsb.2003.08.002 (2004). [PubMed: 14734063]
58. Akkus E et al. Is colchicine effective in Peyronie'sdisease? A pilot study. Urology 44, 291–295, doi:10.1016/s0090-4295(94)80155-x (1994). [PubMed: 8048212]
59. Simon AR, Rai U, Fanburg BL & Cochran BH Activation of the JAK-STAT pathway by reactive oxygen species. Am J Physiol 275, C1640–1652, doi:10.1152/ajpceN.1998.275.6.C1640 (1998). [PubMed: 9843726]
60. Meurer SK, Lahme B, Tihaa L, Weiskirchen R & Gressner AM N-acetyl-L-cysteine suppresses TGF-beta signaling at distinct molecular steps: the biochemical and biological efficacy of a multifunctional, antifibrotic drug. Biochem Pharmacol 70, 1026–1034, doi:10.1016/j.bcp.2005.07.001 (2005). [PubMed: 16098950]
61. Thomson GR Treatment of Dupuytren's contracture with vitamin E. Br Med J 2, 1382, illust, doi:10.1136/bmj.2.4641.1382 (1949). [PubMed: 15408091]
62. Richards HJ Dupuytren's contracture treated with vitamin E. Br Med J 1, 1328, doi:10.1136/bmj.1.4772.1328 (1952). [PubMed: 14935247]
63. Steinberg CL Tocopherols in treatment of primary fibrositis; including Dupuytren's contracture, periarthritis of the shoulders, and Peyronie's disease. AMA Arch Surg 63, 824–833, doi:10.1001/archsurg.1951.01250040840013 (1951). [PubMed: 14868250]
64. Kopp J et al. N-acetyl-L-cysteine abrogates fibrogenic properties of fibroblasts isolated from Dupuytren's disease by blunting TGF-beta signalling. J Cell Mol Med 10, 157–165, doi:10.1111/j.1582-4934.2006.tb00297.x (2006). [PubMed: 16563228]
65. Yu L et al. Combining TGF-beta inhibition and angiotensin II blockade results in enhanced antifibrotic effect. Kidney Int 66, 1774–1784, doi:10.1111/j.1523-1755.2004.00901.x (2004). [PubMed: 15496148]

66. Zimman OA et al. The effects of angiotensin-converting-enzyme inhibitors on the fibrous envelope around mammary implants. Plast Reconstr Surg 120, 2025–2033, doi:10.1097/01.prs.0000287381.93729.e2 (2007). [PubMed: 18090769]

67. Stephen C, Touil L, Vaiude P, Singh J & McKirdy S Angiotensin receptors in Dupuytren's disease: a target for pharmacological treatment? J Plast Surg Hand Surg 52, 37–39, doi:10.1080/2000656X.2017.1319846 (2018). [PubMed: 28486091]

68. Lee RC, Doong H & Jellema AF The response of burn scars to intralesional verapamil. Report of five cases. Arch Surg 129, 107–111, doi:10.1001/archsurg.1994.01420250119015 (1994). [PubMed: 8279934]

69. Rayan GM, Parizi M & Tomasek JJ Pharmacologic regulation of Dupuytren's fibroblast contraction in vitro. The Journal of Hand Surgery 21, 1065–1070, doi:10.1016/s0363-5023(96)80317-0 (1996). [PubMed: 8969433]

70. Gonzalez-Cadavid NF & Rajfer J Treatment of Peyronie's disease with PDE5 inhibitors: an antifibrotic strategy. Nat Rev Urol 7, 215–221, doi:10.1038/nrurol.2010.24 (2010). [PubMed: 20212516]

71. Dunkern TR, Feurstein D, Rossi GA, Sabatini F & Hatzelmann A Inhibition of TGF-beta induced lung fibroblast to myofibroblast conversion by phosphodiesterase inhibiting drugs and activators of soluble guanylyl cyclase. Eur J Pharmacol 572, 12–22, doi:10.1016/j.ejphar.2007.06.036 (2007). [PubMed: 17659276]

72. Ferrini MG, Kovanecz I, Nolazco G, Rajfer J & Gonzalez-Cadavid NF Effects of long-term vardenafil treatment on the development of fibrotic plaques in a rat model of Peyronie's disease. BJU Int 97, 625–633, doi:10.1111/j.1464-410X.2006.05955.x (2006). [PubMed: 16469038]

73. Kilic T et al. Protective and therapeutic effect of molsidomine on bleomycin-induced lung fibrosis in rats. Inflammation 37, 1167–1178, doi:10.1007/s10753-014-9841-1 (2014). [PubMed: 24526289]

74. Ferrini MG et al. Antifibrotic role of inducible nitric oxide synthase. Nitric Oxide 6, 283–294, doi:10.1006/niox.2001.0421 (2002). [PubMed: 12009846]

75. Vernet D et al. Effect of nitric oxide on the differentiation of fibroblasts into myofibroblasts in the Peyronie's fibrotic plaque and in its rat model. Nitric Oxide 7, 262–276, doi:10.1016/s1089-8603(02)00124-6 (2002). [PubMed: 12446175]

76. Kuhn MA, Wang X, Payne WG, Ko F & Robson MC Tamoxifen decreases fibroblast function and downregulates TGF(beta2) in dupuytren's affected palmar fascia. J Surg Res 103, 146–152, doi:10.1006/jsre.2001.6350 (2002). [PubMed: 11922728]

77. Chau D et al. Tamoxifen downregulates TGF-beta production in keloid fibroblasts. Ann Plast Surg 40, 490–493, doi:10.1097/00000637-199805000-00008 (1998). [PubMed: 9600433]

78. Lorizio W et al. Clinical and biomarker predictors of side effects from tamoxifen. Breast Cancer Res Treat 132, 1107–1118, doi:10.1007/s10549-011-1893-4 (2012). [PubMed: 22207277]

79. Degreef I, Tejpar S, Sciot R & De Smet L High-dosage tamoxifen as neoadjuvant treatment in minimally invasive surgery for Dupuytren disease in patients with a strong predisposition toward fibrosis: a randomized controlled trial. J Bone Joint Surg Am 96, 655–662, doi:10.2106/JBJS.L.01623 (2014). [PubMed: 24740662]

80. Martin-Montalvo A et al. Metformin improves healthspan and lifespan in mice. Nat Commun 4, 2192, doi:10.1038/ncomms3192 (2013). [PubMed: 23900241]

81. Park IH et al. Metformin reduces TGF-beta1-induced extracellular matrix production in nasal polyp-derived fibroblasts. Otolaryngol Head Neck Surg 150, 148–153, doi:10.1177/0194599813513880 (2014). [PubMed: 24357397]

82. Baeri A et al. A role for metformin in the treatment of Dupuytren disease? Biomed Pharmacother 150, 112930, doi:10.1016/j.biopha.2022.112930 (2022). [PubMed: 35427821]

83. Nanchahal J et al. Anti-Tumour Necrosis Factor Therapy for Dupuytren's Disease: A Randomised Dose Response Proof of Concept Phase 2a Clinical Trial. EBioMedicine 33, 282–288, doi:10.1016/j.ebiom.2018.06.022 (2018). [PubMed: 29983350]

84. Nanchahal J et al. Study protocol: A multi-centre, double blind, randomised, placebo-controlled, parallel group, phase II trial (RIDD) to determine the efficacy of intra-nodular injection of anti-TNF to control disease progression in early Dupuytren's disease, with an embedded dose response

study. Wellcome Open Res 2, 37, doi:10.12688/wellcomeopenres.11466.2 (2017). [PubMed: 29218326]

85. Nanchahal J et al. Anti-tumour necrosis factor therapy for early-stage Dupuytren's disease (RIDD): a phase 2b, randomised, double-blind, placebo-controlled trial. Lancet Rheumatol 4, E407–E416, doi:10.1016/S2665-9913(22)00093-5 (2022). [PubMed: 35949922]
86. Richeldi L et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 365, 1079–1087, doi:10.1056/NEJMoa1103690 (2011). [PubMed: 21992121]
87. Lappi DA et al. Basic fibroblast growth factor in cells derived from Dupuytren's contracture: synthesis, presence, and implications for treatment of the disease. J Hand Surg Am 17, 324–332, doi:10.1016/0363-5023(92)90415-l (1992). [PubMed: 1314273]
88. Glassberg MK Overview of idiopathic pulmonary fibrosis, evidence-based guidelines, and recent developments in the treatment landscape. THE AMERICAN JOURNAL OF MANAGED CARE 25, S195–S203 (2019). [PubMed: 31419091]
89. Noble PW et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 377,1760–1769, doi:10.1016/S0140-6736(ll)60405-4 (2011). [PubMed: 21571362]
90. Zhou C et al. Anti-fibrotic action of pirfenidone in Dupuytren's disease-derived fibroblasts. BMC Musculoskelet Disord 17, 469, doi:10.1186/sl2891-016-1326-y (2016). [PubMed: 27835939]
91. Zhou C, Zeldin Y, Baratz ME, Kathju S & Satish L Investigating the effects of Pirfenidone on TGF-beta1 stimulated non-SMAD signaling pathways in Dupuytren's disease -derived fibroblasts. BMC Musculoskelet Disord 20, 135, doi:10.1186/sl2891-019-2486-3 (2019). [PubMed: 30927912]
92. Panigrahi S et al. Pirfenidone as a potential antifibrotic injectable for Dupuytren's disease. Pharm Dev Technol 27, 242–250, doi:10.1080/10837450.2022.2038201 (2022). [PubMed: 35129055]
93. Cardoneanu A et al. Targeting Systemic Sclerosis from Pathogenic Mechanisms to Clinical Manifestations: Why IL-6? Biomedicines 10, doi:10.3390/biomedicinesl0020318 (2022).
94. Smith MR Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance. Oncogene 22, 7359–7368, doi:10.1038/sj.one.1206939 (2003). [PubMed: 14576843]
95. Rituxan (rituximab) [package insert]. San Francisco, CA: Genentech, Inc.; 2021.
96. Brenner P, Sachse C, Reichert B & Berger A [Expression of various monoclonal antibodies in nodules and band stage in Dupuytren's disease]. Handchir Mikrochir Plast Chir 28, 322–327 (1996). [PubMed: 9064258]
97. Menzel EJ et al. Collagen types and anticollagen-antibodies in Dupuytren's disease. Hand 11, 243–248, doi:10.1016/s0072-968x(79)80045-5 (1979). [PubMed: 391658]
98. Pereira R, Black C, Turner S & Spencer J Antibodies to collagen types I–VI in Dupuytren's contracture. The Journal of Hand Surgery: Journal of the British Society for Surgery of the Hand 11, 58–60, doi:10.1016/0266-7681(86)90014-8 (1986). [PubMed: 3485693]
99. Berman B, Maderal A & Raphael B Keloids and Hypertrophic Scars: Pathophysiology, Classification, and Treatment. Dermatol Surg 43 Suppl 1, S3–S18, doi: 10.1097/DSS.0000000000000819 (2017). [PubMed: 27347634]
100. Davies NM, McLachlan AJ, Day RO & Williams KM Clinical pharmacokinetics and pharmacodynamics of celecoxib: a selective cyclo-oxygenase-2 inhibitor. Clin Pharmacokinet 38, 225–242, doi:10.2165/00003088-200038030-00003 (2000). [PubMed: 10749518]
101. Salib CG et al. Inhibition of COX-2 Pathway as a Potential Prophylaxis Against Arthrofibrogenesis in a Rabbit Model of Joint Contracture. J Orthop Res 37, 2609–2620, doi: 10.1002/jor.24441 (2019). [PubMed: 31410880]
102. Chen H et al. Silencing COX-2 blocks PDK1/TRAF4-induced AKT activation to inhibit fibrogenesis during skeletal muscle atrophy. Redox Biol 38, 101774, doi:10.1016/j.redox.2020.101774 (2021). [PubMed: 33152664]
103. Baron S et al. The interferons. Mechanisms of action and clinical applications. JAMA 266, 1375–1383, doi:10.1001/jama.266.10.1375 (1991). [PubMed: 1715409]
104. Werker PMN & Degreef I Alternative and Adjunctive Treatments for Dupuytren Disease. Hand Clin 34, 367–375, doi:10.1016/j.hcl.2018.03.005 (2018). [PubMed: 30012296]

105. Rojkind M, Uribe M & Kershenobich D Colchicine and the treatment of liver cirrhosis. Lancet 1, 38–39 (1973).

106. Diegelmann RF & Peterkofsky B Inhibition of collagen secretion from bone and cultured fibroblasts by microtubular disruptive drugs. Proc Natl Acad Sci U S A 69, 892–896, doi:10.1073/pnas.69.4.892 (1972). [PubMed: 4502941]

107. Huddleston EM & Gaffo AL Emerging strategies for treating gout. Curr Opin Pharmacol 65, 102241, doi:10.1016/j.coph.2022.102241 (2022). [PubMed: 35609384]

108. Guy CD et al. Treatment response in the PIVENS trial is associated with decreased Hedgehog pathway activity. Hepatology 61, 98–107, doi:10.1002/hep.27235 (2015). [PubMed: 24849310]

109. Timmermans PB et al. Angiotensin II receptors and angiotensin II receptor antagonists. Pharmacol Rev 45, 205–251 (1993). [PubMed: 8372104]

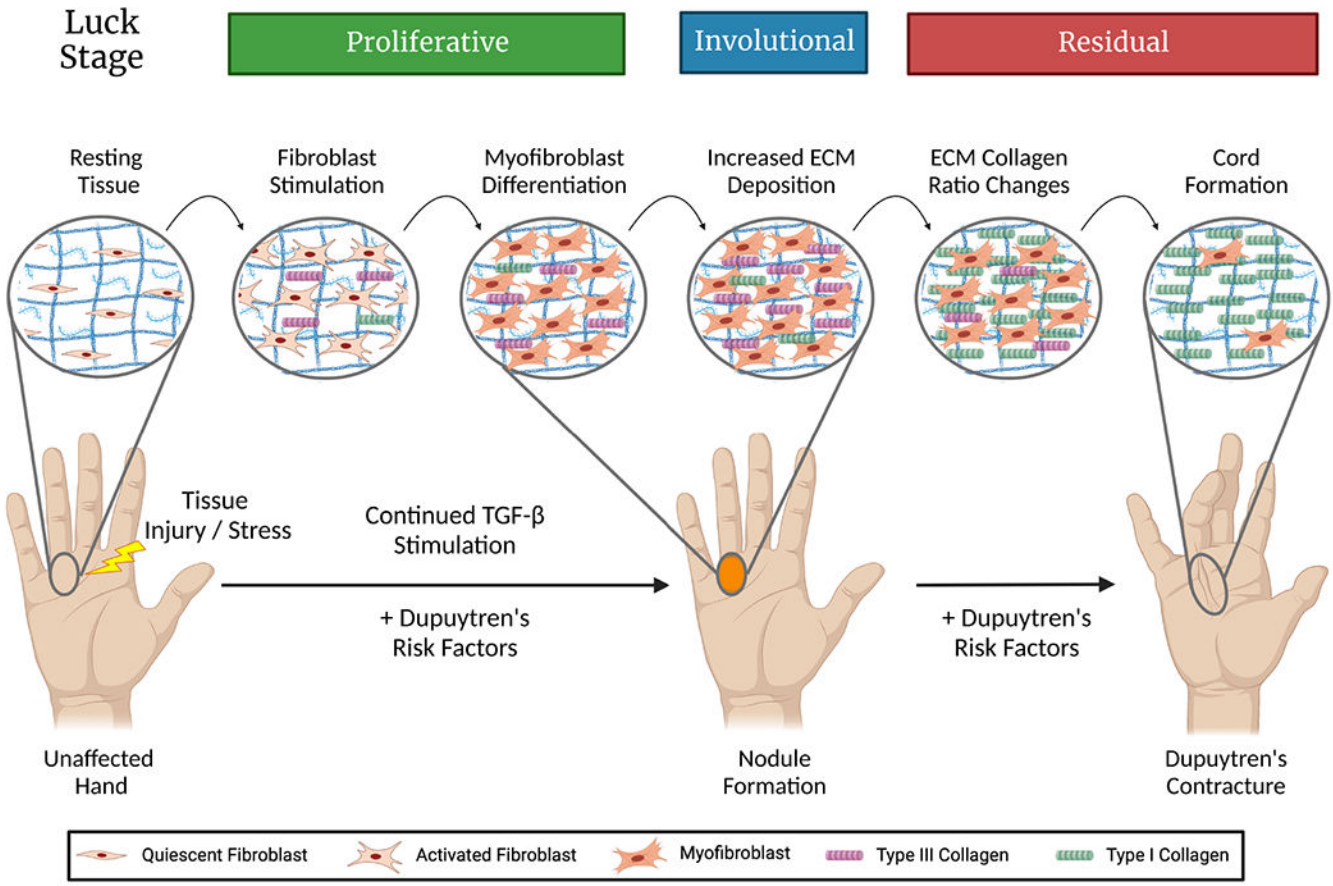

Figure 1. Pathophysiology of Dupuytren's Contracture

Dupuytren's disease progression exists on histologic, cellular, and clinical levels. Resting tissue of the unaffected hand contains quiescent fibroblasts. Upon tissue injury or stress, fibroblasts are activated, proliferate, and differentiate into mature myofibroblasts (Proliferative stage). With continued TGF-β stimulation and Dupuytren's risk factors, disease progresses. Nodule formation occurs as myofibroblasts differentiate and produce extracellular matrix (ECM), with collagen III:I ratio predominating (Involutional stage). The ECM collagen ratio changes to I:III, increased collagen cross-linking occurs, and cellularity decreases as cords form and contraction ensues (Residual stage).

Table 1.

Repurposed Pharmacotherapies Proposed for Dupuytren's Disease

Medication	Basic Mechanism of Drug	Proposed Mechanism in DD	*In vitro* Results in DD model	*In vivo* results in DD patients	Ref.
Anti-Inflammatory					
Corticosteroid	• Non-specific reduction in collagen synthesis, ECM composition, and pro-inflammatory mediators[99]	• Decreased fibroblast activity, density, and maturation[99]	• Inhibition of TGF-β1 expression and fibroblast apoptosis[49] • Potentiate activity of collagenase[50]	• Partial DD nodule resolution[47] • Short-term improvements of flexion deformity when used with PNA[51]	46–51,99
Celecoxib	• COX-2 inhibition, downregulation of pro-inflammatory mediators[100]	• Decreased myofibroblast differentiation through TGF-β signaling pathways[101,102]	• Not tested	• Not tested	100–102
Interferon (IFN)-gamma, alpha2b	• Inhibit cell growth, immunomodulation[103]	• Decreased fibroblast proliferation, myofibroblast differentiation, and collagen production[54,99]	• Decreased fibroblast proliferation and alpha-SMA expression[54] • Decreased fibroblast contraction[55]	• Decreased early DD nodule size[54]	54,55,99, 103
Anti-Mitotic					
5-Fluorouracil	• Inhibits thymidylate synthase needed for nucleic acid synthesis and function[104]	• Inhibit fibroblast proliferation • Inhibit TGF-β-induced expression of collagen[99]	• Inhibition of myofibroblast proliferation and differentiation[56]	• No clinical benefit when topically applied intraoperatively after limited fasciectomy[57]	56,57,99, 104
Colchicine	• Disrupts cytoskeletal functions by inhibiting β-tubulin polymerization • Inhibits cell proliferation by blocking mitosis	• Decrease collagen synthesis • Increase collagenase activity[105,106]	• Not tested	• No effect on DD contracture when administered orally in Peyronie's diseasepts[58]	58,105–107
Anti-Oxidant					
Vitamin E	• Decreases reactive oxygen species	• Decrease myofibroblast differentiation[108]	• Not tested	• No effect when administered orally[62,63]	62,63,108
N-acetyl-L-cysteine (NAC)	• Decreases reactive oxygen species	• Downregulates TGF-β signaling • Decreased production of alpha-SMA and collagen[60,64]	• Not tested	• Not tested	60,64
Anti-Hypertensive					
ACE inhibitors & angiotensin II antagonists	• Disrupt renin-angiotensinaldosteronesystem[109]	• Decrease TGF-β and collagen production[65,66]	• Increased angiotensin II receptors in DD tissue[67]	• Not tested	65–67,109
Verapamil	• Block voltage-gated calcium channels in cardiac nodes and vessel lining smooth muscle	• Decrease myofibroblast-mediated contracture[68]	• Partially block LPA-promoted contraction of DD fibroblasts[69]	• Not tested	68,69

Medication	Basic Mechanism of Drug	Proposed Mechanism in DD	*In vitro* Results in DD model	*In vivo* results in DD patients	Ref.
Vasoactive					
Phosphodiesterase inhibitors	• Inhibits degradation of cyclic GMP by PDE5[70]	• Prevent TGF-β1-induced collagen formation and myofibroblast differentiation[71,72]	• Not tested	• Not tested	70–72
Nitric oxide donors	• Increases release of nitric oxide[70]	• Inhibits TGF-β signaling, collagen synthesis, myofibroblast differentiation[74,75]	• Not tested	• Not tested	70,74,75
Endocrine					
Tamoxifen	• Partial agonist of estrogen receptors	• Modulate TGF-β signaling, decrease fibroblast proliferation and collagen production[77]	• Decreased TGF-β expression in DD fibroblasts, decreased fibroblast contraction[76]	• Short-term improvements after limited fasciectomy, effect lost within 2 years[79]	76–79
Metformin	• Phosphorylate AMP-activated protein kinase, regulating intracellular energy balance[80]	• Reduces TGF-β-induced ECM production in fibroblasts[81]	• Decreased TGF-β-induced contraction of DD fibroblasts[82]	• Not tested	80–82

Table 2.

Currently Approved Pharmacotherapies in Fibrosis and Inflammation

Medication	Basic Mechanism of Drug	Proposed Mechanism in DD	*In vitro* Results in DD model	*In vivo* results in DD patients	Ref.
TNF Inhibitors (e.g. adalimumab)	• Monoclonal antibody targeting and inactivating TNF-alpha	• Decrease TNF-driven fibroblast differentiation and contraction[32]	• Inhibition of myofibroblast contraction • Reduced alpha-SMA expression[32]	• Down regulation of myofibroblast phenotype in DD nodules[83,84] • DD nodule softening and size reduction at 1 year[85]	32,83–85
Nintedanib	• Tyrosine kinase inhibitor targeting pro-fibrogenesis signaling (VEFG, FGF, PDGF)[86]	• Decrease fibroblast differentiation by PDGF- and FGF-signaling[33,87]	• Not tested	• Not tested	33,86,87
Pirfenidone	• Inhibits TGF-β production and TGF-β-mediated fibroblast function[88,89]	• Decrease TGF-β-mediated fibroblast function and differentiation[88,89]	• Decreased fibroblast proliferation, myofibroblast differentiation, and matrix production[90,91]	• Not tested • *Intradermal formulation being investigated for DD*[92]	88–92
Tocilizumab	• Monoclonal antibody targeting IL-6 receptor, preventing binding of IL-6	• Decrease IL-6-mediated myofibroblast development[93]	• No effects on DD cells[32]	• Not tested	32,93
Rituximab	• Monoclonal antibody targeting B-cell surface protein CD20[94]	• Decrease auto-antibody contribution to DD[96–98]	• Not tested	• Not tested	94,96–98