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Commentary

Cytokine Targeted Therapy for Dupuytren's Disease

Latha Satish *

Research Department, Shriners Hospitals for Children, Cincinnati, OH-45229, USA
Department of Pathology and Laboratory Medicine, University of Cincinnati, OH-45229, USA

Dupuytren's disease (DD) is a complex fibroproliferative disease of the hand and a difficult condition to live with for the patients and a puzzling disease for the treating physicians. It has been more than 180 years since Baron Dupuytren was credited with discovering the disease, yet there is no definitive treatment to combat DD. Varying numbers with regards to prevalence rate are reported but a recent systematic review estimated 12% those aged 55 years are affected, rising to 29% in those aged 75 years in the general population in Western countries [1]. DD is a benign condition and early stage disease manifests itself as pits or nodules in the palm that develop into cords [2]. Non-invasive treatments for early stage disease are of limited efficacy [3] and the mainstay of treatment for late stage disease for years has been surgery. Recently, collagenase Clostridium histolyticum (CCH) injection has gained popularity as an alternative to surgery for treating DD. However, it is associated with a high rate of adverse effects [4] and patient satisfaction decreases over time as the disease recurs [5]. Current research is focused on targeting factors (mainly cytokines) that are responsible for mediating matrix production in DD, specifically collagen. Several growth factors mainly TGF-β1, PDGF, IGF, CTGF, bFGF and the pro-inflammatory cytokine TNF are found to play a prominent role in the progression of DD. TNF has been shown to act *via* the Wnt signaling pathway to promote contraction and profibrotic signaling in DD cells. *In vitro* studies also showed that neutralizing antibodies to TNF downregulates myofibroblast activity [6]. In *EBioMedicine*, Nanchahal and colleagues identified TNF as a potential target for clinical translation to treat DD [7].

The study reports a phase 2a double-blind, randomized placebo-controlled clinical trial on the efficacy of injecting nodules of DD with adalimumab, a TNF inhibitor [7]. The authors should be applauded for choosing a local delivery route *via* intra-nodular injection to assess the efficacy of a biologic, which might become routine in the future to avoid the necessity for surgical procedure. In this trial, the authors chose to inject the nodules two weeks prior to the scheduled surgery to test three different doses of adalimumab, which are 15 mg in 0.3 ml ($n = 6$; placebo $n = 2$), 35 mg in 0.7 ml ($n = 9$; placebo $n = 3$) or 40 mg in 0.4 ml (n = 6; placebo n = 2). Surgically excised tissues were subjected to mRNA and protein analyses. The primary outcome measure was to determine the levels of mRNA expression for α-SMA. Secondary outcomes were to determine the mRNA expression for collagen types I, III, and cadherin 11, as well as levels of α-SMA and collagen proteins. The authors found no changes in the mRNA expression for all genes assayed. Expression of α-SMA protein was reduced in patients who received 40 mg of adalimumab compared to those injected with placebo, or 35 mg or 15 mg of adalimumab. These data are in concordance with the previous *in vitro* finding that inhibiting TNF levels can downregulate the myofibroblast phenotype [6]. Previous reports suggest an increased proportion of type III collagen in earlier lesions, which changes to a greater proportion of type I collagen at later stages of the disease [8]. In the present study, the authors reported that TNF inhibition decreased the protein expression of procollagen type I but no differences were noted in procollagen type III levels due to the low sensitivity of the assay for procollagen type III [7]. TNF inhibition also did not reduce nodule size or hardness, which is not unexpected as the injection was administered only on one occasion.

The study also has a few limitations, which hopefully be addressed by the authors in their upcoming trial. An interesting finding would have been if the levels of the growth factors mainly TGF-β1 and PDGF, along with TNF in the excised tissue was reported, which would have added more strength on the utility of adalimumab for DD. Another interesting observation would have been if authors had reported the changes in the expression level of the ECM protein namely fibronectin a known contributor in DD pathogenesis along with type I and type III collagens.

Overall, with this trial, the authors have established safety and determined the effective dose and volume (40 mg in 0.4 ml) of adalimumab to proceed to a phase 2b clinical trial with a larger cohort of patients with early-stage DD to investigate the efficacy of intra-nodular injections every 3 months over a 12-month period. The ongoing phase 2b clinical trial should allow the authors to ascertain whether multiple injections can decrease nodule size and hardness. If a significant decrease in nodule size and hardness is noticed, it indirectly reflects that there might have been a significant decrease in myofibroblast formation and collagen accumulation. The authors should also consider a future clinical trial of patients with the advanced form of the disease to investigate the potential of adalimumab in preventing recurrence.

Disclosure

The author declared no conflicts of interest.

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* Corresponding author at: Shriners Hospitals for Children, Research Department, 3229 Burnet Avenue, Cincinnati, OH 45229, USA.
E-mail addresses: lsatish@shrinenet.org, satishla@uc.edu (L. Satish).

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