JID: Safety and Efficacy of Lenabasum, a Cannabinoid Receptor Type 2 Agonist, in Patients with Dermatomyositis with Refractory Skin Disease: A Randomized Clinical Trial

What is the general condition, procedure or disease under study?
Refractor cutaneous dermatomyositis

What were the research question(s)
What is the safety and efficacy of Lenabasum in patients with refractory cutaneous dermatomyositis?

Was the question answered to your satisfaction - validity? a. If so, on what grounds? b. If not, why not? c. Do you trust the conclusions and recommendations?
This study was a single-center, double-blind, randomized, placebo-controlled phase 2 study. The design of the study was a strength, but the inclusion and exclusion criteria gave me pause. All patients in the study had to have failed or had intolerance HCQ, but all of the participants stayed on their other DM immunosuppressive medication throughout the duration of the study, regardless of which medication they were on. The study did not adjust for specific medications, so while the results are interesting and significant, it is hard to attribute the difference in the two groups specifically to the Lenasbasum treatment. This being said, the tolerability and safety profile were favorable and this may ultimately be a great adjunct treatment for patients with refractory skin limited DM.

Were these good questions? (impact, importance, interest and novelty)
The cutaneous effects of DM can be severe for many patients and cause significant decrease in QOL. This novel treatment is both interesting, novel, and promising for these patients that have failed many of the classic DM medications. Most importantly, this study demonstrates its safety and tolerability- showing that it might be a reasonable adjunct therapy for these patients in addition to their baseline immunosuppressive therapy.

Does this article or research change your treatment or concept of this condition? a. If so why? b. If not, why not?
This article has done an excellent job in educating me on this novel class of medication as it is a class that dermatologists do not typically reach for. It would be interesting to see if it would be helpful for many other dermatologic conditions where shutting down the inflammatory cascade may be of benefit. Regarding my treatment for DM, larger studies need to be conducted in order for me to use this as adjunct therapy, but the results look promising!

Does this study prompt or inspire a different and better study?
It would be interesting to see how this medication performs as a monotherapy for patients who have failed HCQ, but have not yet started a new immunosuppressive medication. It could also be interesting to see a head to head trial in the efficacy of Lenasbasum vs HCT for patients with less severe, skin limited disease.

JAAD: Sentinel lymph node biopsy in patients with clinical stage IIB/C cutaneous melanoma: A national cohort study

What is the general condition, procedure, or disease under study?
Stage IIB/C primary cutaneous melanoma

What were the research question(s)
What is the prognostic significance of SLN staging on disease-specific survival (DSS) for clinical stage IIB/C primary cutaneous melanoma in the pre-immunotherapy era?

Was the question answered to your satisfaction - validity? If so, on what grounds? If not, why not? Do you trust the conclusions and recommendations?

This study represents a large retrospective cohort study of stage IIB/C primary cutaneous melanoma. The SEER database was used and ultimately 8562 patients were included. For a retrospective study, the sample size was

sufficient to validate the claims. As the authors mention, there are limitations as comorbidity data was not included and the validity of what was considered a true SLN biopsy

Were these good questions? (impact, importance, interest and novelty)
There is significant data demonstrating the importance of SLN staging to provide accurate prognostic information and guide treatment options for patients with T1b or higher melanoma. That being said, there has been no study done looking specifically at the prognostic importance of SLN in patients with stage IIB/C Melanoma. This question is particularly important as Pembrolizumab has recently been approved for stage IIB/C disease (both clinicall y and pathologic). The question that these authors have raised is if there is any prognostic advantage to obtaining SLN biopsy in this patient population now that Pembolizumab is approved (since we now have the option to go straight to Pembrolizumab in this population regardless of SLN status). As the authors mentioned, the side effect profile of PD-1 inhibitors can be severe and long lasting, while the side effect profile of SLN is quite minimal. Having a better idea of the survival difference between the two groups may make patients with SLN- status more comfortable deferring and may make patients with SLN+ status more informed about the decision to pursue adjuvant treatment.

Does this article or research change your treatment or concept of this condition? a. If so why? b. If not, why not?
This study certainly provides important prognostic information specific to stage IIB/C disease. With the new FDA approval of Pembrolizumab for this subgroup Melanoma patients, it is extremely important to have the prognostic information available in order to best inform our patients about the risk vs benefit profile of pursuing adjuvant treatment with PD-1 inhibitors.

Does this study prompt or inspire a different and better study?
A study that could better answer the question regarding the role of SLN status in these patients would be to look at the difference in disease specific survival in SNL+ vs SLN- patients with Clinical stage IIB/C receiving adjuvant PD-1 therapy. As this therapy has just recently been approved more time will be needed in order to obtain follow up information in this specific cohort.

LENDING A HELPING HAND TO OUR PATIENTS WITH DUPUYTREN'S DISEASE

Dermatology World Insights and Inquiries

By Warren R. Heymann, MD, FAAD
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When patients trust you, they want your opinion, even if the disorder in question is out of your bailiwick. Although likely to refer patients with Dupuytren's disease (DD, aka Dupuytren's contracture, DC) directly to an orthopedic (hand) surgeon, we dermatologists should have at least a rudimentary knowledge of the malady to help guide our patients.
DD is a connective tissue disorder of the hand characterized by excessive fibrosis of the palmar and digital fascia that may progress to a disabling contracture. DD is common, affecting approximately 3% of the population, and 12% in those older than 55 years. DD appears later in life (fifth decade), more often in men and those of Northern European descent; the incidence rate increases with age. The fourth and fifth digits around the metacarpophalangeal and proximal interphalangeal joints are the most frequently involved sites. (1,2,3) DD is part of the polyfibromatosis spectrum, where it occurs in variable combinations with plantar fibromatosis

(Ledderhose's disease) in 5%, penile fibromatosis (Peyronie's disease) in 3%, and occasionally with knuckle pad and keloids. (1,4) This commentary will focus on DD (DC).

DD appears in three stages: A (asymptomatic nodules); B (progressive cords); and C (permanent contractures). The physical examination includes the Hueston test, which is performed by placing the patient's hand on a flat surface, with fingers extended. A positive test occurs when the fingers cannot lay flat, thereby forming an angle of at least 30 degrees at the metacarpophalangeal joint. (1) Early recognition and treatment of DD may prevent disease progression.

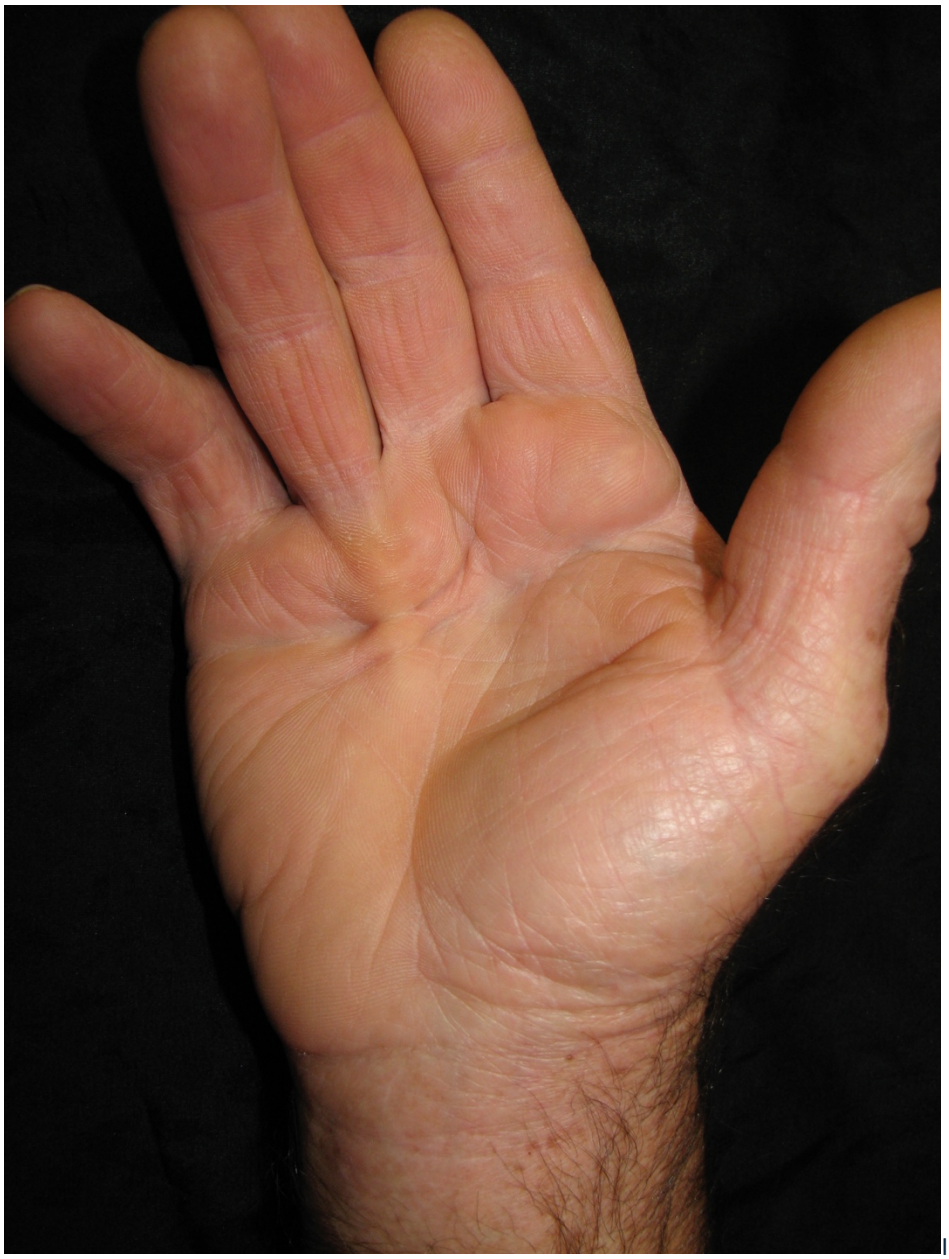
Image from DermNetNZ

Although the precise pathophysiology of DD is unknown, there are emerging concepts, focusing on genetic, immunological, and environmental factors (such as smoking and alcohol). (1) DC has been linked to psoriasis, notably palmoplantar disease, being observed in 19.6% of psoriatic patients compared to 3.6% of controls. (5) DC may also be associated with diabetes, HIV, epilepsy, and manual labor. (1) Anticonvulsant medications and BRAF inhibitors such as vemurafenib have been implicated as being pathogenic. (6)

Although sporadic cases occur, there is a substantial heritability in DD, which has been noted in up to 80% of cases in a recent study from Denmark. A genome-wide association study identified 9 susceptibility genetic loci in DD, 6 of which harbored genes encoding proteins in the Wnt signaling pathway. (1,3) In a study identifying key cellular and molecular pathways driving DD, Dobie et al employed single-cell RNA sequencing, profiling the transcriptomes of 35,250 human single cells from DD, nonpathogenic fascia, and healthy dermis. The authors identified a DD-specific population of pathogenic PDPN+/FAP+ mesenchymal cells displaying an elevated expression of fibrillar collagens and profibrogenic genes. Subsequent analysis demonstrated that resident fibroblasts were the source of this pathogenic population. Genes differentially expressed during fibroblast differentiation were identified, including upregulated TNFRSF12A and transcription factor SCX. Knockdown of SCX and blockade of TNFRSF12A inhibited the proliferation and altered the profibrotic gene expression of cultured human FAP+ mesenchymal cells, demonstrating a functional role for these genes in DD. (7) Ultimately, various cytokines and growth factors (PDGF, TGF-b1 TNF, IL-1b, and IL-6), in concert with diminished extracellular matrix maintenance of homeostasis, results in myofibroblast proliferation with an accumulation of type III collagen in aponeurosis and ligaments ordinarily composed of type I collagen. (1,7) These findings could have therapeutic implications.

Treatment of DD may be considered non-surgical and surgical. In very early cases, observation may be appropriate. Physical therapy, injection of collagenase, and intralesional triamcinolone may be utilized. Radiation (8) and fractionated CO2 laser (9) have shown efficacy. Surgery remains the gold standard, with a partial open fasciotomy being the most common procedure. (1)

In conclusion, you will routinely be seeing patients with DD. Acknowledge it and refer accordingly. Lending your helping hand may help theirs.

Point to Remember: Dupuytren's disease is common and potentially debilitating. Early recognition and referral may prevent contracture formation by non-surgical and surgical means. Advanced molecular studies may herald novel therapeutic interventions.

Our expert's viewpoint

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Dupuytren's Disease (DD) of the hand is a benign, fibroproliferative process that causes hand dysfunction through contracture of the palmar skin. Any finger or even the thumb can be involved. Hand function becomes increasingly compromised as the flexion deformity worsens. Diagnosis is based upon history and clinical examination. Early and proper diagnosis is particularly important to help avoid unnecessary biopsy or other diagnostic studies. The MP joint is the most common site of contracture, followed by the PIP joint and rarely the DIP joint. While the disease process originates in the palmar fascia of the skin, secondary joint contractures can develop in the ligaments and capsules of the joints based upon the chronicity of the skin contracture.

Intervention is indicated once the patient demonstrates a positive Hueston tabletop test as described above. However, with a clear trend toward less invasive treatments, patients will often seek intervention prior to the traditional treatment indications of a 30 degree MP flexion contracture or any PIP flexion contracture. Regardless of the intervention that is chosen, DD is a lifetime disease process and recurrence is almost assured as life expectancy increases. The available interventions for DD are probably better viewed as complementary tools in our armamentarium to treat this disease process, each with its own cost and risk/benefit profile, rather than competing treatments trying to achieve supremacy.

Most patients will opt for a less invasive intervention as a first line treatment. Collagenase clostridium histolyticum injection (CCHI) treatment has gained great popularity over the last decade and is now a proven, safe, and cost-

effective treatment. A joint manipulation is necessary 24 hours following the CCHI, which is performed in the office using a local anesthetic. Skin tears are the most common complication following CCHI treatment occurring in as many as 10% of the treated hands after manipulation. Radiation, laser, and shock wave treatments offer the hope for less invasive treatment, however, they do not seem to have the more widespread acceptance that CCHI currently does.

Needle fasciotomy (NF) remains a less invasive viable treatment option compared to surgical fasciectomy. For the NF, the contracted cord of palmar fascia is punctured with multiple passes of a needle tip and then the finger is manipulated. If the cord is adequately weakened with the NF, then the manipulation can rupture the residual cord in a similar fashion to the manipulation after CCHI. Clinical results can be similar between NF and CCHI. More distally in the digits, where the skin is thinner and the neurovascular structures may be more vulnerable, complications of these less invasive procedures may be higher.

Surgery has long been the gold standard treatment with excellent outcomes and still may be a viable first-choice treatment for some patients. Surgery is the most invasive and has the longest recovery period, but still seems to be the approach that can most fully remove the disease with a single treatment. Surgery has variations and requires careful planning to either simply release the fascial cord (fasciotomy), remove the fascial cord (fasciectomy), or remove the fascial cord as well as the overlying skin (dermofasciectomy). The dermofasciectomy will require either a skin graft or an open granulating wound but may still be associated with the lowest recurrence rate of all treatments.