Cannabis sativa as a Potential Treatment for Systemic Sclerosis

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Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by visceral organ and skin fibrosis and vascular damage. Different disease subtypes are classified according to the extent of the skin involvement. Heart, lung and kidney complications may have a high prevalence, especially in diffuse SSc, leading to an increase in morbidity and mortality [1,2]. Cannabinoids have recently been suggested as a possible novel treatment that may limit progression of the disease [3].

PATIENT DESCRIPTION

We describe a 59-year-old man of Yemenite descent with diffuse SSc that had been diagnosed 5 years earlier. The disease was originally triggered by multiple pricks in his palm with the *Cyca revoluta* thorn, and he first presented with severe proximal and distal cutaneous thickening of the upper limbs and trunk, joint involvement, and severe Raynaud's phenomenon with digital pitting scars [4]. In the first year of the disease, he complained of dyspnea, and a computed tomography (CT) scan revealed mild interstitial pulmonary fibrosis. He also developed arterial hypertension that was successfully treated with captopril and lercanidipine. Furthermore, his renal function was also a matter of concern, with creatinine levels reaching 1.7 mg/dl. The patient is currently medicated with bosentan, methotrexate, captopril, and lercanipine. His personal and family medical history is otherwise unremarkable.

Over the past few years, the patient developed severe flexion contractures of the hands due to progressive skin thickening, which precludes him from working [Figure 1]. Following the medical interventions described above, the patient independently made the decision to smoke 30 g per day of *Cannabis sativa* leaves. Since then he has reported an amelioration of all symptoms, and complete resolution of the Raynaud's phenomenon and dyspnea. Despite his severe disabilities due to the hand deformities, he is able to perform some daily activities without the need of any analgesic therapy. Furthermore, his renal function had stabilized with a creatinine level of 1.1 mg/dl and absence of proteinuria. Other laboratory parameters, such as hemogram and liver function, were unremarkable. The patient recently underwent pulmonary function tests with normal results, despite the pulmonary involvement initially diagnosed. Recent echocardiography did not show any significant alterations and no adverse events were reported by the patient.

COMMENT

Cannabinoids are a group of compounds that can be categorized as endocannabinoids, phytocannabinoids, synthetic cannabinoids, and purified cannabinoids [5]. They act on the endocannabinoid system, discovered only in the early 1990s, through different types of receptors [3]. Two of the most studied receptors are cannabinoid receptor type 1 (CB1) and type 2 (CB2) that immune cells and fibroblasts are able to express [5]. There has been increasing evidence on the immunomodulatory effects of cannabinoids. Some studies postulate the modulation of Th1/Th2 cells balance towards the enhancement of Th2 cell response, inhibition of the fibroblast activation, and reduction of transforming growth factor-beta (TGFβ) levels, in mouse models of scleroderma [3]. In another murine model study, a CB2 agonist prevented the development of skin and lung fibrosis and decreased the levels of anti-DNA-topoisomerase

Figure 1. Severe hand deformities in a patient with diffuse systemic sclerosis

antibodies and fibroblast proliferation [5]. A novel oral selective CB2 agonist is currently in a phase 3 trial (clinicaltrials.gov, NCT03398837), and has already demonstrated a satisfactory safety profile as well as a statically significant reduction on the modified Rodnan Skin Score in diffuse SSc patients (clinicaltrials.gov, NCT02465437).

In our patient, *Cannabis sativa* consumption might have had a role in ameliorating the respiratory symptoms and preventing the progression of the lung involvement. It also provided effective pain control and a higher quality of life, considering his severe disabilities.

Although concerns may be raised with the use of *Cannabis sativa*, especially due to its psychoactive and addictive effects, the potential benefits should be weighed against these risks. Legalization of medical cannabis has been discussed in many countries in recent years in view of recent research results and some already available clinical data.

In conclusion, further clinical research is needed to establish a standard therapy with cannabinoids. However, their potential role should not be dismissed

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Capsule

Revisiting TGFβ and EMT

Cancer progression is enhanced by the epithelial-to-mesenchymal transition (EMT), a process mediated by transforming growth factor-β (TGFβ). EMT is thought to be a reversible process. However, **Katsuno** et al. found that TGFβ withdrawal did not reverse EMT induced by long-term exposure to TGFβ, which mimics what occurs during carcinoma progression. By contrast, an inhibitor of the kinase mammalian target of rapamycin reversed some EMT features in cells and metastatic breast cancer models in mice. These results may explain why TGFβ inhibitors are not effective in some cancer patients and highlight a potential alternative therapy.

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Capsule

Structure-based selection of human metabolite-binding P4 pocket of *DRB1*15:01* and *DRB1*15:03*, with implications for multiple sclerosis

Binding of small molecules in the human leukocyte antigen (HLA) peptide-binding groove may result in conformational changes of bound peptide and an altered immune response, but previous studies did not consider a potential role for endogenous metabolites. **Mirsa** et al. performed virtual screening of the complete Human Metabolite Database (HMDB) for docking to the multiple sclerosis (MS) susceptible *DRB*1*15:01 allele and compared the results to the closely related yet non-susceptible *DRB*1*15:03 allele; and assessed the potential impact on binding of human myelin basic peptide (MBP). The authors observed higher energy scores for metabolite binding to *DRB*1*15:01 than *DRB*1*15:03. Structural comparison of docked metabolites with *DRB*1*15:01 and *DRB*1*15:03 complexed with MBP revealed that PhenylalanineMBP92 allows binding of metabolites in the P4 pocket of *DRB*1*15:01 but ValineMBP89 abrogates metabolite binding in the P1 pocket. They observed differences in the energy scores for binding of metabolites in the P4 pockets of *DRB*1*15:01 vs. *DRB*1*15:03, suggesting stronger binding to *DRB*1*15:01. This study confirmed that specific, disease-associated human metabolites bind effectively with the most polymorphic P4 pocket of *DRB*1*15:01, the primary MS susceptible allele in most populations. These results suggest that endogenous human metabolites bound in specific pockets of HLA may be immunomodulatory and implicated in autoimmune disease.

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"The real man smiles in trouble, gathers strength from distress, and grows brave by reflection"

Thomas Paine (1737–1809), English-born American political activist, philosopher, political theorist and revolutionary