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Medical Cannabis in Treatment of Resistant Familial Mediterranean Fever

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Case series
Patient: Male, 30 • Male, 23
Final Diagnosis: Familial Mediterranean fever
Symptoms: Abdominal pain
Medication: —
Clinical Procedure: —
Specialty: Rheumatology

Objective: Unusual setting of medical care

Background: Colchicine-resistant familial Mediterranean fever can be treated by anti-IL-1 biologic therapy; however, such treatment needs approval by the health insurance company, and many patients are denied such treatment or do not respond to it.

Case Reports: Two familial Mediterranean fever (FMF) patients, both homozygous for M694V mutation and resistant to colchicine treatment, were treated with medical cannabis. Prior to that, 1 patient was denied biologic treatment and the other had no significant response to anakinra. Under medical cannabis treatment, both patients had remarkable improvement in the severity of the attacks and also a decrease in the frequency of the attacks, from once every 2 weeks to 1 attack every month in 1 patient; this patient had also a remarkable reduction in the C-reactive protein level during the attacks.

Conclusions: Cannabis is a therapeutic option for treating the most complex patients with FMF.

MeSH Keywords: Colchicine • Familial Mediterranean Fever • Medical Marijuana

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Background

Familial Mediterranean fever (FMF) is a common hereditary disease in the Middle East [1]. Classically, patients with FMF have recurrent attacks of serositis, including pleuritic chest pain, abdominal pain, and high fever. Articular involvement can also occur. These attacks usually occur every few weeks to months and last 1–4 days, significantly affecting quality of life [2].

FMF management is based on the various available drugs. Management of acute attacks is mainly by non-steroidal anti-inflammatory drugs (NSAIDs) and other supportive treatment.

Colchicine is an effective treatment for the prevention of these attacks in about 70% of patients [3], and it also prevents secondary amyloidosis**,** a serious complication of FMF [4]. However, about 10% of patients are totally resistant to treatment. Biologic treatment like canakinumab and anakinra are considered second-line treatments for the prevention of FMF attacks [5,6]. Biologic treatment is expensive and must be approved by a special committee of health insurance providers.

Medical cannabis (MC) is helpful for a wide spectrum of syndromes, including chronic pain syndromes [7]. Its use in Israel requires a special license issued by the Israeli Medical Cannabis Agency (IMCA) in the Ministry of Health, or by physicians approved by the IMCA for this purpose. Other than chronic pain syndromes, it is also indicated by the IMCA for a variety of resistant neuropathies, seizures, and inflammatory diseases like Crohn's [8]. To the best of our knowledge, there are no reports on the effect of cannabis use in FMF patients. Here, we report 2 cases of resistant FMF patients who reported remarkable improvement with MC treatment.

Case Report

Case 1

A 30-year-old male was diagnosed with FMF (qualifying Tel Hashomer criteria) since the age of 5 years. He was homozygous for the mutation M694V and had recurrent attacks of abdominal pain, fever, pleuritic chest pain, and arthralgia, despite treatment with colchicine 0.5 mg 2–3 times a day. Higher doses were associated with diarrhea. These attacks occurred nearly every month and lasted for 3–4 days. He was treated by NSAIDs, mainly diclofenac potassium (Cataflam) 50 mg 2–3 times a day, and sometimes intramuscular diclofenac sodium (Voltaren) and intravenous fluids given at the emergency room. During the attacks, he would stay at home on sick leave. The patient had been denied biologic treatment with either canakinumab or anakinra. His renal function was normal.

MC treatment was approved by the IMCA by smoking, using 2 species (products of IMC Agriculture MC Growing Company, Israel). The first, Ella (60% Sativa+40% Indica), contains 10% delta-9-tetrahydrocannabinol (THC)+2% cannabidiol (CBD) for daytime use, and the second species, Roma (60% Indica+40% Sativa), contains 20% THC+4% CBD for evening use. Under this treatment, the patient reported remarkable improvement in the severity of the attacks and quality of life, including decreased abdominal, joint, and chest pain, as well as a temperature below 38°C. During these attacks, he could move around in and outside his home without the need for bedrest. The patient consumed 20 g of MC per month and denied any adverse effects of this treatment. Eventually, the patient gave up the request for biologic treatment and requested to use MC treatment only.

Case 2

A 23-year-old male patient had resistant FMF for 15 years despite treatment with 3–4 tablets of colchicine a day. He was also homozygous for M694V mutation. He had recurrent attacks of pleuritic chest pain, fever up to 40°C, and exacerbation of bilateral ankle pain nearly every 2 weeks. These attacks lasted 2–3 days, and during the attacks he spent most of the time in bed, frequently changing position due to chest pain. He was treated at home with oral NSAIDs, proton pump inhibitors, and sometimes antiemetics. His ankle pain never disappeared between the attacks. During a physical examination at the clinic (while free of attack), his lungs were clear without pleuritic rub, his abdomen was soft, and his ankles had local tenderness without synovial swelling. His routine lab test results were normal, including renal function and urine analysis. C-reactive protein (C-RP) levels during the attacks were elevated. The patient was started on anakinra 100 mg/d subcutaneously, which improved his ankle pain but had a minimal effect on the fever and chest pain during the attacks. The patient started using MC by smoking, which he purchased from the black market without a license from the IMCA. He consumed 20–30 grams a month, mainly in the evening, using the species Erez (70% Indica+30% Sativa), which contains 18% THC and 1% CBD. Occasionally, during the daytime or in the morning, he would use the species Alaska (predominantly Sativa), which has 18% THC and 1% CBD. Both species are products of a local MC company named Tikun Olam. Following the use of MC, he reported a significant improvement in the severity of pleuritic chest pain with only a mild fever during the attacks. Most of the time he was out of bed during the attacks, with mild limitation of deep breathing. Further, there was a prolongation of the timespan between the attacks to a single attack every month. This patient had a repeat test for C-RP level 1 month after starting MC, which showed a decrease during FMF attacks, from 37 mg prior to beginning MC use to 6.09 mg after its use (normal range, 0.1–0.5 mg).

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Discussion

MC is becoming increasingly popular in the treatment of different diseases, especially resistant ones such as convulsions, Parkinson's disease, and chronic pain syndromes [9–11]. There are more than 100 phytocannabinoids, but the main active compounds are THC and CBD [12]. THC has psychoactive, anti-pain, and anti-emetic properties. CBD is free of psychoactive properties but has strong anti-pain, anti-inflammatory, and spasmolytic properties. These compounds act mainly through the CB1 receptors, which are located primarily in the central nervous system (CNS), and CB2, which is located in different organs, especially those related to the immune system, such as the spleen and lymph nodes [13]. The activation of these receptors is eventually translated into distinct intracellular signaling pathways through coupling to specific intracellular effector proteins [14]. The human body itself has also its own cannabinoids, called endocannabinoids (15). *In vitro* studies in humans have shown that CBD results in the reduction of IL-1β levels in mitogen-activated human peripheral blood monocytes, in addition to other cytokines [16]. Clinically, a prospective, placebo-controlled trial showed that cannabis induced clinical response in patients with Crohn's disease, which is an inflammatory disease [8].

The pathogenesis of FMF is still not fully defined. It is hypothesized that a mutation in the MEFV gene results in abnormal production of pyrin, a type of protein that that has been widely investigated in recent years. Normally, it has an inhibitory effect on IL-Iβ processing [16]. Pyrin affects IL-1β and is believed to recruit white blood cells to the serosal areas participating in the inflammatory process [18]. Colchicine is believed to act through stabilizing inflammatory cells and preventing the release of the inflammatory contents [19]. Biologic treatments like anakinra and canakinumab block IL-1β and neutralize its effect [20]. Therefore, the beneficial effect of MC on the symptoms/signs of FMF is at least through its inhibitory effect on IL-1β, in addition to its central effect in the CNS. This favorable effect was manifested in our study by attenuation in the severity of attacks and decreasing their frequency**.** More studies are needed on this issue.

Conclusions

Cannabis is a therapeutic option for treating the most complex patients with FMF.

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