

Juvenile Idiopathic Arthritis

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Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies of cannabis therapy are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Though the MN medical cannabis program does not allow smoked or vaporized dried cannabis, studies using these forms of cannabis administration were allowed for insight they could provide. Finally, the federal government-maintained web site of clinical trials, clinicaltrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

Juvenile idiopathic arthritis (JIA), formerly known as juvenile rheumatoid arthritis, is the most common type of arthritis in children. It can cause persistent joint pain, swelling, and stiffness. In some children the symptoms last for only a few months; others have symptoms for the rest of their lives. Some types of JIA can result in serious complications, such as growth problems, joint damage, and eye inflammation. Treatment focuses on controlling pain and inflammation, improving function, and preventing joint damage (Mayo Clinic 2018).

JIA encompasses a diverse group of immune-mediated medical disorders affecting children under 16 years of age which share as a common feature arthritis lasting more than six weeks. Much remains to be discovered about what causes these diseases. Despite the unknowns, important advancements in therapy have occurred over the past 20 years. There is hope that, as the causes are better understood, therapies treating the underlying biologic processes will be developed and genetic information will help guide treatment (Eisenstein 2014).

In the late 1990s the International League of Associations for Rheumatology adopted the JIA classification of chronic childhood arthritis, effectively replacing earlier classification systems: the juvenile rheumatoid arthritis (jra) and juvenile chronic arthritis (jca) systems. The JIA classification system is based on clinical findings (example – number of joints affected), family history, and in some cases, information from a limited number of laboratory tests. Around 50% of European children have the oligoarticular form of JIA (<5 joints involved during the first six months of disease) (Eisenstein 2014).

Prevalence

JIA is the most common pediatric autoimmune musculoskeletal condition (Kessler 2014). Prevalence estimates from around the world have varied greatly. These differences might be due to a combination of true differences in different geographic regions and use of varying inclusion criteria. Studies in the United States produce estimated prevalence in the range of 1 to 10 per 10,000 children (Gewanter 1983, Helmick 2008).

Current Therapies

Over the last two decades, significant efforts have been made to improve the quality of research in children with JIA, resulting in dramatic advances in management. These efforts include the creation of better classification criteria, validated outcome measures and a definition of clinical remission for select subsets of JIA. Also, placebo-controlled clinical trials have become more acceptable to children with JIA and their families through innovative methodologies that minimize time on placebo. And development of research consortiums has aided in the ability to conduct well-defined, standardized, multi-center research protocols. Therapeutic goals have become more ambitious and physicians have higher expectations for complete remission (Wahezi 2013).

Initial therapy, primarily to manage pain and acute inflammation, is non-steroidal anti-inflammatory drugs (NSAIDs), sometimes with the addition of corticosteroids either injected into the joint or administered systemically. Though these therapies reduce suffering from symptoms, they do relatively little to slow progression or eliminate the underlying disease processes. Disease-modifying anti-rheumatic drugs (DMARDs) have the ability to reduce and prevent long-term clinical and radiological progression of disease. DMARDs are divided into two types: older non-biologic drugs and the newer biologic therapies. Each of these types of therapy are discussed below, drawing on good recent reviews by Wahezi (2013) and Kessler (2014).

Use of only NSAIDs as therapy is possible in some children with few joints involved and mild

disease activity. There are several different kinds of NSAIDs, but naproxen has become the initial drug of choice for most children with JIA due to availability in liquid preparation, limited dosing schedule and minimal side effect profile. Due to concerns regarding potential heart toxicity and because of the availability of more effective and relatively safe treatments, treatment with any NSAID is currently recommended at the lowest effective dose and for the shortest amount of time possible.

Corticosteroids are potent anti-inflammatory drugs, but due to potential toxicity systemic use is typically reserved for severe cases of certain types of JIA or in low doses as a temporary measure until disease modifying drugs take effect. For cases where few joints are involved but with high disease activity, where there is poor prognosis, or where NSAIDs didn't help enough, corticosteroids can be injected into the joints. Clinical response is typically rapid and may persist for up to 4-12 months.

Methotrexate, a non-biologic DMARD, is the most commonly used DMARD for treatment of JIA. Traditionally a second-line agent (after use of NSAIDs and steroid joint injections), it is now also recommended as initial treatment for patients with high disease activity and/or poor prognosis. There are other non-biologic DMARDs, but they are used much less frequently than methotrexate. Previously used therapies, such as gold, penicillamine and anti-malarials have not been shown to be effective and are now rarely used in the treatment of JIA.

The first class of biologic DMARD approved for use in JIA is directed against tumor necrosis factor alpha, a pro-inflammatory chemical released by macrophages, a type of white blood cell. Current guidelines suggest the use of TNF inhibitors as a second- or third-line agent in patients with JIA who continue to have persistent disease activity despite an adequate trial of initial therapeutic agents. There is concern about potential for increased risk of infection with TNF inhibitors, especially tuberculosis. There is also concern about increased risk of malignancies, though the true magnitude and nature of these risks are not clear, due to the relatively recent history of use of these agents. Another type of biologic DMARD, IL-1 inhibitors, have been shown to be effective for a sub-type of JIA that does not respond well to TNF inhibitors. There are also other biologic DMARDs in addition to TNF inhibitors and IL-1 inhibitors.

Pre-Clinical Research

No preclinical studies using tissue from patients with JIA or using animal models of JIA were found. There is a body of pre-clinical research related to rheumatoid arthritis. But it is now known that the underlying pathogenesis of JIA differs from adult rheumatoid arthritis, as well as among sub-sets of patients with JIA (Wahezi 2015). So, it is unclear to what degree findings from these studies are relevant to patients with JIA. For the sake of completeness, some of those studies are summarized below.

Cox ML, Haller VL, Welch SP. Synergy between Δ^9 -tetrahydrocannabinol and morphine in the arthritic rat. *Eur J Pharm* 2007;567:125-130.

The effects of morphine and THC, separately and in combination, were tested in a rat model of inflammatory arthritis. The model involves administering a killed mycobacterium preparation (Freund's complete adjuvant) into the skin, which results in a generalized inflammatory arthritis. Drug effect was measured by the paw pressure test. In this test the rat's hind paw is exposed to increasing mechanical pressure. The pressure at which the rat withdraws its limb is defined as the pain pressure threshold. A higher threshold is interpreted as a reduction in pain. In this study THC and morphine were found to have a synergistic interaction in pain reduction in both normal rats and the arthritic-model rats.

Smith FL, Fujimori K, Lowe J, Welch SP. Characterization of Δ^9 -tetrahydrocannabinol and anandamide antinociception in nonarthritic and arthritic rats. *Pharmacol Biochem Behav* 1998;1:183-191.

The effect of THC and the endocannabinoid anandamide were tested separately in a rat model of arthritis similar to the model used in Cox 2007. The investigators found that both THC and anandamide reduced pain in normal rats and had a similar pain-reducing effect in arthritic rats. Exploration of impact of a CB1 receptor antagonist showed different results for THC and for anandamide in pain reduction: the pain reduction produced by THC was decreased, but there was no change in the pain reduction produced by anandamide. And naloxone blocked the pain reducing effect of both THC and anandamide. These findings led the authors to conclude, "This study indicates that anandamide and THC may act at different receptor sites to modulate endogenous opioid levels in mechanical nociception."

Krustev E, Reid A, McDougall JJ. Tapping into the endocannabinoid system to ameliorate acute inflammatory flares and associated pain in mouse knee joints. *Arthritis Res Ther* 2014;16:437

The effect of a synthetic inhibitor (URB597) of an enzyme (FAAH) that degrades the endocannabinoid anandamide was tested using a mouse model of inflammatory arthritis. Inhibition of the enzyme results in higher levels of anandamide. Anandamide has anti-inflammatory and analgesic qualities, and it was hypothesized that local administration of URB597 would result in evidence of decreased joint inflammation and pain. The mouse model of inflammatory arthritis was created by injecting an irritating substance (kaolin and carrageenan) into the mouse's right knee joint. White blood cell adherence and blood flow within the joint were measures of inflammation. Hind limb weight bearing and sensitivity to hair filament testing were measures of pain. Hallmarks of decreased inflammation, decreased white blood cell rolling and decreased hyperemia were seen with low doses of URB597, but not with high doses. And injection of URB597 improved both hind limb weight bearing and the hair withdrawal thresholds. This led the authors to conclude, "These results suggest that the endocannabinoid system of the joint can be harnessed to decrease acute inflammatory reactions and the concomitant pain associated with these episodes."

Fukuda S, Kohsaka H, Takayasu A, Yokoyama W, et al. Cannabinoid receptor 2 as a potential therapeutic target in rheumatoid arthritis. *BMC Musculoskelet Disord* 2014, 15:275.

This article describes both studies done on mice and studies done on human tissues:

1. A selective CB2 receptor agonist (JWH133) was tested on mice with murine-model rheumatoid arthritis. Use of JWH133, injected intraperitoneally, resulted in less synovial inflammation and bone destruction than in control mice.
2. CB2 receptor density was found to be higher in humans with RA than in humans with OA
3. Fibroblast-like synovial cells from human RA synovium were cultured and then stimulated with a chemical that stimulates production of inflammatory mediators. Co-administration of JWH133 was found to dose-dependently suppress production of the inflammatory mediators.

Malfait AM, Gallily R, Suariwalla PF, Malik AS, Adreakos E, Mechoulam R, Feldmann M. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. *Proc Natl Acad Sci USA* 2000;97:9561-9566.

Intradermal injection of collagen derived from cows and from mice was injected deep in the skin of mice to induce either an acute (cow collagen) or chronic relapsing (mouse collagen) model of rheumatoid arthritis. At time of symptom development, CBD was administered either by intraperitoneal injection or orally. Mice with injection of collagen and administration of only the vehicle used in administering the CBD served as controls. CBD was found to exert a dose-dependent suppressive action, both on the clinical arthritis and joint damage. Additional study findings suggest that the therapeutic mechanism of CBD includes the suppression of TNF- α , the pro-inflammatory cytokine known to be a major mediator of arthritis.

Clinical Trials

No clinical trials of cannabis or cannabinoids for treatment of JIA were found. One clinical trial of a cannabinoid for rheumatoid arthritis pain has been published (Blake 2006). But, as mentioned above, it is now known that the underlying pathogenesis of JIA differs from adult rheumatoid arthritis, as well as among sub-sets of patients with JIA. So, it is unclear to what degree findings from this study are relevant to patients with JIA. For the sake of completeness, that trial is summarized below.

Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology* 2006;45:50-52.

This was a double-blind, randomized, placebo-controlled study carried out for five weeks in patients diagnosed with rheumatoid arthritis (RA) on a stable regimen of traditional therapy but who did not gain adequate pain relief from standard treatments. A total of 58 participants (12 male/46 female; average age 62.8 years) met the inclusion criteria and 31 were randomized to treatment, while 27 received placebo. The patients were instructed to limit use to evening dosing to prevent daytime intoxication from the Sativex oral spray (2.7mg THC/2.5 mg CBD per 100 μ l actuation [spray]) that was used throughout the trial. The titration schedule started with

one actuation before bed then increased by one actuation every two days, based on patient response, up to a maximum of six actuations per night.

The primary endpoint tested was based on a 0-10 pain scale assessing pain upon movement each morning and comparing the baseline rating to the average of the last 14 days of the trial. Secondary outcomes were pain at rest, sleep quality, morning stiffness, the Short Form McGill Pain Questionnaire (SF-MPQ), and the 28-Joint Disease Activity score (DAS28). All outcomes except morning stiffness and SF-MPQ intensity showed a statistically significant improvement when compared to placebo, including the SF-MPQ “pain at present” rating. Side effects were approximately twice as common in the active treatment group than in the placebo group. All but two of the side effects in the active treatment group were mild or moderate; two patients rated side effects as severe (constipation, malaise). The side effects more common in the active treatment group than in the placebo group were mild dizziness, dry mouth, light-headedness and fall. Three patients withdrew from the study because of side effects – all 3 from the placebo group. There were no serious adverse events in the active treatment group and two in the placebo group.

A recent Cochrane Review of neuromodulators for pain management in rheumatoid arthritis (Richards 2012) included the Blake 2006 study and provides detailed discussion of its strengths and weaknesses. The authors conclude there is weak evidence that oromucosal cannabis is superior to placebo in reducing pain in patients with RA, but that the potential harms from side effects outweigh any modest benefits achieved.

Observational Studies

No published observational studies of cannabis or cannabinoids for the treatment of JIA were found.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of JIA were found.

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