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Relief and Resolution of Fibromyalgia Symptoms with Low Dose Methotrexate – The Origin of Pain is Inflammation and the Inflammatory Response

Sota Omoigui*, Akinkunle Fadare and Chiedu Ogbechie

Division of Inflammation and Pain Research, L.A. Pain Clinic, Hawthorne, California, USA

Abstract

Methotrexate is a Disease Modifying Anti Rheumatic Drug (DMARD) we used in the treatment of patients with severe fibromyalgia symptoms. We present two case discussions of low dose methotrexate treatment resulting in dramatic relief of widespread body pain in patients diagnosed with fibromyalgia. These patients had been refractory to prior treatment with opioids, NSAIDs, anti-seizure medications, anti-depressant medications, pregabalin and corticosteroids. Our case reports endorse Sota Omoigui's theory of pain which states that the origin of all pain is inflammation and the inflammatory response. Low dose methotrexate has unique broad spectrum anti-inflammatory activity that is not found in any other medication. The drug may significantly decrease or resolve generalized body pain associated with fibromyalgia. The use of low dose Methotrexate co-administered with folic acid should be considered as an adjunct to pain medication to help decrease and sometimes eliminate pain and improve other symptoms such as fatigue and disability in fibromyalgia. Limiting factors include the ability of patients to tolerate the medication.

Keywords: Fibromyalgiai; Pain; Inflammation; Methotrexate; Inflammatory response

Introduction

Fibromyalgia is a central nervous system disorder characterized by chronic widespread pain and heightened/painful response to pressure. Other symptoms include debilitating fatigue, sleep disturbance, and joint stiffness. Some patients also report difficulty with swallowing, bowel and bladder abnormalities, numbness and tingling and cognitive dysfunction [1-4]. Fibromyalgia is frequently comorbid with psychiatric conditions such as depression and anxiety and stress-related disorders such as posttraumatic stress disorder [5,6]. Not all fibromyalgia patients experience all associated symptoms. The exact cause is unknown but has been attributed to neurochemical imbalances, including activation of inflammatory pathways in the brain leading to abnormal processing of pain. Psychological, genetic, neurobiological and environmental factors are thought to be involved in its etiology [7-9]. The incidence is estimated to be 2-4% of the population with a 9:1 female to male preponderance.

Disease-modifying anti-rheumatic drugs (DMARDS) such as Methotrexate are a group of otherwise unrelated drugs categorized by their use in curbing the underlying processes that cause some forms of inflammatory arthritis including rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. They can also be used to treat other conditions such as cancer, inflammatory bowel disease, systemic lupus erythematosus (SLE), idiopathic thrombocytopenic purpura, myasthenia gravis and to reduce the risk of transplanted organ rejection. They include a diverse variety of drugs such as Methotrexate, an antifolate that inhibits purine metabolism, Azathioprine (inhibition of purine synthesis) and Leflunomide (inhibition of pyrimidine synthesis. Others include Tumor Necrosis Factor (TNF) inhibitors like Adalimumab, Golimumab, Certolizumab, Infliximab and Etanercept. Other DMARDS include Hydroxychloroquine (Suppression of IL-1 & TNF-alpha, induce apoptosis of inflammatory cells and decrease chemotaxis), Tocilizumab (Interleukin-6 receptor inhibitor), Rituximab (chimeric monoclonal antibody against CD20 on B-cell surface), Abatacept (T-cell costimulatory signal inhibitor), Sulfasalzine (SuppressInterleukin-1 (IL-1) & TNF-alpha, induce apoptosis of inflammatory cells and increase chemotactic factors), D-Penicillamine (Reduce numbers of T-lymphocytes), Cyclosporine (calcineurin inhibitor) Minocycline (5-LO inhibitor) and Gold salts (blocks the release of Prostaglandin E2 and prevents the activation of Nuclear factor kappa-beta). The common mechanism of action of all of these drugs is that they inhibit various aspects of the inflammation and inflammatory response pathway. Many of these drugs have the potential for toxicity and patients require to be closely monitored. Some of the drugs can be used in combination [10]. In appropriate doses these drugs treat symptoms of inflammation and can slow down progressive joint and cartilage destruction.

We utilized the disease modifying anti-inflammatory effect of Methotrexate to reduce and in some cases resolve refractory chronic widespread pain in patients with fibromyalgia. When used in the drug management of fibromyalgia, Methotrexate can ease symptoms of severe pain and distress which have been refractory to every other medication.

Case Report 1–Patient HT

A 47 year old female with a history of fibromyalgia, right hip bursitis, low back pain, osteoporosis and anxiety presented to the clinic for the first time with complaints of generalized body pain and restlessness. Further history revealed that the pain was severe, 10 of 10 on the pain scale, aching, burning, throbbing and spasmic in nature and aggravated by activity and by change in weather. Patient had been disabled and bedridden by her severe pain and was unable to participate in any of the school or social activities of her teenage daughter.

***Corresponding author:** Sota Omoigui, L.A. Pain Clinic, 4019 W. Rosecrans Ave, Hawthorne, California 90250, USA, Tel: (310) 675 9121; Fax: (310) 675 7989; E-mail: medicinechief@aol.com

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The patient had a history of generalized body pain for the previous 12 years, and was first diagnosed with fibromyalgia after she had repeatedly presented in hospital emergency rooms with widespread body pain and fatigue for 2 years. The patient had a family history of rheumatoid arthritis. Her brother, sister and grandmother had rheumatoid arthritis. The patient had been worked up in several hospitals and her blood tests were essentially negative except for a mild leucocytosis which was being followed up by her primary Physician. Her medications at that time included Savella, Lortab (Hydrocodone/Acetaminophen), Lyrica (Pregabalin), Ibuprofen, Arthrotec (Diclofenac/Misoprostol) and Ergocalciferol.

On physical examination, the patient had mild to moderate tenderness in the bilateral shoulders, the right hip, cervical and lumbar spine. There were 18 out of 18 fibromyalgia tender points on digital palpation. Blood work revealed a mild neutrophilia and low vitamin D. The arthritis panel was significant for an elevated C reactive protein (CRP), increased anti-nuclear antibody (ANA) titer and slightly increased C3 complement (Tables 1a and 1b). Other tests including bone density scan were normal. The patient's Savella and Lortab were discontinued and she was placed on Trileptal (Oxcarbazepine) 150 mg tablets - one tablet PO at bedtime, Dilaudid 4 mg tablets - 1 to 2 tablets every 4 hours as needed for pain, no more than 6 tablets a day and MS Contin 15 mg tablets - one tablet PO at bedtime.

The patient was given pain and anti-inflammatory injections as well as intravenous (IV) infusions of Depacon and Magnesium Sulfate at intervals for her generalized body pain but showed only short lived improvement with each intervention. Two months after her first visit she was placed on Methotrexate 2.5 mg tablets - 3 tablets once a week which was subsequently increased to 4 tablets once a week with Folic acid 1 mg tablets – 1 tablet per oral (PO) once a day. The patient stated that she felt better when she took Methotrexate and within 2-3 months of starting on the medication, she reported a dramatic improvement of her generalized body pain. She commented that the pain was significantly reduced, occurring only intermittently instead of constantly and she could get around more, unlike previously when she was bedridden from generalized pain and fatigue. The patient's presenting pain scores improved within 2 months of starting on the medication. About six months after starting on Methotrexate, the patient's fibromyalgia tender points resolved with no tender points (0/18) being elicited on examination during her clinic visits. (See Chart 1, 2, 3, 4) The patient was kept on a maintenance dose of Methotrexate 2.5 mg tablets-4 tablets once a week and now nine months after commencing Methotrexate, her generalized body pain has resolved. She continues to show great improvement in her fibromyalgia symptoms and is seen in the clinic now for only her low back pain.

Case Report 2 - MC

A 50 year old female with a history of fibromyalgia, neck and back pain, bilateral carpal tunnel syndrome, asthma, angina, migraine, sciatic nerve injury, and post traumatic stress disorder presented to the clinic for the first time. She had complaints of migraine, neck and back pain, subsequent to a work related injury several years previously, when the patient fell on her head. Her pain was further aggravated by an ice skating accident 5 years later which caused her to be unconscious for 3 days and interfered with her memory. Further history revealed that the pain was severe, 10 of 10 on the pain scale. The back pain was sharp and stabbing in nature with the migraine being associated with photophobia, phonophobia and nausea. Her back pain was aggravated by prolonged standing or sitting and by cold. The patient had received physical therapy for several weeks with minimal response.

The patient had a history of generalized body pain and a family history of rheumatoid arthritis. Her sister had rheumatoid arthritis. The patient had been worked up in several hospitals and her blood tests were negative. Her medications at that time included Imitrex (Sumatriptan), Motrin (Ibuprofen) and Darvocet (acetaminophen andpropoxyphene).

On physical examination, the patient had moderate to severe tenderness in the entire spine, the greater trochanter of bilateral hips and the temporo-parietalis, frontalis and occipitalis muscles. The patient had sensory deficits in the C6, C7, L3 and L5 nerve roots on the left extremities and motor weakness at 2-3/5 in the bilateral upper extremities and the left lower extremity. There were 18 out of 18 fibromyalgia tender points on digital palpation.

The patient was scheduled for blood work, which was negative except for a low vitamin D level, a mildly raised anti-nuclear antibody titers and an indeterminately elevated anti-double stranded DNA (Tables 2a and b). Cervical and lumbar MRI revealed lumbar and cervical facet arthropathy and neuropathy. The CT scan of the brain was negative.

The patient's medication, Darvocet and Motrin were discontinued and she was placed on Lyrica 75 mg capsules - one capsule PO twice a day, Tolmetin Sodium 400 mg capsules - one capsule PO twice a day, Nexium 20 mg capsules – 1 capsule once a day, Roxicodone (oxycodone) 15 mg tablets - 1 to 2 tablets every 4 hours as needed for pain, no more than 6 tablets a day, Phenergan 25 mg tablets – 1 tablet every 6 hours as needed for nausea and Methadone 5 mg tablets - one tablet PO twice a day.

Tests	Results	Reference range
CRP	23.6 mg/L (High)	<10.0 mg/L
RA	<10 IU/mL	<14 IU/mL
ANA Titer	1:80 (H)	<1/40
DsDNA Autoantibodies	<5.0 IU/mL	<5.0 IU/mL
RPR	Non-reactive	Non-reactive
Hepatitis ABC Panel	Non-reactive	Non-reactive
CCP IgG	Normal < 16 UNITS	< 20 UNITS
SMITH IgG Autoantibodies	Normal < 11 UNITS	< 11 UNITS
SCL-70 IgG Autoantibodies	Normal < 11 UNITS	< 11 UNITS
SS-A and SS-B IgG Autoantibodies	Normal < 11 UNITS	< 11 UNITS
Centromere Autoantibodies	Normal <10 IU/ mL	<14 IU/mL
C4 Serum complement	Normal 42 mg/ dL	16 - 47 mg/dL
C3 Serum complement	185 mg/ dL (H)	90 - 180 mg/dL

Table 1a: Patient HT Arthritis Panel - – Before Methotrexate.

Tests	Results	Reference range
CRP	1.9 mg/L	<10.0 mg/L
RA	<10 IU/mL	<14 IU/mL
ANA Titer	Normal (<7.5 IU/ml)	<1/40
DsDNA Autoantibodies	<5.0 IU/mL	<5.0 IU/mL
RPR	Non-reactive	Non-reactive
Hepatitis ABC Panel	Non-reactive	Non-reactive
CCP IgG	Normal < 16 UNITS	< 20 UNITS
SMITH IgG Autoantibodies	Normal < 11 UNITS	< 11 UNITS
SCL-70 IgG Autoantibodies	Normal < 11 UNITS	< 11 UNITS
SS-A and SS-B IgG Autoantibodies	Normal < 11 UNITS	< 11 UNITS
Centromere Autoantibodies	Normal <7.5 IU/ mL	<7.5 IU/ mL
C4 Serum complement	Normal 36 mg/ dL	16 - 47 mg/dL
C3 Serum complement	Normal 164 mg/ dL	90 - 180 mg/dL

Table 1b: Patient HT Arthritis Panel - – After Methotrexate.

Tests	Results	Reference range
CRP	Normal 8.1 mg/L	<10.0 mg/L
RA	Normal <10 IU/mL	<14 IU/ mL
ANA Titer	1:160 (H)	<1/40
DsDNA Auto antibodies	6.0 IU/mL (Indeterminate)	<5.0 IU/ mL
RPR	Non-reactive	Non-reactive
Hepatitis ABC Panel	Non-reactive	Non-reactive
CCP IgG	Normal < 16 UNITS	< 20 UNITS
SMITH IgG Autoantibodies	Normal < 11 UNITS	< 11 UNITS
SCL-70 IgG Autoantibodies	Normal < 11 UNITS	< 11 UNITS
SS-A and SS-B IgG Autoantibodies	Normal < 11 UNITS	< 11 UNITS
Centromere Autoantibodies	Normal <10 IU/ mL	<14 IU/ mL
C4 Serum complement	Normal 20 mg/ dL	16 - 47
C3 Serum complement	215 mg/ dL (H)	90 - 180

Table 2a: Patient MC Arthritis Panel – Before Methotrexate.

Tests	Results	Reference range
CRP	Normal 8.7 mg/L	<10.0 mg/L
RA	Normal <10 IU/mL	<14 IU/ mL
ANA Titer	1/40 (H)	<1/40
DsDNA Autoantibodies	6.1 IU/mL (Indeterminate)	<5.0 IU/ mL
RPR	Non-reactive	Non-reactive
Hepatitis ABC Panel	Non-reactive	Non-reactive
CCP IgG	Normal < 16 UNITS	< 20 UNITS
SMITH IgG Autoantibodies	Normal < 11 UNITS	< 11 UNITS
SCL-70 IgG Autoantibodies	Normal < 11 UNITS	< 11 UNITS
SS-A and SS-B IgG Autoantibodies	Normal < 11 UNITS	< 11 UNITS
Centromere Autoantibodies	Normal <10 IU/ mL	<14 IU/ mL
C4 Serum complement	Normal 22 mg/ dL	16 - 47
C3 Serum complement	215 mg/ dL (H)	90 - 180

Table 2b: Patient MC Arthritis Panel – After Methotrexate.

The patient was regularly evaluated at approximately 1-2 week intervals but she repeatedly complained of generalized body pain during her clinic visits until she was started on Methotrexate 2.5 mg tablets - two tablets once a week which was gradually increased to 4 tablets once a week, along with Folic acid 1 mg tablets – 1 tablet PO once a day. (See Chart 1, 2, 3, 4) The patient stated that her pain scores dropped to an average of 5/10 from 8/10 after 2-3 months of commencing Methotrexate. The patient continued to improve after several months on Methotrexate as indicated by her decreased pain scores and improved fibromyalgia tender points. The patient however developed mucositis after her first six months on Methotrexate and her maintenance dose was decreased to Methotrexate 2.5 mg tablets - 2 tablets once a week. The patient's mucositis resolved and she continued to be stable on the reduced dose.

Discussion

Sota Omoigui's theory of pain, states that the origin of all pain is inflammation and the inflammatory response. Inflammation occurs when there is infection or tissue injury. Tissue injury may arise from a physical, chemical or biological trauma or irritation. The biochemical mediators of inflammation include cytokines, neuropeptides, growth factors and neurotransmitters. Irrespective of the type of pain whether it is acute or chronic pain, peripheral or central pain, nociceptive or neuropathic pain, the underlying origin is inflammation and the inflammatory response [11-13]. Fibromyalgia (FM) has been around for centuries, when the muscle pains were known as rheumatism, and then as muscular rheumatism. Physicians have written about conditions resembling FM since the early 1800s. Reports of illnesses with strikingly similar symptoms can even be found as far back as around 1500 B.C. Probably, the earliest description of a fibromyalgia-like condition is found in the Biblical account of Job's physical anguish."I, too, have been assigned months of futility, long and weary nights of misery. When I go to bed, I think, `When will it be morning? But the night drags on, and I toss till dawn…And now my heart is broken. Depression haunts my days. My weary nights are filled with pain as though something were relentlessly gnawing at my bones." (Job 7:3-4 and 30:16-17-New Living Translation). In the 19th century, the English army nurse and Red Cross pioneer Florence Nightingale was taken ill with fibromyalgia-like symptoms. She became ill while working on the front lines during the Crimean War (October 1853 – February 1856) and never really recovered. Until her death in 1910, Nightingale was virtually bedridden much of the time, suffering with unrelenting pain and fatigue [14].

History of Fibromyalgia-In the 1600s, Fibromyalgia-like symptoms were first given a name: muscular rheumatism. In 1816, Dr. William Balfour, surgeon at the University of Edinburgh, gave the first full description of fibromyalgia. In 1824, Dr. Balfour described tender points. In 1904, Sir William Gowers coined the term fibrositis (literally meaning inflammation of fibers) to denote the tender points found in patients with muscular rheumatism. In 1972, Dr. Hugh Smythe laid the foundation for the modern definition of fibromyalgia by describing widespread pain and tender points. In 1976, because no evidence of inflammation could be found, physicians changed the name from fibrositis to fibromyalgia (meaning pain in muscles and tissues). In 1981, the first controlled clinical study with validation of known symptoms and tender points was published. In 1987, The American Medical Association recognized fibromyalgia as a real physical condition. In 1990, The American College of Rheumatology developed diagnostic criteria for fibromyalgia to be used for research purposes. The criteria soon began to be used by clinicians as a tool to help them diagnose patients. In the 1990s, the concept of neuro-hormonal mechanisms with central sensitization was developed. In 2002, Dr. Sota Omoigui published his law of pain, stating that the origin of all pain is inflammation and the inflammatory response [11]. In 2007, the U.S. Food and Drug Administration approved the drug Lyrica for the treatment of fibromyalgia. This was the first drug ever to receive FDA approval for fibromyalgia. Since then, two additional medications (Cymbalta and Savella) have also received FDA approval for the treatment of FM.)

Fibromyalgia is an inflammatory state characterized by chronic widespread pain and allodynia (a heightened and painful response to pressure). The pain is associated with other symptoms including debilitating fatigue, sleep disturbance, and joint stiffness. The inflammatory state is accompanied by an altered stress response. This is mainly manifested by high circulating levels of IL-8, high circulating levels of cortisol, and increased systemic levels of Noradrenaline (NA) and extracellular heat shock protein (eHsp72). There is also increased release of inflammatory cytokines (IL-1β, TNFα, IL-6, IL-10, IL-18 and monocytic chemotactic protein (MCP-1)) by monocytes, and enhanced activation of the functional capacity of neutrophils (chemotactic, phagocytic and fungicidal activities) [15]. Fibromyalgia is associated with increased levels of substance P, a pro-inflammatory mediator and pain causative agent. The association of fibromyalgia with inflammation is further evidenced by the frequent occurrence of other inflammatory conditions in those with fibromyalgia, and by the observation that pro-inflammatory cytokines are found at higher levels in the blood and cerebro-spinal fluid (CSF) of fibromyalgia patients. There is evidence

of increased corticotropin-releasing hormone (CRH) and substance P (SP) in the CSF of FM patients, as well as increased SP, IL-6 and IL-8 in their serum. Increased numbers of activated mast cells have also been noted in skin biopsies [16]. Patients with fibromyalgia often have other inflammatory conditions, including migraines, interstitial cystitis and irritable bowel syndrome.

Methotrexate (Rheumatrex, Trexall), an antifolate that inhibits purine metabolism, has been used for decades to treat rheumatoid arthritis, psoriasis and some cancers, including breast, leukemia and lymphomas. Although methotrexate was originally designed as a chemotherapy drug (in high doses), in low doses methotrexate is a generally safe and well tolerated drug in the treatment of certain autoimmune diseases. In its low-dose regimen, Methotrexate blocks the binding of interleukin 1 beta to the interleukin 1 receptor on target cells [17-19]. Methotrexate, through adenosine increase and binding to A3 receptors, promotes the anti-inflammatory IL-1 receptor antagonist (IL-1ra) transcription and its production. Recent studies have shown that Methotrexate treatment generates a less inflammatory type of circulating monocyte in patients with RA treated with low doses, by inhibiting IL-1 and IL-8 secretion and, in parallel, by inducing the IL-1ra (Figure 1) [20,21]. Methotrexate also reduces the production of pro-inflammatory cytokines such as IL-1, IL-2, IL-6 and interferon (INF)-γ, while the gene expression of anti-inflammatory Th2 cytokines like IL-4 and IL-10 is increased - altogether resulting in the anti-inflammatory effect. Methotrexate may also reduce the gene expression of IL-12A independently of corticosteroid application in patients. This impact is further enhanced by a reduction of IL-12A-producing lymphocytes and neutrophils [22]. Methotrexate is also known to suppress TNF activity by suppressing TNF-induced nuclear factor-κB activation *in vitro*, in part related to a reduction in the degradation and inactivation of an inhibitor of this factor, I κBα (inhibitory kappa beta), and mediated also by the release of adenosine [20]. The generation of TNF-α by peripheral blood mononuclear cells is suppressed by an adenosine kinase inhibitor, by virtue of its ability to limit adenosine uptake and metabolism and thereby enhance extracellular adenosine concentration [21]. TNF-α synthesis in T cells and macrophages is suppressed [23]. Serum IL-6 levels have also declined after Methotrexate treatment in RA patients in some studies [24]. Constantin et al. reported that ex vivo treatment of peripheral blood monocytes with methotrexate increased expression of anti-inflammatory IL-4 and IL-10 while proinflammatory IL-2 and interferon-γ expression were decreased, suggesting that the immunoregulatory role of Methotrexate is also targeted at adjusting the balance between Th1 proinflammatory and Th2 anti-inflammatory cytokines [25]. The success of Methotrexate as an antirheumatic agent rests on its many actions that affect a wide variety of the inflammatory response pathway, many of which are mediated by the release of adenosine [26]. In fact, a number of anti-inflammatory effects exerted by Methotrexate seem to be related to the extracellular adenosine increase and its interaction with specific cell surface receptors, with

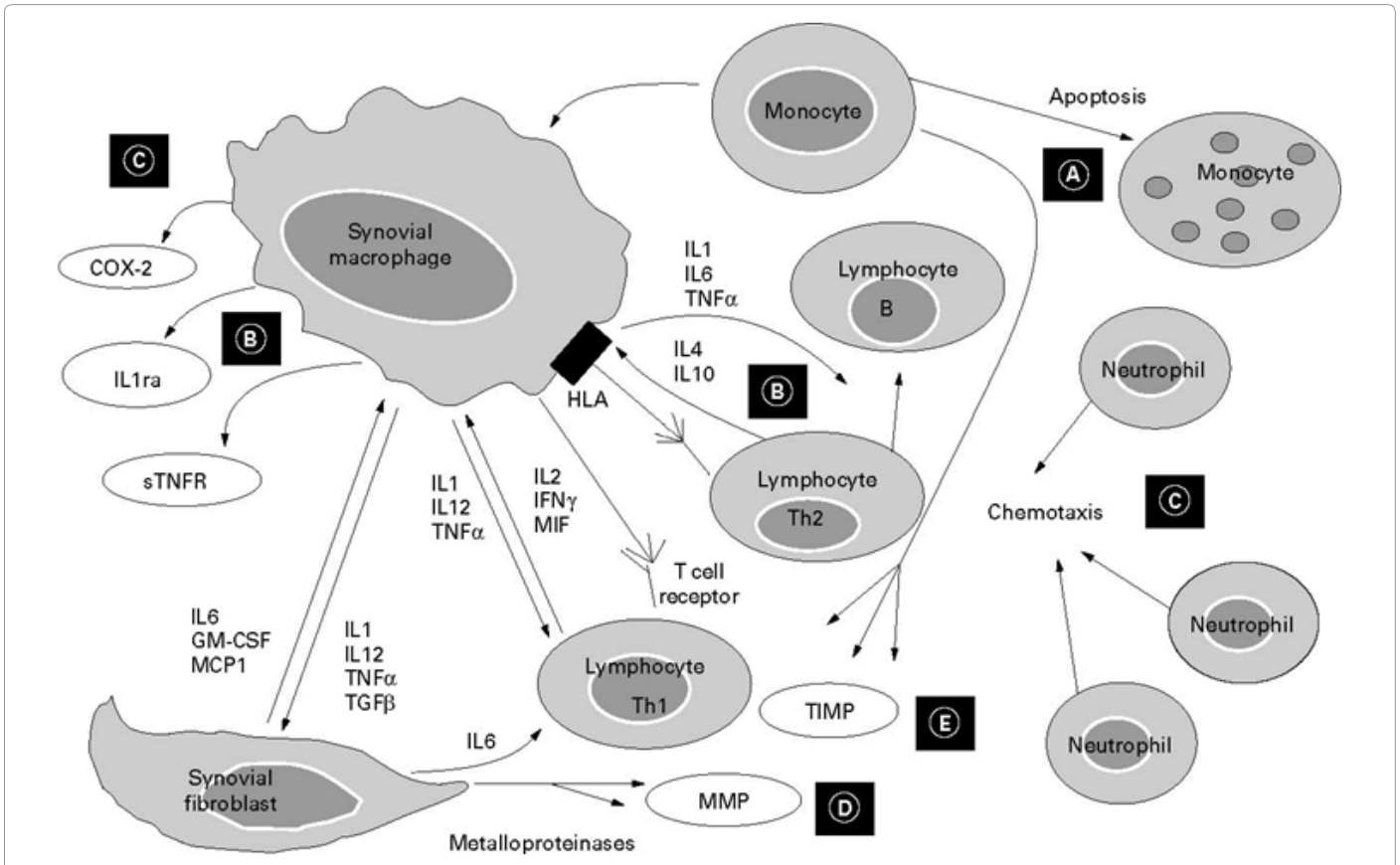

Figure 1: Mechanism of action of Methotrexate [27]. Figure 1 Anti-inflammatory effects exerted by low dose MTX at the level of the synovial tissue in RA. (A) MTX reduces monocytic cell growth and increases their apoptosis. (B) MTX decreases the IL-1 and IL-6 secretion and increases IL-1ra production. At the same time, MTX increases IL-4 and IL-10 gene expression and decreases gene expression of proinflammatory Th1 cytokines (IL-2 and IFNy). (C) MTX seems to exert indirect inhibition of COX-2 synthesis and neutrophil chemotaxis. (D) MTX exerts indirect inhibitory effects (through modulation of cytokines) on synovial metalloproteinase (MMP) production and stimulates their inhibitors (TIMP) (E). MTX = methotrexate; IL-1ra = interleukin-1 receptor antagonist; IFNy= interferon y; COX-2 = cyclo-oxygenase-2; MMP = metalloproteinase; TIMP = tissue inhibitor of metalloproteinase. Used with permission [27].

subsequent inhibition such as IL-8 production by peripheral blood mononuclear cells (PBMC), IL-6 secretion by human monocytes, leucotriene B4 synthesis in neutrophils, and decreased synovial collagenase gene expression [27,28].

Methotrexate is one of the most effective and commonly used medicines in the treatment of several forms of arthritis, psoriasis and other rheumatic conditions. It is also used in the treatment of neoplasms such as Burkitt's lymphoma, osteosarcoma and some leukemias. It is known as a disease-modifying anti-rheumatic drug (DMARD), because it not only decreases the pain and swelling of arthritis, but it also can decrease damage to joints and long-term disability. Methotrexate may be used to treat systemic lupus erythematosus, inflammatory myositis, vasculitis and some forms of childhood arthritis such as juvenile idiopathic arthritis. Improvements in arthritis and other conditions usually are first seen in 3-6 weeks. The full benefit of this drug may not be seen until after 12 weeks of treatment.

The use of low dose Methotrexate may be associated with serious side effects including bone marrow toxicity, hepatotoxicity, renal damage leading to acute renal failure and development of malignant lymphomas. Minor toxic effects, such as stomatitis, malaise, nausea, diarrhea, headaches and mild alopecia, are common but respond to folate supplementation [29,30]. Co-administration with daily folic acid (1 mg PO per day) is required to significantly reduce the incidence of toxicity. Patients on Methotrexate require careful monitoring of liver enzymes, hemoglobin, complete blood count (CBC), and serum creatinine. This should be done two weeks after initiation of treatment and then every eight weeks. More frequent laboratory monitoring may be needed to assess increasing values. Methotrexate is administered once weekly as a single dose or in divided doses given over a 24-hour period. To reduce the incidence of major toxic effects, Methotrexate should never be given in daily doses. Relative contraindications include renal dysfunction, liver disease, active infectious disease and excessive alcohol consumption. Both women and men of reproductive age should use birth control during Methotrexate therapy.

The various biochemical mediators of inflammation (cytokines, neuropeptides, growth factors and neurotransmitters) are present in differing amounts in all pain syndromes and are responsible for the pain experience. Irrespective of the type of pain whether it is acute or chronic pain, peripheral or central pain, nociceptive or neuropathic pain, the underlying origin is inflammation and the inflammatory response. Activation of pain receptors, transmission and modulation of pain signals, neuroplasticity and central sensitization are all one continuum of inflammation and the inflammatory response. Irrespective of the characteristic of the pain, whether it is sharp, dull, aching, burning, stabbing, numbing or tingling, all pain arise from inflammation and the inflammatory response [11-13]. Every pain syndrome has a unique inflammatory profile with a predominance of certain inflammatory mediators. Our current imaging techniques such as MRI, CT-scans, X-rays are structure based and cannot image the inflammatory profiles of pain syndromes. Our current blood tests are not advanced enough to identify all derangements of the inflammatory pathway. Structural imaging studies cannot provide any information on the biochemical mediators causing pain. Presence of a structural defect cannot predict pain and neither can the absence do the opposite. The lack of structural abnormality and negative blood tests is why physicians historically have had a difficulty with the diagnosis of fibromyalgia. In the future, as MRI spectroscopy becomes commercially available, physicians will be able to routinely image the inflammatory mediators.

In order to relieve pain, the end result of any medical or surgical intervention must be a decrease in inflammation and the inflammatory response. This principle also applies to alternative therapies such as physical therapy, aquatic therapy, yoga, hypnosis, music therapy, aromatherapy etc. Medical interventions include medications (including herbal supplements), intravenous infusions, injection and neuromodulation procedures. All interventions that relieve pain do so in different ways that affect the final common pathway - decreasing inflammation and the inflammatory response. The treatment goal of any pain syndrome should be inhibition or suppression of production of the inflammatory mediators and inhibition, suppression or modulation of neuronal afferent and efferent (motor) transmission. A successful outcome is one that results in less inflammation and thus less pain.

Our patients in these two case reports had shown minimal response to various medications including opioids, steroids, anti-depressants, Lyrica (Pregabalin), anti-seizure medications e.g. Trileptal. These medications affect various points of the inflammation and inflammatory response pathways. Nevertheless, the lack of efficacy in our patients is evidence that these medications did not mitigate the inflammatory mediators that caused their fibromyalgia symptoms. Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, tolmetin sodium, indomethacin and ibuprofen, inhibit the enzyme cyclooxygenase and therefore decrease synthesis of inflammatory prostaglandins. Glucocorticoids prevent or suppress inflammation and immune responses when administered at pharmacological doses. At the molecular level, unbound glucocorticoids readily cross cell membranes and bind with high affinity to specific cytoplasmic receptors. This binding induces a response by modifying transcription and, ultimately, protein synthesis to achieve the steroid's intended action. Such actions include inhibition of leukocyte infiltration at the site of inflammation, interference in the function of mediators of inflammatory response, and suppression of humoral immune responses. Corticosteroids inhibit the activation of phospholipase A_2 by causing the synthesis of an inhibitory protein called lipocortin. It is lipocortin that inhibits the activity of phospholipases and therefore limits the production of potent mediators of inflammation such as prostaglandins and leukotriene. Opioids mimic the actions of endogenous opioid peptides by interacting with mu, delta or kappa opioid receptors. The opioid receptors are coupled to G1 proteins and the actions of the opioids are mainly inhibitory. They close N-type voltage-operated calcium channels and open calcium-dependent inwardly-rectifying potassium channels. This results in hyperpolarization and a reduction in neuronal excitability. They also decrease intracellular cAMP which modulates the release of nociceptive neurotransmitters (e.g. substance P). Opioid medications produce pain relief by binding and activating specialized opioid receptors at the site of tissue injury and in the substantia gelatinosa of the spinal cord. Once activated, the opioid receptors inhibit the release of inflammatory mediators such as bradykinin at site of tissue injury and Substance P from C nerve fibers. There is also suppression of the signal traffic in the C fibers and A-delta fibers that carry pain impulses to the spinal cord and brain. Morphine and other opioids also alter emotional processing of painful input by acting on opioid receptors in the limbic and cortical area of the brain [31]. Anti-inflammatory effects of opioids also include inhibition of IL-1 beta converting enzyme (ICE), a proteolytic enzyme that converts the inactive precursor of IL-1 beta to its mature active form [32]. Opioids also inhibit production of inflammatory cytokine mediator's interferon-alpha (IFN-alpha) and interferon-beta (IFN-beta) by lymphocytes and fibroblast cells [33]. Additional mechanisms include inhibition of TNF-alpha production by activated macrophages

[34] as well as induction of apoptosis of immune cell lymphocytes. Opioids also increase release of anti-inflammatory cytokines such as transforming growth factor-beta1 (TGF-beta1) and IL-10 [35].

Subsequent to tissue injury, the expression of sodium channels in nerve fibers is altered significantly thus leading to abnormal excitability in the sensory neurons. Studies have shown that the inflammatory mediators IL-1beta, IL-6, IL-1 receptor antagonist and inducible nitric oxide synthetase are significantly increased when there is excessive nerve traffic as occurs during seizures or persistent pain [36]. Anti-seizure medications such as Oxcarbazepine or Gabapentin decrease pain by reducing the rate of continuing discharge of injured and inflamed nerve fibers. Blockade of sodium channels in nerve cells leads to a decrease in electrical activity and a subsequent reduction in release of the excitatory nerve transmitter glutamate. Anti-seizure drugs also inhibit the initiation and propagation of painful nerve impulses by inhibiting Nitric Oxide Synthetase activity [37]. Nitric Oxide Synthetase is the enzyme responsible for the production of the inflammatory mediator Nitric Oxide. Anti-seizure drugs may also protect nerve cells from free radical damage by Nitric Oxide and/or hydroxyl radicals (OH*) [38]. The anti-seizure drug Sodium valproate has been shown to significantly inhibit immune cell production of TNF-alpha and IL-6 [39]. Sodium valproate suppresses TNF-alpha and IL-6 production via inhibition of activation of the nuclear transcription factor kappa B (NF-kappa B). In immune cells and human nerve cells, NF-kappa B is essential to the expression of inflammatory cytokines. In addition anti-seizure medications reduce painful muscle spasm. Spasticity from different causes is associated with a deficiency of inhibitory nerve transmitters like gamma aminobutyric acid or an excess of excitatory nerve transmitters such as glutamate. Anti-seizure drugs enhance the inhibition of nerve-muscle activity by gamma aminobutyric acid in the spinal cord [40].

The mechanism of action of pregabalin is similar to gabapentin [41]. Pregabalin decreases central neuronal excitability by binding to an auxiliary subunit (α2-δ protein) of presynaptic voltage-gated calcium channels that are widely distributed throughout the central and peripheral nervous system [42,43]. Pregabalin binds to the α_2-δ subunit six times more potently than gabapentin [44] and thereby reduces the release of several neurotransmitters like glutamate, norepinephrine, serotonin, dopamine, and substance P [45,46].

Selective serotonin reuptake inhibitors (SSRIs),Serotonin–norepinephrine reuptake inhibitors (SNRIs) such as Cymbalta (Duloxetine) and Savella (Milnacipran) and tricyclic antidepressants such as Elavil (Amitriptyline), act on serotonin, norepinephrine and dopamine receptors, and have been shown to be immunomodulatory and anti-inflammatory against pro-inflammatory cytokine processes, including the regulation of IFN-gamma and IL-10, as well as TNF-alpha and IL-6. Antidepressants have also been shown to suppress TH1 up-regulation [47-50].

Addition of Methotrexate to the medication regimen of our patients resulted in a dramatic relief of symptoms and the patients resuming activities of daily living that they had previously not been able to do. Patient HT had a dramatic decrease in the C reactive protein level (23.6 mg/L to 1.9 mg/L), and the ANA level became undetectable after Methotrexate (from a titer of 1/80), the serum complement C3 also dropped to within normal limits from slightly elevated at 185 mg/dl to a normal value of 164 mg/dl (normal range of 90-180 mg/dl). See Table 1a and 1b. Patient MC was maintained on a decreased dose of Methotrexate due to mucositis but also showed a fourfold decrease in her ANA titer from 1/160 to 1/40. Patient MC had CRP levels within normal limits before and after Methotrexate (Table 2a and 2b).

Conclusion

We decided to utilize Methotrexate in our patients after they had failed all other classes of medications. These other medications had acted on various aspect of the inflammatory pathway but did not relieve the pain and other symptoms of fibromyalgia. Methotrexate has a broad spectrum anti-inflammatory activity and was able to reduce the inflammation present in these patients with fibromyalgia

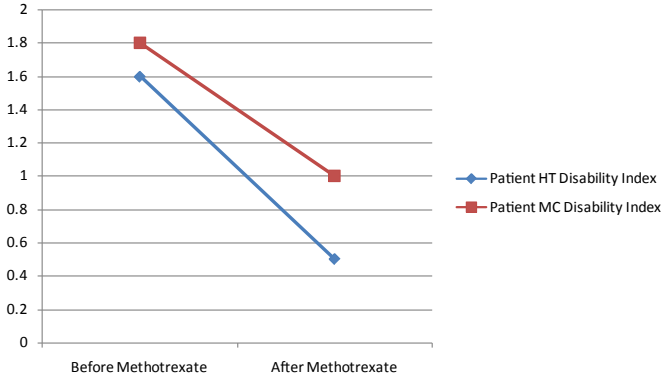

Chart 1: Average Disability Index Graph.

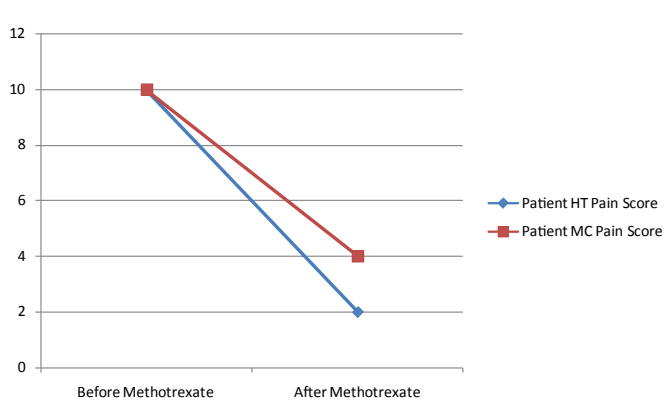

Chart 2: Average Pain Score Graph.

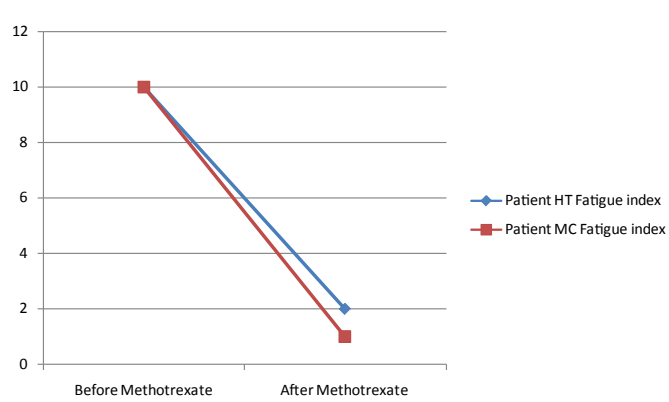

Chart 3: Average Fatigue Index Graph (Stanford Health Assessment Questionnaire).

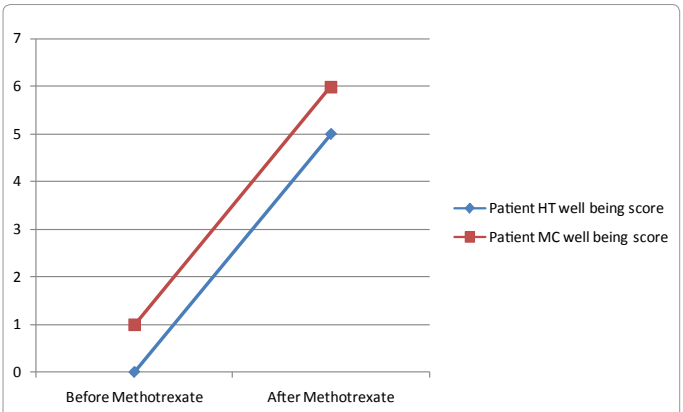

Chart 4: Average Well Being Score Graph.

	Before Methotrexate	After Methotrexate
Patient HT	1.8	1.0
Patient MC	1.6	0.5

Table 3: Disability Scores (Stanford Health Assessment Questionnaire).

	Before Methotrexate	After Methotrexate
Patient HT	10	4
Patient MC	10	2

Table 4: Average Pain Score (Numerical Rating Scale).

	Before Methotrexate	After Methotrexate
Patient HT	10	2
Patient MC	10	2

Table 5: Average Fatigue Index Score (Stanford Health Assessment Questionnaire).

	Before Methotrexate	After Methotrexate
Patient HT	0	5
Patient MC	1	6

Table 6: AverageWell-being Score (Stanford Health Assessment Questionnaire).

Tables 1a, 1b, 2a and 2b. The inflammatory profile varies based upon the pain syndrome. It also varies from one patient to another and at different times in the same patient. Until we are able to image these inflammatory mediators, clinicians must try various combinations of interventions (medications, herbal supplements, diet modification, intravenous infusions, injection and neuromodulation procedures, alternative therapies, surgery) until they find the right combination to decrease inflammation and relieve pain while minimizing side effects. These principles apply to every pain syndrome irrespective of the cause. The successful use of Methotrexate to relieve and resolve fibromyalgia symptoms in these patients was based upon the Omoigui theory of pain that the origin of all pain is inflammation and the inflammatory response. In 1904, Sir William Gowers was correct when he coined the term fibrositis (literally meaning inflammation of fibers) to denote the tender points found in patients with muscular rheumatism. Our case reports demonstrate that low dose Methotrexate can be a very effective treatment for the widespread body pain and heightened responses to pressure that are characteristic of fibromyalgia. The use of Methotrexate to treat inflammation and the inflammatory response in Fibromyalgia can be applied to other intractable pain syndromes. In the L.A. Pain Clinic we have used Methotrexate with success in a few patients with intractable pain arising from conditions as diverse as rheumatoid arthritis, failed back syndrome and severe osteoarthritis. However, more research is needed in this area.

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