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Mast Cell Stabilizer (Ketotifen) in Fibromyalgia: Phase 1 Randomized Controlled Clinical Trial

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Abstract

Objectives—Compared to healthy controls, patients with fibromyalgia (FM) have more mast cells in the skin. Whether mast cells are involved in the pathogenesis of FM is unclear. We sought to determine the effects of a mast cell stabilizer (ketotifen) on FM symptoms.

Methods—Fifty-one FM subjects were randomized to daily oral ketotifen 2 mg BID (n=24) for 8 weeks or placebo (N=27). Mean age of subjects was 51.2 years (standard deviation/SD 8.4); 88% were female and 88% were white; 22% were taking concomitant opiates; and mean pressure pain sensitivity (range 0-20) was 10.0 (0.4). At study entry, the weekly average pain intensity was 6.4 (1.1) and the mean score on the Revised Fibromyalgia Impact Questionnaire (FIQR) was 66.8 (14.0).

Results—We found no statistically significant treatment group differences from baseline in either group for the two primary measures: weekly average pain intensity [ketotifen −1.3 (1.9) vs. placebo −1.5 (1.9), p=0.7]; and FIQR score [−12.1 (19.5) vs. −12.2 (18.1), p=0.9]. No secondary outcome measures (BPI pain intensity, and pressure pain sensitivity) reached statistical significance; results did not differ in the intent-to-treat and completer analyses. Other than transient sedation [6 (28.6%) vs. 1 (4.0%)], ketotifen was well tolerated.

Discussion—The study results question whether skin mast cells play a major role in the pathogenesis of FM. However, given the role of mast cells in peripheral and central nociception, and the minimal side effects of ketotifen, a randomized clinical trial using increasing doses of ketotifen may be warranted.

Keywords

Fibromyalgia; Mast Cell Stabilizer; Ketotifen; Pain

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INTRODUCTION

Despite the enormous societal and personal burden of fibromyalgia (FM) (1;2), its treatment remains suboptimal. Only one-third of patients in randomized clinical trials achieve some benefit from FDA-approved drugs for FM (3-5). Poor treatment outcomes may be explained by the lack of clear understanding of the pathophysiology of FM. In the last 15 years, studies on the pathogenic mechanisms of FM have mostly focused on central sensitization, meaning the enhanced responsiveness of neurons in the central nervous system that leads to pain amplification. In previous studies, FM patients showed increased sensitivity to mechanical, thermal, and electrical stimuli (6;7).

The role of peripheral impulse activity in dynamically maintaining central sensitization has also been proposed as a mechanism for FM (8;9). For example, ongoing afferent input from peripheral sources may contribute to increased tonic nociceptive input into the spinal cord that results in augmented pain processing and central sensitization. In one study, a single lidocaine injection into a trapezius muscle tender point of FM subjects resulted in decreased mechanical hyperalgesia at the shoulder, and reduced distal secondary heat hyperalgesia in the forearm (10). Thus, reductions of impulse input from painful muscle tissue at least partially normalize distal hyperalgesia in FM patients.

Because the skin is the most extensive organ of the human body, ongoing peripheral input to maintain central sensitization may also arise from the skin. Several investigators have reported abnormalities in skin biopsies from FM patients. Kim et al reported increased expression of N-methyl-D-aspartate receptors (subtype 2D) in the skin of patients with FM vs. controls (11) . Littlejohn et al noted a reduced threshold for capsaicin-induced vasodilatation skin response in FM patients compared to healthy controls (12). The detection of interleukin-1b, interleukin-6, and tumor necrosis factor-alpha (TNF-alpha) in the skin of about 30% of FM patients suggests an inflammatory component in their FM-related pain (13). Other immunohistochemical and morphological skin changes in FM include significantly higher values of IgG deposits in the dermis and vessel walls, and a higher mean number of mast cells (14). The percentage of damaged / degranulated mast cells and the individual IgG immunofluorescence scores were correlated (14). More recently, Blanco et al reported increased number of mast cells in 100% of study participants with FM, and mast cells were increased up to 14 times compared to controls (15). With the close functional and anatomical association of mast cells with sensory nerves in the skin (16-18), increased amount of mast cell inflammatory mediators (i.e., histamine, proteases, prostaglandins and leukotrienes) and neurosensitizing molecules (i.e., TNF-alpha, monocyte chemoattractant protein-1, and interleukin-8) (19;20) may contribute to increased tonic input into the central nervous system. To date, no study has examined if the reported increased number of activated skin mast cells is clinically relevant in FM or just an epiphenomenon.

Ketotifen is a mast cell stabilizer used for the management of bronchial asthma and allergic disorders such as atopic dermatitis, allergic rhinitis/conjunctivitis, and chronic urticaria (21-25). Oral ketotifen possesses both anti-mediator and mast cell-stabilizing properties (25). In experimental and clinical conditions, ketotifen reduced antigen-induced mast cell degranulation and decreased the release of histamine, tryptase, and various prostaglandins

(21;25). Ketotifen also stabilizes calcium permeability in mast cell membranes (21;26-28). Additionally, ketotifen reduces TNF-alpha levels (29;30), macrophage-derived chemokines (31), and IL-8 (32).

Given the potential role of skin mast cells in FM pathogenesis, we hypothesized that subjects receiving oral ketotifen would exhibit larger reduction in pressure hyperalgesia and greater improvement in the severity of FM symptoms than subjects who received placebo. Confirmation of the latter hypothesis would support the pathogenic role of skin mast cells in FM.

MATERIALS AND METHODS

Study Design and Procedures

We conducted a 10-week randomized, double-blind, placebo-controlled trial in which participants were randomized either to oral ketotifen or placebo (control). Randomization was stratified by use of opiates at study entry. The study had 3 phases: 1 week for screening and baseline assessment, 1 week for dose escalation, and 8 weeks for either ketotifen or placebo. Outcome assessment was performed at the end of week 1 (baseline) and week 10. During the 1-week screening phase, subjects entered their daily pain scores on a wristwatch monitor (Actiwatch). At the end of the 1-week screening period and after completing baseline assessments, eligible subjects were randomized to oral ketotifen or placebo. During the 1-week dose escalation, subjects received ketotifen 1 mg BID or an identical placebo. We used the SAS statistical package software to randomly assign subjects to the two groups by using a random number generator. Thereafter, subjects received ketotifen 2 mg BID or an identical placebo throughout the 8-week stable-dose phase. The 4 mg daily dose of oral ketotifen is the most commonly used dose for allergic skin disorders and bronchial asthma (21;22;33). Both the active medication and placebo were manufactured (Tiofarma in the Netherlands) with no difference in odor and/or appearance between the capsules containing ketotifen and the placebo.

Subjects were allowed to continue use of centrally-acting medications, including anticonvulsants, opiates, muscle relaxants, and other analgesics. To reduce co-intervention effects, subjects were instructed to stay on the same baseline medication regimen (including dose and frequency) throughout the 10-week study period. To avoid drug effects on pressure pain sensitivity, subjects were asked to avoid any as-needed medications (e.g., hydrocodone, acetaminophen, etc.) for at least 6 hours and any non-steroidal anti-inflammatory agents (NSAIDs) for 48 hours before each outcome assessment. Using a standardized side effects questionnaire medication safety assessments were conducted at the end of the 1-week escalation phase and once weekly until the week 10 outcome assessment visit.

The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Study procedures, including written informed consent, were approved by Indiana University-Purdue University Indianapolis Institutional Review Board.

Eligibility—The inclusion criteria were as follows: (1) met the American College of Rheumatology (ACR) criteria for FM(34); (2) age range: 18-65; (3) had weekly average pain intensity score ≥ 4; and (3) on stable doses of medications for FM for at least 4 weeks.

Excluded were individuals (1) had any history of seizures; (2) had atopic dermatitis or chronic urticaria; (3) had chronic thrombocytopenia; (4) were pregnant or lactating; (5) had active psychoses; (6) had inflammatory rheumatic diseases (e.g., rheumatoid arthritis, lupus, etc.); (7) planned elective surgery; (8) had an ongoing unresolved disability claim; (9) had abnormal clinical laboratory parameters (i.e., elevated SGPT and low platelet count); or (9) currently using anti-allergy drugs (ophthalmic or oral histamine antagonist), leukotriene inhibitors (e.g., montelukast), or prednisone.

Primary Outcome Measures

Weekly average pain intensity—Using the Actiwatch, subjects entered their daily pain scores twice a day for one week at baseline and week 10. Subjects rated their pain intensity on a 0-to-10 numerical rating scale, with 0 = no pain sensation and 10 = the most intense pain sensation imaginable. The weekly average pain intensity was the average of the 14 pain intensity scores obtained during the 7-day assessment window. This composite measure of weekly average pain intensity had shown sensitivity to change in chronic pain intervention studies (35-37). The change in the weekly average pain intensity over time was one of the study's primary endpoints.

Fibromyalgia Impact Questionnaire-Revised (FIQR)—FIQR is a disease-specific measure assessing a number of functioning domains related to fibromyalgia (38). The FIQR has 3 linked sets of domains: FIQ-symptom, FIQ-overall impact and FIQ-function. The FIQR has excellent correlation with the original FIQ (38;39). A higher score (score range= 0-100) indicates greater severity of global symptoms. Change in the FIQR scores from baseline (end of week 1) to week 10 was the second primary endpoint.

Secondary Outcome Measures: The (long form) Brief Pain Inventory (BPI) is a measure of pain with proven reliability and validity across different pain conditions (40;41) . The BPI rates the intensity of pain (BPI pain intensity) and interference of pain with mood, physical activity, work, social activity, relations with others, sleep, and enjoyment of life (BPI pain interference).

The Thumb Pressure Pain Sensitivity Test was used to assess pain sensitivity. The test uses a random direct scaling method to deliver stimuli of varying pressures (5 pressure levels with 3 repetitions at each level) in a random sequence (42-44). Because subjects are unaware of this random sequence, they must attend to, and rate, the stimulus-evoked sensations; therefore, the results are more meaningful (less prone to bias) (45). In this study, discrete 5-second pressure stimuli were applied to the left thumb by a 1-cm^2 hard rubber probe. Using a numeric verbally anchored (0-20) pain scale (42), subjects rated the intensity of evoked pressure-pain sensations. During the screening visit, each subject completed a stair step acclimatization program in which stimulus pressures were applied to determine the individual's pain threshold and tolerance. Based on the pain threshold and tolerance, the software generated 5 stimulus pressures. Three random sequences of these 5 stimulus

pressures (total of 15 pressures) was then applied to the left thumb at baseline and week 10 visits. Higher evoked pain scores on the numeric (0-20) pain scale represent greater sensitivity to pressure pain stimuli.

We also collected data on FM-related medications, depression severity (Patient Health Questionnaire 8-item) (46-48) and body mass index at baseline.

Analysis—Based on feasibility and precision around estimates for designing future studies Julious SA recommends a minimum of 12 evaluable participants per group be considered for pilot studies (49). In our study, we over-recruited 24 subjects per group to account for a potential large dropout rate.

Treatment group comparisons were performed on baseline variables using t-tests for continuous variables and chi-square tests for categorical variables. Efficacy outcomes were analyzed with t-tests comparing ketotifen and placebo groups on change from baseline to 10 weeks. Linear mixed effects models were used for evoked pain scores, since subjects had multiple scores for varying baseline pressure stimuli. These models controlled the within-person correlation due to multiple scores per subject. Baseline pressure stimulus was also included as a covariate. The primary method of analysis was intent to treat analysis. If subjects did not complete follow-up questionnaires, the last observation carried forward (LOCF) was used to impute 10-week scores but only for 5 participants (3 subjects in the active group and 2 in the placebo). Given that the LOCF method is prone to bias (50) results from the completer analyses were also reported. Statistical analyses were performed using SAS version 9.1.

RESULTS

A total of 59 subjects were screened for potential participation in the study. Of these, 51 (86%) met the inclusion criteria, enrolled, and were randomized to ketotifen (n=24) or placebo (n=27). Table 1 (last column) shows the demographic characteristics of the entire cohort. Most screening failures were due to abnormal laboratory results at entry (5/8, 62%). Baseline characteristics were similar across treatment group except for race (Table 1). The active treatment group had fewer white subjects compared to the placebo group (p=0.09).

We found no statistically significant treatment group differences from baseline in either weekly average pain intensity [ketotifen −1.3 (1.9) vs. placebo −1.5 (1.9), p=0.7] or FIQR scores [−12.1 (19.5) vs. −12.2 (18.1), p=0.9] (Table 2). Further, no secondary outcome measures (BPI pain intensity, BPI pain interference, and evoked pain score) reached statistical significance (p>0.5). Results did not differ in the intent-to-treat and completer analyses. Three subjects in the ketotifen group and 2 in the placebo group discontinued the study due to either work schedule conflict or study protocol violations.

Other than transient sedation [6 (28.6%) vs. 1 (4.0%)], oral ketotifen was well tolerated (Table 4).

DISCUSSION

The goal of this randomized clinical trial was to determine if the reported increased number of skin mast cells in FM is clinically relevant or just epiphenomenon. We found that ketotifen, a well-known mast cell stabilizer, did not reduce pain sensitivity, improve clinical pain, or reduce overall FM symptom severity.

Several studies have shown that mast cells play a role in chronic pain, particularly at the visceral level (51-54). For example, the degranulation of mast cells, in close proximity to the nerves innervating the colonic mucosa, is correlated with abdominal pain in patients with irritable bowel syndrome (IBS) (51;52). Ketotifen, but not placebo, decreased abdominal pain, improved quality of life, and increased the threshold for discomfort in IBS patients with visceral hypersensitivity (55).

Despite the common elements of IBS and FM (56-58), in contrast to the IBS study (55), our null findings in this FM study may be explained by one or a combination of the following: (1) mast cells are not major players in the pathogenesis of FM; (2) mast cells play a pathogenic role, but only in a subset of FM subjects who are highly pain sensitive (similar to IBS); or (3) the degree of mast cell stabilization may have been inadequate, since we used a much lower daily dose of ketotifen than in the IBS study (4 mg vs.16 mg) (55). Unfortunately, we lacked funding to collect skin samples to directly assess the effects of ketotifen (e.g., release of histamine and tryptase) on skin mast cells. Given that a third of FM patients report sensitivity or intolerance to medications and/or chemicals (59) we opted to use the lower 4 mg daily dose, a commonly used dose for various allergic disorders (21;22;33). Finally, our null findings also may be attributed to low statistical power. To achieve 80% power and detect a moderate effect size, 64 participants are needed in each group to detect one-half standard deviation difference between groups.

In conclusion, our study shows that ketotifen at 4 mg daily was well tolerated but was not associated with significant changes on pain sensitivity and FM symptoms. The study results question the clinical significance of the previously reported increase number of skin mast cells in the pathogenesis of FM. However, given the epidemiologic and biologic link between IBS and FM (56-58), the role of mast cells in peripheral and central nociception (60), and the minimal side effects of oral ketotifen, investigators should consider conducting adequately powered randomized clinical trials using increasing doses of ketotifen for FM patients, who have limited treatment options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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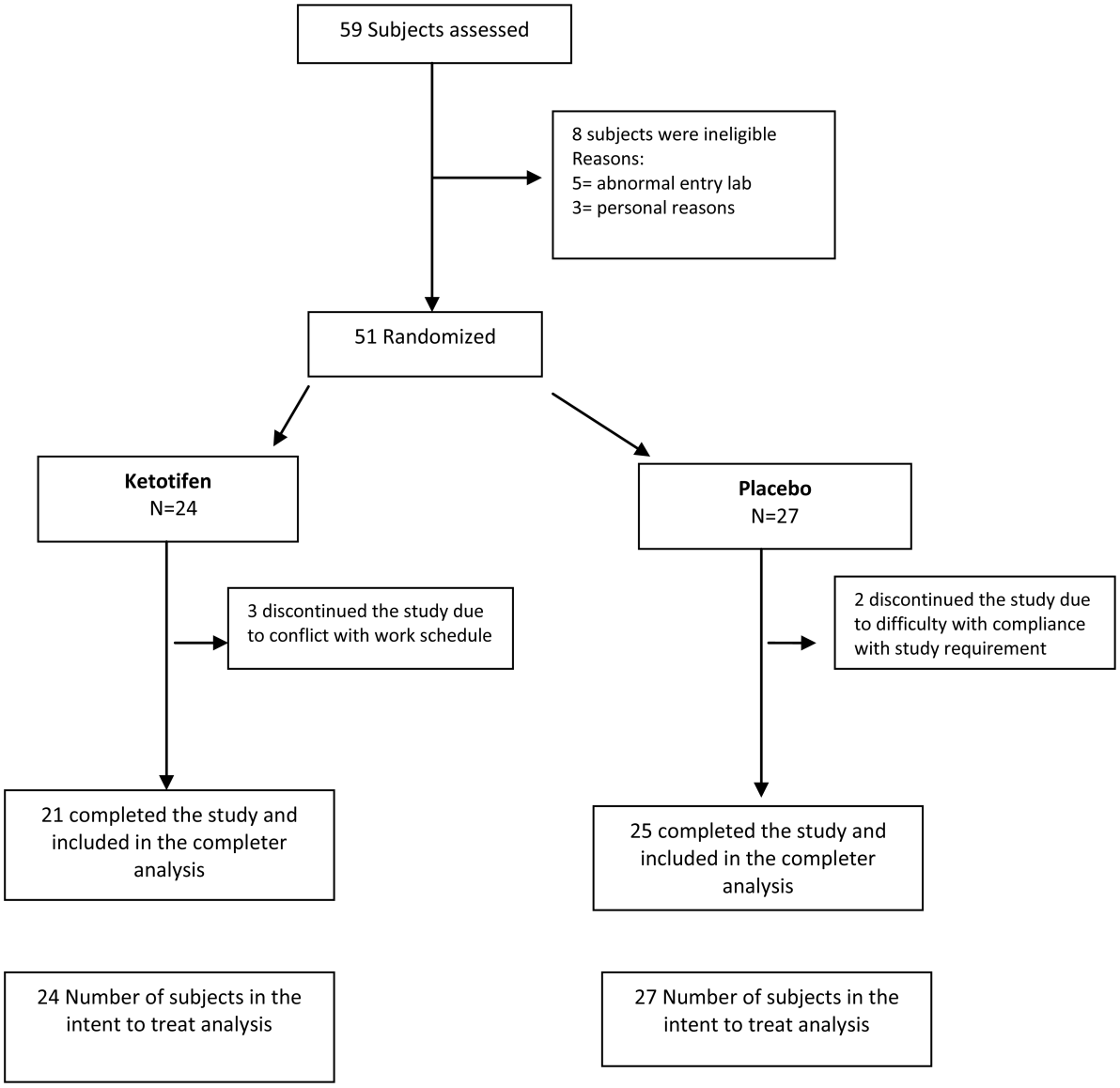

Figure 1.
Flow of Participants in the Trial