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Research paper

Blocking extracellular Galectin-3 in patients with osteoarthritis

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ABSTRACT

Objective: This pilot clinical trial examined the efficacy of blocking extracellular Galectin-3 (Gal-3) with modified citrus pectin (MCP), in patients suffering from knee osteoarthritis (OA).
Methods: 50 patients were randomized in a 1:1 ratio to receive MCP or placebo at a dose of 4 g (5 capsules) twice daily for 12 weeks. Serum Gal-3 levels and OA severity were evaluated at baseline and 12 weeks. Gal-3 levels were detected by sandwich ELISA and OA severity was determined using WOMAC-knee, SF-36, and RAPID3 surveys during these visits. MCP tolerability was assessed by a basic metabolic panel during a week 6 follow up visit.
Results: Patients enrolled in both the MCP treatment and placebo groups shared similar baseline characteristics in OA severity, serum Gal-3 levels, and pain management. Improvement across all surveys was noted independent of supplement or placebo treatment. No significant change in Gal-3 levels were observed in either cohort over the 12-week study.
Conclusion: Treatment of knee OA with a 12-week course of MCP did not significantly improve disease burden compared to placebo.

1. Introduction

Knee osteoarthritis (OA) is a degenerative joint condition marked by cartilage loss, damage to supporting bone (including femur, patella, and tibia), and alterations in ligaments and vascular supply, culminating in a debilitating condition that inhibits proper movement. Repeated mechanical stress and injury contribute significantly to the onset of knee OA. However, clinical evidence suggests that chronic inflammation drives disease progression. [1,2]. Synovitis caused by lymphocyte infiltration of the synovial fluid is associated with advanced stages of OA. [3]. Accompanying synovial lymphocyte infiltration is an increase in inflammatory cytokines and proteolytic enzymes which are capable of damaging cartilage and remodeling the extracellular matrix, promoting the breakdown of knee joint components. [4,5].

Targeted therapies to resolve underlying inflammation are limited in OA, and current treatments such as NSAIDs and corticosteroids are ineffective in long term utilization due to associated side effects and a lack of compelling evidence supporting their benefit. [6]. Comorbidities commonly affecting the elderly population such as diabetes, cardiovascular disease, and gastrointestinal disorders further limit the pharmacologic options to address OA.

Galectin-3 (Gal-3) is a β-galactoside binding lectin with pleiotropic functions, both intra- and extracellularly. When Gal-3 is secreted into the extracellular environment by activated macrophages, induction of growth factor and pro-inflammatory signaling cascades initiate tissue fibrosis in chronic heart failure. [7]. Elevated serum Gal-3 levels correlate with numerous inflammatory and fibrotic conditions including cardiovascular disease, autoimmune diseases, cancer, and OA. [8–11]. Inhibitors of extracellular Gal-3, such as modified citrus pectin (MCP), have been proven to reduce inflammation in preclinical models. [12]. MCP is thought to disrupt the pro-inflammatory pathway through the binding of pectin-derived galactose chains to the carbohydrate recognition domain of Gal-3 in the extracellular space.

In this study, the efficacy of MCP was evaluated in a randomized,

Abbreviations: OA, Osteoarthritis; Gal-3, Galectin-3; MCP, Modified Citrus Pectin.

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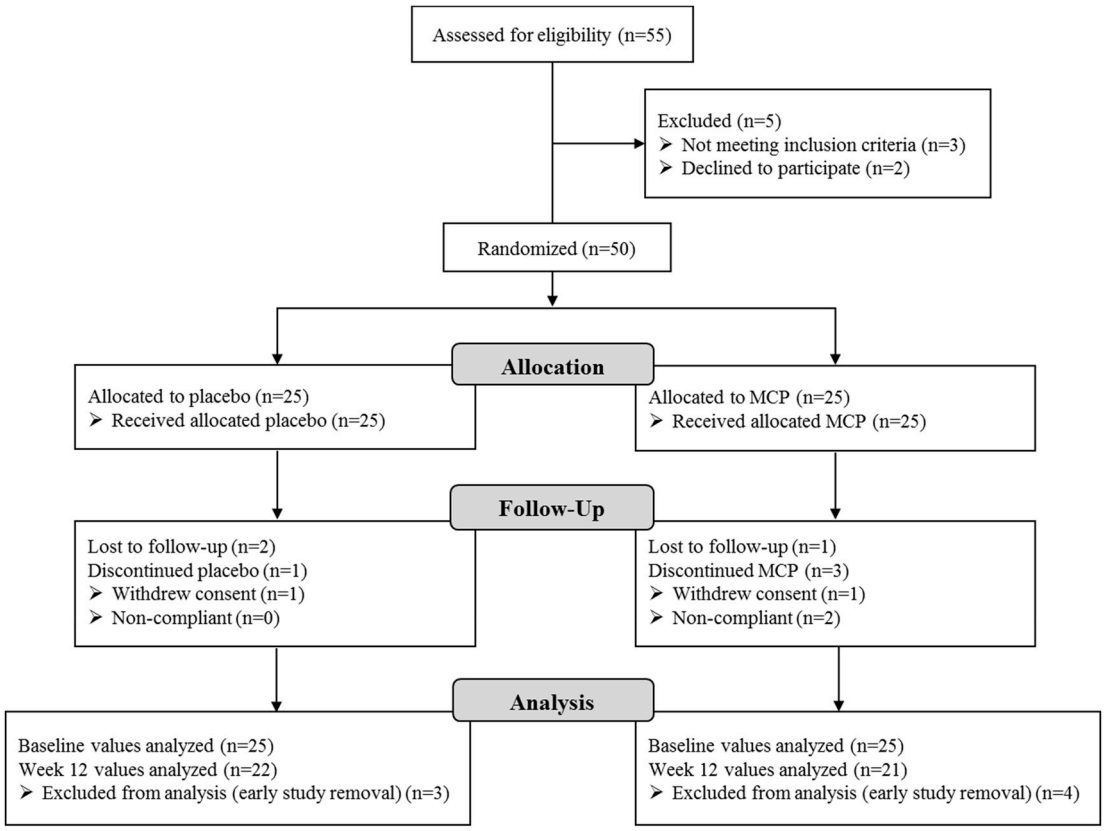

Fig. 1. Clinical trial flow diagram.

double blind, placebo controlled, clinical trial in patients suffering from OA.

2. Materials and methods

A randomized, double blind, placebo controlled, clinical trial was conducted to assess the impact of MCP on knee OA symptoms. Patients were recruited from the rheumatology clinic and general population at Massachusetts General Hospital (MGH) through public posting of trial advertisement from January 2017 to February 2018. Eligibility criteria included patients between the age of 35–80 and those who experienced knee arthritis for at least 50% of the last month with a Kellgren and Lawrence (KL) Grade 2 or 3 classification of OA as determined by radiographic exam. Patients were omitted if they had active fibromyalgia, active inflammatory arthritis, no longer had native knee(s), or a KL Grade of 0, 1 or 4. Patient consent was obtained during the baseline visit after eligibility was confirmed. During this visit, study participants also completed WOMAC-Knee, SF-36, and RAPID3 surveys and a

Table 1
Demographics, baseline and week 12 values.

	MCP			Placebo			
	Baseline	Median	Range	Baseline	Median	Range	p-value
Age (years)	62.2	65.0	47.0–77.0	63.7	63.5	53.0–72.0	0.6
BMI ($kg/m^{2)}$	28.7	29.0	20.1–36.8	27.6	27.0	18.5–43.0	0.1
Gender (% female)	65.0			80.0			0.7
NSAID use (%)	60.0			50.0			1
Tylenol use (%)	20.0			10.0			1
Neuropathic med use (%)	10.0			10.0			1
Supplement use (%)	20.0			10.0			0.5
RAPID3 (nu)	14.1	11.0	3.0–36.3	13.9	12.0	2.0–31.3	0.8
WOMAC-Knee (nu)	32.1	28.0	9.0–86.0	34.8	29.0	7.0–62.0	0.5
WOMAC-Pain (nu)	7.1	7.0	0.0–17.0	7.7	7.0	1.0–15.0	0.6
WOMAC-Stiffness (nu)	2.9	2.0	0.0–8.0	3.8	4.0	1.0–7.0	0.7
WOMAC-Function (nu)	22.1	18.0	7.0–61.0	23.3	21.0	3.0–45.0	0.5
Galectin-3 Level (ng/ml)	6.3	5.8	2.1–11.0	6.5	6.0	2.4–14.3	0.8
	Week 12	**Median**	**Range**	**Week 12**	**Median**	**Range**	**p-value**
RAPID3 (nu)	1.5	1.0	0.0–5.7	1.5	1.0	0.0–4.7	0.7
WOMAC-Knee (nu)	26.0	19.0	3.0–78.0	22.9	18.0	4.0–58.0	1
WOMAC-Pain (nu)	6.0	5.0	1.0–14.0	4.8	5.0	1.0–12.0	0.7
WOMAC-Stiffness (nu)	3.1	3.0	0.0–8.0	2.5	3.0	0.0–6.0	0.6
WOMAC-Function (nu)	16.9	13.0	1.0–57.0	15.5	12.0	3.0–45.0	1
Galectin-3 Level (ng/ml)	9.1	6.8	2.9–17.8	7.8	7.0	1.1–22.0	0.2

Table 2
Change in WOMAC, RAPID3, and Galectin-3.

	MCP			Placebo			p-value
	Baseline	Week 12	Δ	Baseline	Week 12	Δ	
RAPID3 (nu)	14.1	1.5	−12.5	13.9	1.5	−12.5	0.7
WOMAC-Knee (nu)	32.1	26.0	−6.1	34.8	22.9	−11.9	1
WOMAC-Pain (nu)	7.1	6.0	−1.1	7.7	4.8	−2.9	0.7
WOMAC-Stiffness (nu)	2.9	3.1	0.2	3.8	2.5	−1.2	0.6
WOMAC-Function (nu)	22.1	16.9	−5.2	23.3	15.5	−7.8	1
Galectin-3 Level (ng/ml)	6.3	9.1	2.8	6.5	7.8	1.3	0.2

baseline serum was collected to assess Gal-3 level.

MGH research pharmacy randomized 50 patients in blinded fashion to receive either MCP or placebo (25 participants in each group) at a dose of 4 g (5 capsules) twice daily for 12 weeks. A week 6 follow up visit was scheduled to assess adverse events and collect a basic metabolic panel. An additional 6-week course of treatment was dispensed to complete the study. Patients completed the study with a week 12 visit to assess efficacy as reported by WOMAC-Knee, SF-36, and RAPID3 surveys, in addition to a final Gal-3 serum level. Survey results are reported as normalized units (nu).

Chi-squared testing was performed to determine significance of categorical variables. Numerical variables were assessed by t-tests.

3. Results

A description of patient enrollment, group allocation, and the total number of study participants included in the final analysis are provided in Fig. 1. At baseline, there were no significant differences in age, gender, pain management, self-reported OA involvement, or Gal-3 levels between the MCP and placebo groups (Table 1).

Treatment with a 12-week course of MCP significantly improved OA symptoms as demonstrated by WOMAC, RAPID3 scoring (Table 2). However, a robust response with similar improvement occurred in the placebo group. SF-36 improvement was also noted in both groups (data not shown). Gal-3 levels slightly increased in both cohorts over the 12 weeks and no significant differences were detected when comparing MCP and placebo. Side effects were minimal, reported by 19% of patients in the MCP treatment arm and 14% of patients in the placebo arm. One case of hyperkalemia and one case of loose stool were potentially related to MCP treatment.

4. Discussion

The efficacy of MCP on OA symptoms was evaluated by changes in WOMAC-Knee and RAPID-3 score. These patient reported outcome tools reliably gauge physiological burden of disease in OA patients, and their results are used by clinicians when prescribing OA treatment. [13]. Despite improvement across all surveys in the 12-week study, MCP treatment outcomes did not significantly differ from placebo. The small sample size in our pilot study possibly inflated the response to placebo, misrepresenting potential outcomes if this analysis was carried out in a larger population.

Baseline serum Gal-3 levels for the MCP and placebo group were 6.31 ng/ml and 6.51 ng/ml respectively. These values are considerably lower than those detected in patients with other fibrotic conditions. [14–16]. For example, patients who experienced an ST-elevation myocardial infarction (STEMI) 24–48 h before sample collection had an average serum Gal-3 level of 13.1 ng/ml (n = 96). [16]. The low baseline serum Gal-3 levels in this OA patient cohort likely reduced the therapeutic response to blocking Gal-3 function with MCP.

In conclusion, this study failed to show a benefit for knee OA with 12 weeks of supplementation with MCP compared to placebo.

Financial disclosure statement

The authors declare no conflicts of interest.

Trial Registration Number

NCT02800629

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