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Is Phlogenzym Effective in Reducing Moderate to Severe Osteoarthritis Pain in Adults?

Vanessa K. Wood
Philadelphia College of Osteopathic Medicine, vanessawo@pcom.edu

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not Phlogenzym (or ERC) effective in reducing moderate to severe osteoarthritis pain in adults.

Study Design: Review of three randomized controlled trials in the English language from 2001 to 2006.

Data Sources: Two double blind RCTs and one open RCT was found using Cochrane Library EBM Online Database, Ovid Medline, and PubMed Online.

Outcomes Measured: Each of the three studies measured for pain at rest, pain with motion, and restricted function at baseline assessing efficacy using the Lequesne's Algofunctional Index, visual analog scales, and global judgment. The participants were assessed at baseline, during, and at the end of the study.

Results: Two double blind RCTs and one open RCT were included in this review and it was found that phlogenzym did not benefit osteoarthritis symptom improvement. Adverse events were reported in the two double blind RCTs.

Conclusions: The results of the three studies reviewed demonstrated that phlogenzym does have association with minimal osteoarthritis symptom reduction, but does not provide adequate statistical difference between the intervention and control.

Key Words: Phlogenzym, Bromelain, Osteoarthritis, Knee pain

INTRODUCTION

Osteoarthritis (OA) is a chronic and progressive disease, and is the most common form of arthritis affecting both men and women. OA is known as the "wear-and-tear arthritis" due to the degeneration of cartilage and underlying bone.[1] This disease affects over 26 million adults and is a major cause of morbidity and mortality for adults aged 55 years and older.[1] Primary OA is idiopathic and is associated with aging; while secondary OA is associated with trauma, congenital, metabolic, endocrine, neuropathic, and other medical conditions[1]. This condition has a large impact on a person's overall health and quality of life.

Currently there is no cure available for OA and despite research and education efforts, the Center of Disease Control and Prevention (CDC) reports an overall prevalence of 13.9% for adults over the age of 25 years, and 33.6% for age 65 years and older. The health care cost of OA is estimated at $7.9 billion for knee and hip replacements, with the annual disease cost equaling $5,700 and an average of $2,600 per year out-of-pocket expense for individuals[1]. In 1997, patients with a primary diagnosis of osteoarthritis accounted for 7.1 million ambulatory care visits[1]. These numbers are thought to be vastly underestimated due to approximately 39% of people's inability to access needed healthcare[1].

Patients seek treatment from physician assistants and health care providers on a daily basis for pain relief and improvement of quality of life and function. There are few medications that can be prescribed and many are associated with multiple side effects, which have stimulated a market for alternative approaches for joint pain improvement and relief. No cure is currently available for osteoarthritis. Typically a combination of patient education, physical therapy, weight control, medications, and surgery are used to relieve symptoms, minimize disability, and

improve function.[1,2] Phlogenzym may offer a safe alternative to medications and surgery in combination with therapy and weight loss to relieve OA symptoms and improve function.

The specific causes of osteoarthritis is unknown, but is thought to be due to mechanical and molecular events that damage the joint. These events lead to a progressive and gradual onset of changes that result in degeneration of the hyaline cartilage and bone within a joint.[1,2] Symptoms are characterized by joint pain, swelling, and stiffness with radiographic changes. [1,2] The joints that are commonly affected are the knees, hips, hands, and spine. Klein et al. describes the chronic disease as a "degenerative, non-systemic joint disease with clinical manifestation of pain, stiffness, and limitation of movement due to cartilage loss and local inflammation" that primarily affects people older than 55 years and the incidence increases with age.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not Phlogenzym (or ERC) is effective in reducing moderate to severe osteoarthritis pain in adults.

METHODS

A detailed search was performed by the author of this review between December 2011 and January 2012 using the Cochrane Library EBM Online Database and PubMed Online, with the key words "phlogenzym", "bromelain", osteoarthritis", and "knee pain". All three articles selected in this review were published in English and in peer-reviewed journals between 2001 and 2006. Only studies that reported patient-oriented outcomes were accepted by the author and also the relevance of the topic of interest. The population was limited to patients greater than 18 years of age with symptomatic osteoarthritis. Only blinded, randomized, controlled trials that compared phlogenzym and diclofenac were considered. Outcomes of interest included efficacy, tolerability, and safety of phlogenzym as compared to diclofenac in the treatment of

osteoarthritis. Inclusion criteria included osteoarthritis confirmed radiographically, a Lequesne's Functional index ≥10, a WOMAC pain scale of ≥20. Exclusion criteria included patients less than 18 years of age, current or recent use of anti-rheumatic therapy within two weeks, pregnant or lactating women. A full report of demographics of the three final selections are reported and displayed in Table 1. The studies either reported p-values or contained dichotomous data, which could be used to calculate Relative Risk Reduction/Increase (RRR/RRI), Absolute Risk Reduction/Increase (ARR/ARI), and Number Needed to Treat/Harm (NNT/NNH).

Ahktar et al. selected 116 male and female patients with confirmed OA who met the inclusion and exclusion criteria were divided into two groups and assigned to two separate clinical centers in Pakistan. After written consent was obtained, the participants were given the medication and dosing instructions, and compliance was monitor by pill counting at each visit.[3]

Klein et al. selected 90 patients who met the inclusion and exclusion criteria, and were randomized into separate groups at a specialized rheumatology center in Austria. After receiving written, informed consent, patients were provided the assigned medications and dosing instructions. Patient compliance was monitored by pill counting at the 3rd and 6th week visit.[4]

Tilwe et al. selected 50 patients who met the inclusion and exclusion criteria for an open randomized controlled trial. Patients were provided the assigned medications and dosing instructions after written, informed consent was obtained.[5]

Table 1: Demographics of included studies

Study	Type	# pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Akhtar[3] (2004)	Double Blind RCT	116	>18 yrs	OA of one knee confirmed radiographically with a Lequesne's Functional Index ≥10	- Treatment within 2 weeks prior to the study for RA. - Disease causing secondary arthritis. - Patients who had systemic or intra-articular corticosteroid therapy	20	Phlogenzym (ERC) 1 tablet TID
Klein[4] (2006)	Double Blind RCT	90	>20 yrs Avg: 51-53yrs	- Men and women >20 years old, with hip OA lasting at least 3 months and confirmed radiographically or CT. - A WOMAC pain scale of ≥20 and a Lequesne's pain and functional index between ≥10 and ≤14.	- Arthritic or concurrent medical disease. - Abnormal lab results that had potential to interfere with evaluation. - Allergies or hypersensitivities to NSAIDS or an investigational drug. - Subject has received an investigational drug within 30 days of study or received steroids or hyaluronic acid within 2 months	2	Phlogenzym 2 tablets TID
Tilwe[5] (2001)	Randomized Controlled Clinical Trail (open)	50	40-75 yrs Avg: 56-58	Radiograph confirmation of arthroses	- Current or use of anti-rheumatic therapy within 2 weeks - Arthroses secondary to systemic disease or bacterial infection of the joint. - Pregnant or lactating women. - Allergies or hypersensitivities to medicine components. - Steroid or anticoagulant therapy in the last 2 months	0	Phlogenzym 3 tablets BID

OUTCOMES

The primary outcomes measured in all three studies were reports collected from participants regarding pain at rest and motion, and restricted function from baseline.

For primary efficacy criteria, Akhtar et al. used Lequesne's Algofunctional Index (LFI) and a complaint index, which was rated by using visual analog scales (VAS) ranging from 0 = best to 10 = worst, and reports were collected at baseline, 2 weeks, 4 weeks, and 6 weeks. Global efficacy, assessed by both participant and physician, was based on a 5-point scale ranging from 1= very good to 5= poor. Patient and physician both reported a global judgment for safety and adverse events on a 5-point scale ranging from 1 = very good to 5 = poor.[3] Kleine et al. also used Lequesne's Algofunctional Index (LFI) and visual analog scales to assess primary efficacy at baseline, 3 weeks, and 6 weeks. Global judgment for safety was based on a 4-point categorical scale of 1 = bad to 4 = very good.[4] Tilwe et al. evaluated participants for primary efficacy of pain, joint tenderness and swelling at baseline, week 3, and 4 weeks after completing therapy. Participants assessed pain at rest and with movement subjectively as: none, mild, moderate, severe; improvement was determined as any improvement from baseline results[5]. Joint tenderness was determined by physicians by applied pressure and reported as: none, slight, moderate, severe, very severe. Joint swelling was measured by physicians with a tape measure in centimeters, and range of motion was determined using a goniometer. Global judgment was assessed by participant and physician as poor, good, or very good.[5]

RESULTS

The results for two of the studies were reported as dichotomous data, and the continuous data in the Tilwe et al study was converted to dichotomous data.

Akhtar et al. reported the global judgment efficacy as receiving at least a minimum of "good" rating and was resulted as 51.4% and 37.2% in the phlogenzym and diclofenac groups respectively. The confidence interval was determined to be 97.5% for the groups and established p-value <0.05 demonstrating statistical significance during the time period. (Table 2) The adverse events that occurred between the groups were similar at 27.5% (14 patients) for phlogenzym and 23.1% (12 patients) for diclofenac, though majority were related to diarrhea, moderate severity adverse effects did result in five patients withdrawing from the phlogenzym group. One reported diarrhea, edema, and breathing complications; one reported epigastric burning; one reported dryness of mouth and loss of appetite; and one reported lumbosacral muscle spasms – all moderate severe adverse effects occurred within 2 weeks of starting the treatment. The relative risk increase (RRI) was calculated to be 19.0% and the absolute risk increase (ARI) was calculated to be 4.4%, these resulted in a numbers needed to harm (NNH) of 23 patients when using the 1 tablet of phlogenzym three times a day (Table 3).

Klein et al. reported a global judgment efficacy at least of "good" or "very good" and was resulted as 62.8% for phlogenzym and 50.0% for diclofenac. Reports for LFI and complaint index were established at p=0.0025 demonstrating statistical significance during the time period (Table 2). Drug study adverse events that occurred were similar between the phlogenzym and diclofenac groups at 24.4% (11 patients) and 28.9% (13 patients) respectively, majority of the complaints regarded gastrointestinal disruption. Two severe adverse events occurred – one in

each group and were not contributed to the respective medication. The RRI was calculated to be 15.6% and the ARI was calculated at 4.5%, these resulted in a NNH of 23 patients when using two tablets of phlogenzym three times a day (Table 3).

Tilwe et al. reported an average improvement from baseline of 34.5% and 20.9% for phlogenzym and diclofenac respectively. The data is statistically significant with $p < 0.05$ between the groups during the time period evaluated (Table 2). All participants were accounts for at the end of the study and no adverse events were reported; therefore, NNH could not be calculated (Table 3).

Table 2 – Efficacy of Phlogenzym for Osteoarthritis

Study	Phlogenzym: Improvement of symptoms[%]	Diclofenac: Improvement of symptoms[%]	*p*-value	RBI[%]	ABI[%]	NNT
Akhtar, 2004	51.4	37.2	<0.05	19.0	4.4	8
Klein, 2006	62.8	50.0	0.0025	25.6	12.8	8
Tilwe, 2001	34.5	20.9	<0.05	19.0	16	7

% = Values are reported in % from baseline

Table 3 – Adverse effects that result in Numbers Needed to Harm

Study	Phlogenzym[%]	Diclofenac[%]	RRI[%]	ARI[%]	NNH
Akhtar, 2004	27.5	23.1	19.0	4.4	23
Klein, 2006	24.4	28.9	15.6	4.5	23
Tilwe, 2001	0[*]	0[*]	0[*]	0[*]	0[*]

% = Values are reported in %

* = No adverse effects occurred per study

DISCUSSION

Osteoarthritis is a disease that commonly occurs in adults greater than 55 years.[1] The disease is characterized by inflammation caused by progressive loss of cartilage and bony growth due to degeneration or trauma. The goal of treatment is to reduce symptoms, loss of function, and disease progression.[1,2]

Phlogenzym is a compounded medication that consists of three different enzymes: bromelain, rutin, and trypsin.[3,4,5] This medication was designed to target the edema, inflammation, and healing process that occur with osteoarthritis. Bromelain is a plant protease that breaks down plasma proteins and decreases inflammation and edema of the interstitium.[4,5] Trypsin is an animal protease that helps to improve blood flow to the affected area by exerting a fibrinolytic action. Rutin is an antioxidative compound that eliminates radicals and stabilizes vascular endothelium and reduces intravascular space fluid.[4,5]

All three studies consisted of both male and female participants, and used visually matched tablets for both the experiment and controlled medications. Ahktar et al. was the only study that allowed participants to receive physical therapy during the trial period. Each of the studies lasted approximately six weeks, consisted of sample sizes of 120 participants or less, and it was reported that the blinding was not compromised in any of the studies.

CONCLUSION

The studies reviewed demonstrated that phlogenzym does have an association with osteoarthritis pain reduction, but does not provide an adequate statistical difference between the intervention and control. Adverse events did occur during the study and mainly caused

gastrointestinal disturbances in the experimental group. Further investigation is warranted to determine if phlogenzym can improve OA disease. The studies only occurred over a six week period, thus lengthening the time period may provide more accurate data. Including physical therapy during the study period may improve the effectiveness of the drug. By evaluating participants at more frequent intervals may prove to offer a more tightly controlled study. Also, these studies used small populations of participants and did not compare the medication to a placebo. Thus, evaluating a larger population of patients over a longer time period, at more frequent intervals, while comparing the medication to a placebo may determine if phlogenzym is statistically significant in reducing moderate to severe osteoarthritis pain in adults.

References

1. Osteoarthritis. Centers for disease control and prevention website. http://www.cdc.gov/arthritis/basics/osteoarthritis.htm. Accessed 9/20/2012.
2. Pharmacologic therapy of osteoarthritis. UpToDate website. http://ezproxy.pcom.edu:2068/contents/pharmacologic-therapy-of-osteoarthritis?source=search_result&search=osteoarthritis+treatment&selectedTitle=1~150. Accessed 9/20/2012.
3. Akhtar,N.M.; Naseer,R.; Farooqi,A.Z.; Aziz,W.; Nazir,M. Oral enzyme combination versus diclofenac in the treatment of osteoarthritis of the knee--a double-blind prospective randomized study. Clin.Rheumatol., 2004, 23, 5, 410-415, Belgium.
4. Klein,G.; Kullich,W.; Schnitker,J.; Schwann,H. Efficacy and tolerance of an oral enzyme combination in painful osteoarthritis of the hip. A double-blind, randomized study comparing oral enzymes with non-steroidal anti-inflammatory drugs. Clin.Exp.Rheumatol., 2006, 24, 1, 25-30, Italy.
5. Tilwe,G.H.; Beria,S.; Turakhia,N.H.; Daftary,G.V.; Schiess,W. Efficacy and tolerability of oral enzyme therapy as compared to diclofenac in active osteoarthrosis of knee joint: an open randomized controlled clinical trial. J.Assoc.Physicians India, 2001, 49, 617-621, India.