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Is Tanezumab More Effective than a Placebo in Reducing Pain in Patients with Osteoarthritis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not, “Is tanezumab more effective than a placebo in reducing pain in patients with osteoarthritis?”

STUDY DESIGN: Review of three randomized, double-blind, placebo controlled trials from 2012 to 2015.

DATA SOURCES: Three double-blind randomized clinical trials (RCTs) were found using PubMed, and selected based on outcomes measured and relevance to the objective.

OUTCOMES MEASURED: Clinical outcomes of knee and hip osteoarthritis pain were measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale to assess pain before and after treatment with tanezumab and comparison.

RESULTS: All three randomized studies showed treatment with tanezumab was statistically significant (p-value ≤ 0.001) for improvement in pain at 16 weeks after injections. An adverse event was reported in each study.

CONCLUSIONS: Based on the studies reviewed in this paper, the evidence suggest the efficacy of tanezumab for hip and knee osteoarthritis pain is conclusive as an effective treatment.

KEY WORDS: Osteoarthritis, tanezumab, knee pain, hip pain

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, affecting millions of people worldwide. OA is a slowly progressive joint disease typically seen in middle-age to elderly individuals.¹ It causes debilitating pain and can lead to a loss of function in mobility, which eventually decreases an individual's quality of life. OA is characterized by the breakdown of cartilage on the ends of bones, bony changes to the joints, deterioration of tendons and ligaments, and various degrees of inflammation of the joint lining.¹ At least 15 percent of all adults over the age of 60 are believed to suffer from this disorder with females having greater prevalence of osteoarthritis than males.² While the definitive treatment for OA is total joint replacement, patients seek less invasive forms of treatment to relieve their pain, improve their function, and prolong their quality of life. This paper evaluates three randomized controlled trials (RCTs) comparing the efficacy of tanezumab as an oral medication for reducing pain in patients with osteoarthritis.

Osteoarthritis ranks fifth among all forms of disability worldwide.² Hip and knee osteoarthritis represent a significant cause of that disability.² Osteoarthritis pain, swelling, and stiffness make it difficult to perform ordinary tasks at work or at home. When the lower body joints are affected, activities such as walking, climbing stairs and lifting objects become difficult. Medical costs for adults with osteoarthritis are approximately \$2,079 per person per year.³ In 2010, there were 21.7 million ambulatory care visits and over 6.7 million inpatient hospitalizations for people with OA.³ These statistics demonstrate the importance of providing pain relief to patients with OA in efforts to decrease health care visits and health care costs.

Long-term management of osteoarthritis requires a multidisciplinary approach, including the help from physician assistants, to manage symptoms, improve joint mobility and flexibility,

and maintain a healthy weight. OA can affect any joint, but it occurs most often in knees, hips, lower back and neck, small joints of the fingers and the bases of the thumb and great toe.⁴ Several specific risk factors have been identified including obesity and metabolic disease, age, sex, nutrition, smoking, bone density and muscle function.⁴ Aside from non-medical treatments including weight loss, physical therapy, assistive devices, and dietary supplements, there are very few medications that can be used in the management of this disease due to their association with multiple side effects. These medications include acetaminophen, NSAIDs, topical NSAIDs, including capsaicin cream and diclofenac gel, opioids, and joint injections with corticosteroids or hyaluronic acid. Thus, when lifestyle modifications are ineffective and patients have exhausted all the recommended medications, their last option is surgery and not all elderly patients are suitable for that option. Therefore, this paper will be reviewing tanezumab as an alternative medication. Tanezumab is a humanized monoclonal antibody that targets, binds to, and inhibits nerve growth factor (NGF).⁵ NGF increases in the body when there is injury, inflammation or chronic pain. Tanezumab inhibits the NGF and thereby stops pain signals from reaching the spinal cord and brain.⁵ This mechanism is different from that of conventional opioids and analgesics.⁵

OBJECTIVE

The objective of this selective EBM review is to determine whether or not tanezumab is more effective than a placebo in reducing pain in patients with osteoarthritis.

METHODS

Three double-blind randomized clinical trials (RCTs) were selected for this review. These studies consisted of males and females with hip or knee osteoarthritis pain. The intervention was tanezumab 10 mg IV, and comparisons were done between the treatment group receiving

tanezumab and the experimental group who received a comparison drug. The studies measured the efficacy of tanezumab on reducing knee or hip osteoarthritis pain using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale.

All articles were published in peer-reviewed journals between 2012 and 2015, and they were published in English. Key words used during research via PubMed were “tanezumab,” “osteoarthritis,” “knee pain,” and “hip pain.” The articles chosen were based on their relevance to the clinical question and on importance of outcome to the patient (patient oriented evidence that matters). Inclusion criteria for the studies selected required the use of randomized control double-blinded trials and studies published after 2006. Exclusion criteria involved the use of DOE outcome measures. The statistics reported in the selected studies were p-values. Table 1 represents the demographics and characteristics of the included studies.

Table 1- Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion criteria	W/D	Interventions
Brown et al. ⁵ (2013)	RCT	621	32-87	-Unwillingness/inability to take nonopiate pain medications, inadequate pain relief from nonopiate pain medications, or candidacy for intraarticular injections or total hip joint replacement. -WOMAC score of ≥ 4 at screening and ≥ 5 at baseline, and an increase of ≥ 1 from screening to baseline if they had been regularly taking pain medications prior to screening and were required to wash out prior to baseline.	-Pregnant or intent to become pregnant during the study -BMI >39 kg/m ² -Had moderate to severe pain other than that related to OA -Had any condition that could confound OA pain assessment -Had significant cardiac, neurologic, or psychiatric conditions.	10	tanezumab 10 mg IV

Brown et al. ⁶ (2012)	RCT	690	21-92	<ul style="list-style-type: none"> -X-ray taken within the previous 12 months -Kellgren-Lawrence X-ray grade ≥ 2 -At least 1 of the following: unwillingness or inability to take nonopiate medications, inadequate pain relief from nonopiate medications, candidacy for intraarticular injections, knee arthroplasty, or knee replacement surgery. -WOMAC score in the index knee ≥ 4 at screening and ≥ 5 at baseline, and in patients who washed out of regularly taken pain medications after screening, an increase ≥ 1 from screening to baseline. 	<ul style="list-style-type: none"> -Patients who were pregnant or intended to become pregnant during the study -BMI > 39 kg/m² -Patient who had pain syndromes that could confound assessment of pain from OA (e.g. fibromyalgia, systemic lupus erythematosus), or had significant cardiac, neurologic, or psychological conditions 	72	tanezumab 10 mg IV
Schnitzer et al. ⁷	RCT	2700	20-93	<ul style="list-style-type: none"> -Kellgren-Lawrence grade ≥ 2 -BMI ≤ 39 kg/m² -Taking stable oral NSAID (naproxen 500-1000 mg/day or celecoxib 200 mg/day for minimum of 30 days prior to screening, and experiencing at least some analgesic benefit -WOMAC score ≥ 4 at screening -Have at least 70% compliance with study-supplied oral NSAID treatment over at least 14 days directly prior to baseline 	<ul style="list-style-type: none"> -“Similar to other tanezumab trials” -Any abnormality that would preclude continued NSAID therapy, including country-specific restrictive exclusion criteria for naproxen or celecoxib use in subjects with cardiac disease 	376	tanezumab 10 mg IV

OUTCOMES MEASURED

The primary outcome measured in the selected studies were based on pain assessment before and after treatment with tanezumab or comparison drug using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale. All three studies used the WOMAC pain scale for evaluation of pain at baseline (study day 1) and at week 16. This was measured using a numerical rating scale of 0 to 10, in which increasing scores represent greater pain intensity. All three studies provided an adverse event as dichotomous data, reporting the number of patients in both experimental and comparison groups who experienced paresthesias.

RESULTS

In the study by Brown et al.⁵ (2013), efficacy data was based on a modified ITT population (611 patients), which was defined as all patients who were randomized and treated with at least 1 dose of study medication, but which excluded all patients from 1 study site because of significant deviations from good clinical practice and 1 additional patient from another site due to possible unblinding.⁵ Patients were randomized equally to receive intravenous tanezumab 10 mg or a comparison drug. For both groups, study medication was administered at 8-week intervals, and efficacy data was measured at baseline and at week 16. Patient demographics and baseline characteristics were similar across treatment groups, as shown above in Table 1.

At the conclusion of the study, the WOMAC pain scale changed from baseline to week 16, producing statistically significant improvements ($p \leq 0.001$) relative to the comparison. At the start of the study (study day 1), both the experimental group and comparison group had an average WOMAC pain scale score of 7.3. By week 16, the mean change from baseline was -1.62 for the comparison group and -3.37 for the experimental group, producing a p-value of ≤ 0.001 for the experimental group. This is demonstrated below in Table 2.

Table 2 – Statistical outcome measures for patients with osteoarthritic hip pain

	Outcome measured	Scoring system	Baseline	Mean change from baseline	P-value
Comparison	Pain	WOMAC	7.3	-1.62	≤ 0.001
Tanezumab	Pain	WOMAC	7.3	-3.37	

In this study safety data was based on the ITT population, which was defined as all patients who were randomized and treated with at least 1 dose of study medication.⁵ Brown et al.⁵ (2013) demonstrated that 5.1% of the patients in the experimental group experienced paresthesias while 3.9% in the comparison group. This correlates with a NNH of 83, concluding

that for every 83 people treated with tanezumab, 1 more person will experience paresthesias when compared to the control (Table 5 below).

In the study by Brown et al.⁶ (2012), 690 individuals (ITT population) received study medication, however a modified intent-to-treat (mITT) population of 618 was established. mITT population was defined as all patients randomized and treated with ≥ 1 dose of study medication and excluding patients from any study site that was found to have significant deviation from good clinical practices or patients from whom there were possible breaches in study blinding.⁶ Results from analyses performed using the ITT population were consistent with those obtained using the mITT population and led to the same conclusions.⁶ Patients received blinded study medication at 8 week intervals on 3 occasions: baseline (study day 1), week 8 (study day 57), and week 16 (study day 113). Primary efficacy results were measured at week 16.

At the completion of this study, treatment with tanezumab produced significant improvement in pain from baseline to week 16 in primary efficacy measures. Baseline scores for the comparison group and experimental group were 7.1 and 7.0 respectively. The mean change from baseline in the comparison group was approximately -2.5, and in the experimental group it was approximately -3.5, based on the graphical data provided in the study (Table 3). Treatment with tanezumab had a significant improvement in the primary WOMAC pain scale compared to the control with a p-value of ≤ 0.001 .

Table 3 - Statistical outcome measures for patients with osteoarthritic knee pain

	Outcome measured	Scoring system	Baseline	Mean change from baseline	P-value
Comparison	Pain	WOMAC	7.1	-2.5	≤ 0.001
Tanezumab	Pain	WOMAC	7.0	-3.5	

Brown et al.⁶ (2012) provided dichotomous data to calculate NNH on the adverse event of paresthesias due to the treatment. The study demonstrated that 5.1% of the patients in the experimental group experienced adverse events while 1.7% in the comparison group. This correlates with a NNH of 29, concluding that for every 29 people treated with tanezumab, 1 more person will experience an adverse event when compared to control (Table 5 below).

In the study by Schnitzer et al.⁷, participants were randomized by a computer-generated randomization code to either the tanezumab group or the comparison group. Tanezumab or matching comparison was given intravenously at baseline and every 8 weeks for a total of 7 administrations. Efficacy and safety were assessed using ITT populations and results were measured on week 16.

At the completion of this study, it was determined that at the 16-week mark tanezumab resulted in significant greater mean improvement of WOMAC pain compared to the comparison drug with a p-value of ≤ 0.001 . The baseline score for both groups was 6.3, with the mean change from baseline being -1.5 for the comparison group and -2.25 for the experimental group. This correlates with a p-value ≤ 0.001 for the experimental group versus the comparison group.

Table 4 - Statistical outcome measures for patients with osteoarthritic knee and hip pain

	Outcome measured	Scoring system	Baseline	Mean change from baseline	P-value
Comparison	Pain	WOMAC	6.3	-1.5	≤ 0.001
Tanezumab	Pain	WOMAC	6.3	-2.25	

Schnitzer et al.⁷ demonstrated that 7.2% of the patients in the experimental group experienced an adverse event while 3.1% in the control group. This correlates to a NNH of 24, concluding that for every 24 people being treated with tanezumab, 1 more person will experience an adverse event of paresthesias when compared to control (Table 5).

Table 5 – Statistical data on the adverse event in each study

AE: Paresthesias	Control event rate (%)	Experimental event rate (%)	Relative risk increase (RRI)	Absolute risk increase (ARI)	Number needed to harm (NNH)
Brown et al. ⁵ (2013)	3.9	5.1	0.31	0.012	83 patients
Brown et al. ⁶ (2012)	1.7	5.1	2	0.034	29 patients
Schnitzer et al. ⁷	3.1	7.2	1.3	0.041	24 patients

DISCUSSION

The results above demonstrate a benefit to the use of tanezumab in patients with knee or hip osteoarthritis pain. The p-value for the treatment of tanezumab in all three studies are ≤ 0.001 indicating that there is significant improvement in pain after using tanezumab. The NNH for Brown et al.⁵ (2013), Brown et al.⁶ (2012) and Schnitzer et al.⁷ are 83, 29 and 24 respectively, indicating that a large number of people can be treated with tanezumab before the adverse event of paresthesias occur (Table 5). Even so, the adverse events reported were not consistent with progressively worsening peripheral nerve damage with tanezumab treatment leading to peripheral polyneuropathy. Evidence from neurologic evaluations of patients reporting adverse events revealed symptoms were associated with focal mononeuropathy, such as carpal tunnel syndrome, that was preexisting or possibly aggravated by tanezumab treatment.^{5,6,7}

There is a limitation noted in the study by Schnitzer et al.⁷ that should be discussed. During this study, the FDA placed all clinical studies of tanezumab on clinical hold due to unexpected adverse events initially described as osteonecrosis that required total joint replacement. The primary efficacy objectives of this study were not impacted by the clinical hold, however assessment of long-term efficacy (beyond 16 weeks) was limited.⁷

It is important to mention that the title of this systemic review is incorrect. The word “placebo” was used in the title of this review when in fact tanezumab has been compared to both placebos and an NSAID in the RCTs selected for this review. In the studies by Brown et al. (2012 and 2013) the efficacy of tanezumab for reducing pain is compared to placebos. In the study by Schnitzer et al. the efficacy of tanezumab for reducing pain is compared to Naproxen. Therefore, the title of this review is incorrect and must be corrected and generalized so it states that tanezumab has been compared to comparison drugs.

CONCLUSION

The results of this systematic review suggest that tanezumab is more effective than comparison drugs in reducing pain in patients with osteoarthritis of the knee or hip. The p-value in each study revealed statistical significance in the use of tanezumab when compared to the comparison drugs, and the NNH calculated in each study demonstrated little adverse events. However, paresthesias can be relatively bothersome to live with as an adverse event from treatment with tanezumab. Therefore, future study populations should consist of patients with little to no medical histories that could predispose those patients to findings suggestive of neuropathy during the study. This could help determine if the adverse event of paresthesias is related to treatment with tanezumab.

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