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Is Valdecoxib an Effective Treatment Option to Improve Pain in Adults with Diagnosed Osteoarthritis of the Hip or Knee?

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not Valdecoxib is an effective treatment option to improve pain in adults with osteoarthritis of the hip or knee.

STUDY DESIGN: This review consists of three randomized control trials; two were published in 2002 and the third in 2006.

DATA SOURCES: Sources were studies comparing groups taking Valdecoxib 10mg QD to placebo, which were found via Pubmed, MEDLINE, Ovid, and Cochrane databases.

OUTCOMES MEASURED: The three articles measured various outcomes: pain improvement, stiffness, physical improvement, adverse effects, and onset of analgesia during acute pain flare. Outcomes were measured via the Patient's Assessment of Arthritis Pain- Visual Analog Scale (PAAP-VAS), WOMAC osteoarthritis, Patient's (PaGAA) and Physician's (PhGAA) Global Assessment of Arthritis.

RESULTS: Kivitz et al found that Valdecoxib 10mg & 20mg daily doses were similar in efficacy and both were superior to placebo. Valdecoxib 5mg was not found to be superior to placebo.[5] Makarowski et al also found that Valdecoxib 5mg and 10mg QD were superior to placebo. They also found that Valdecoxib 10mg QD was superior in efficacy to Valdecoxib 5mg QD.[6] Moskowitz et al found that patients had both a significant improvement in pain at 3 hours with Valdecoxib as compared to placebo, and a statistically significant increase in percentage of patients with analgesia after 4hrs compared to placebo.[7]

CONCLUSION: These three randomized control trials all concluded that Valdecoxib is superior to placebo in doses of at least 10mg as compared to placebo. Further studies should review safety of Valdecoxib in a risk/benefit analysis to provide useful conclusions about the continued use of it for treatment of osteoarthritis.

KEY WORDS: "Osteoarthritis", "Valdecoxib"

INTRODUCTION

Osteoarthritis is a very common condition in the adult and older populations in the US. Although there are with various forms of treatment focused on symptom improvement, there is currently no cure for OA.[1] Also known as degenerative joint disease, OA is the most common form of arthritis, classified as Idiopathic or Secondary. Osteoarthritis is usually diagnosed by symptomatology and radiographic findings, most commonly affecting the hips, knees, hands, and feet.

In the United States, osteoarthritis affects 13.9% of adults 25 years and older and 33.6% of those over 65 years.[1] In 2005 it was estimated that 26.9 million US adults were affected by OA. Additionally, in 1997 it was estimated that approximately 409,000 hospitalizations occur annually with osteoarthritis as the principal diagnosis. Osteoarthritis is the most common cause of disability in elderly patients in the developed world.[2] OA is not only affecting thousands of patients annually, it is also very costly. Job-related osteoarthritis costs approximately $3.4-13.2 billion per year, and it was estimated that $7.9 billion was spent on hip and knee replacements in 1997.[1]

Specific causes of OA are unknown, but it is believed to be a result of both mechanical and molecular events in the affected joint.[1] OA is characterized by focal and progressive loss of hyaline cartilage as well as bony changes like osteophytes, bony sclerosis and joint space narrowing.[1] Patients often experience joint pain, stiffness, and loss of ADLs due to osteoarthritis.

Initial treatment regimens include moderate physical activity, weight loss, and use of assistive devices.[3] Pharmacologic treatments typically start with oral acetaminophen for mild disease, and then progress to oral NSAIDs of various strengths including selective COX-2

inhibitors.[3] Diclofenac—a topical NSAID—has also shown some efficacy in knee and hand OA.[3] Other treatment options include intra-articular injections of corticosteroids or sodium hyaluronate.[3] The only curative option for hip and knee arthritis at this point is surgical replacement of the joint, which has many limitations including cost, lifespan of the replacement joint, and patient's ability to undergo major surgery.[3]

Chronic NSAID use has various side effects including GI upset and ulceration, so it has been proposed that COX-2 specific inhibitors such as Valdecoxib may be equally as effective without the adverse affects of non-selective NSAIDs.[4] Various studies are looking at the safety and efficacy of COX-2 specific inhibitors for osteoarthritis patients since their introduction.[4] Although Valdecoxib has recently been pulled off the market, it is important still to look at the effects of all different COX-2 inhibitors to make improvements for the future.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not Valdecoxib is an effective treatment option to improve pain in adults with osteoarthritis of the hip or knee.

METHODS

The three articles used in this selective EBM review were found via Ovid, Medline, Pubmed, and Cochrane databases. All articles selected were published in English in peer-reviewed journals between 2002 and 2006, using the keywords "Valdecoxib" and "osteoarthritis" to search the above mentioned databases. Inclusion criteria for the studies selected require the use of patient oriented outcomes (POEMs), RCT's, studies published after 1996, and those evaluating efficacy of Valdecoxib. Exclusion criteria involved the use

of DOE outcome measures, studies that looked at pediatric populations, and those that only looked at safety profiles of Valdecoxib.

All three studies were double blinded, randomized controlled trials looking at adult populations over the age of 18 with diagnosed osteoarthritis of the hip or knee. The outcomes measured in these studies were efficacy of Valdecoxib for the treatment of osteoarthritis of the hip or knee. Each study utilized an intervention of Valdecoxib po daily, although other interventional drugs were used in comparison as well. The comparison group in every study reviewed was one that received placebo. Two of the studies evaluated alleviation of pain with consistent daily use of Valdecoxib, and the third study evaluated onset of analgesia during acute pain flare with the addition of Valdecoxib. A summary of statistics includes numbers needed to treat (NNT), mean change from baseline, confidence interval (CI), and p-values. The demographics of included studies can be found in Table 1.

Table 1: Demographics & Characteristics of included studies

Study	Type	# pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W / D	Intervention
Kivitz[5]	RCT	1,016	59.8 ± 10.9 years	Ambulatory adults with mod-severe OA of the knee Pts with baseline scores >40mm on PAAP-VAS & "poor" or "very poor" on PaGAA and PhGAA	Pts with inflammatory arthritis, gout, pseudogout, paget's, or any other chronic pain syndrome; Pts with OA of hip ipsilateral to Index Knee (IK), severe anserine bursitis, acute joint trauma, complete loss of articular cartilage on IK	269	Randomized to control (placebo) or experimental groups receiving Valdecoxib 5mg, 10mg, 20mg QD, or Naproxen 500mg BID
Maka-rowski[6]	RCT	467	62.4 ± 11.8 years	Pts with symptomatic OA of the hip: pain + 2 of the following: ESR<20mm/ hr, radiographic osteophytes, joint space narrowing; Baseline PAAS-VAS ≥ 40 PaGAA or	Pts with inflammatory arthritis, gout, pseudogout, paget's, or any chronic pain syndrome; Pts with OA of the knee ipsilateral to the Index Hip (IH), symptomatic trochanteric bursitis, or acute joint trauma of IH; Pts with complete loss of articular cartilage on WT-bearing xray of IH Pts with active GI disease, GI tract ulceration within 30 days of study medication, or significant bleeding	209	Randomized to control group (placebo) or experimental groups receiving Valdecoxib 5mg or 10mg QD, or Naproxen 500mg BID

				PhGAA "poor" or "very poor"	disorder		
Mosko -witz[7]	RCT	530	63.9 ± 9.2 years	≥45 years old with knee OA; Functional capacity classification I or II; OA in flare state at baseline assessment: defined as ≥3 of the following: PAAP-VAS ≥40mm, Lequesne OA severity index ≥7, PaGAA or PhGAA of "poor" or "very poor"	Inflammatory arthritis or acute joint trauma of Index Joint (IJ); Hx of malignancy, active GI disease, chronic or acute renal/hepatic/ coagulation disorder; Abnl screening lab values >1.5x the upper limit for AST or ALT, serum creatinine ≥2.0, or other lab abnormality within 14 days of baseline assessment; Pts who received oral, IM, or intra-articular corticosteroids within 8 weeks, or intra-articular hyaluronic acid in IJ with in 6 months of study drug admin; Pts who have taken anticoagulants, NSAIDs, COX-2 specific inhibitors or analgesic agents	95	Randomized to control group (placebo) or experimental groups receiving Valdecoxib 10mg QD or Rofecoxib 25mg QD

OUTCOMES MEASURED

The outcomes measured in the reviewed studies are all Patient Oriented Evidence that Matters (POEMs); in this case pain improvement and onset of analgesia. Kivitz et al[5] measured pain improvement using the Patient's (PaGAA) and Physician's (PhGAA) Global Assessment of Arthritis, Patient's Assessment of Arthritis Pain- Visual Analog Scale (PAAP-VAS), and Western Ontario & McMaster Universities (WOMAC) OA indexes reported by patients and physicians. In this study, baseline measurements were made for comparison and then subsequent assessments were done with each tool at 2, 6, and 12 weeks. Analysis was done by least square mean (LSM) change from baseline and reported as statistically significant based on p-values and confidence intervals. Makarowski et al[6] had a similar study design for reporting efficacy; they measured mean changes from baseline using PaGAA, PhGAA, PAAP-VAS and WOMAC scales to report pain improvement. Again, LSM changes from baseline were reported at 2, 6, and 12 weeks and analyzed via p-values and confidence intervals compared to placebo. Moskowitz et al[7] measured onset of analgesia during an acute pain flare, defined as ≥3 of the following: PAAP-VAS ≥40mm, Lequesne

OA severity index ≥7, PaGAA or PhGAA of "poor" or "very poor." Patients who met criteria for the study were asked to walk for 10 minutes prior to baseline measurements using the WOMAC scale. Pain intensity (PI) on a visual analog scale (VAS) was then measured at 0.5, 1.0, 1.5, 2, 3, 4, 5, and 6 hours after administration of study medication, each following a 10-minute walk. Statistical analysis of the data was based on percentage of patients with "analgesia" at each time interval, defining onset of analgesia as a 25% reduction in PI from baseline.

RESULTS

In the study done by Kivitz et al,[5] 1019 patients were recruited from 85 different primary care and rheumatology specialty settings across the United States and Canada. Patients were randomized into treatment groups and self-administered oral medications.[5] Patients and researchers were blinded during this process.[5] For all three studies, statistical analysis was done on the intent to treat (ITT) population, which included those who randomized and had taken at least one dose of study medication. This particular study only included continuous data that could not be converted into dichotomous data.

Three patients did not take any study medication and therefore were not included in efficacy analysis. Of the 1016 remaining patients, 269 withdrew before the end of the study. Using the Fisher exact test, it was calculated that 20% of the withdrawals were due to treatment failure.[5] It is noted that patients in the placebo group withdrew at a significantly faster rate than those in active treatment groups. There were no significant differences in withdrawal rates across the four active treatment groups.[5]

The PaGAA and PhGAA assessments are measured on a 5 point categorical scale where 1=very good, 2=good, 3=fair, 4=poor, and 5=very poor. PAAP-VAS is a patient

questionnaire measured on a scale of 1-100mm where 0=no pain and 100=most severe pain. The WOMAC indices include pain, stiffness, physical function, and composite; data was reported for stiffness (scale 0-8) and composite (scale 0-96). In order to establish statistical significance, the Hochberg procedure was used for Valdecoxib 10mg and 20mg to calculate p-values. A p-value of 0.05 was used for Valdecoxib 5mg and placebo.[5]

The LSM change for PaGAA was significantly improved at most assessments for 10mg and 20mg of Valdecoxib QD compared to placebo.[5] Valdecoxib 5mg QD did not reach statistical significance.[5] Using the PhGAA, significant improvements were observed at all doses and assessments. The PAAP-VAS displayed a significant improvement in pain for Valdecoxib 20mg QD, while 10mg and 5mg daily doses were significantly better than placebo at all assessments except for week 12.[5] The experimental study treatments improved WOMAC indices compared to placebo at 2, 6, and 12 weeks. Valdecoxib 20mg produce a statistically significant change in all WOMAC scores compared to placebo. Valdecoxib 10mg daily only showed a statistically significant improvement in indices at week 2.[5] Data is shown in Table 2.

Table 2: Kivitz et al[5] least square mean changes from baseline in PaGAA, PhGAA, PAAP-VAS, and WOMAC indices.

	Placebo (n=205)	Valdecoxib 5mg QD (n=201)	Valdecoxib 10mg QD (n=205)	Valdecoxib 20mg QD (n=201)
PhGAA[§]				
Baseline Mean	4.10	4.07	4.09	4.09
LSM change				
Week 2 (CI)	-1.04 (-1.16, -0.91)	-1.31[‡] (-1.44, - 1.19)	-1.37[‡] (-1.50, -1.25)	-1.42[‡] (-1.54, - 1.29)
Week 6 (CI)	-1.22 (-1.35, -1.08)	-1.44[*] (-1.58, - 1.31)	-1.50[†] (-1.63, -1.36)	-1.41[*] (-1.55, - 1.28)
Week 12 (CI)	-1.22 (-1.36, -1.08)	-1.43[*] (-1.58, -1.28)	-1.52[†] (-1.67, -1.38)	-1.45[*] (-1.60, -1.31)
PAAP[£]				
Baseline Mean	71.20	71.41	72.41	72.54
LSM change				
Week 2 (CI)	-21.19 (-24.80, -	-28.46[†] (-32.11, - 24.82)	-30.21[‡] (-33.83, -26.59)	-32.07‡(-35.73, -

	17.58)			28.41)
Week 6 (CI)	-23.92 (-27.72, -20.12)	-30.81† (-34.65, - 26.97)	-29.85* (-33.67, -26.04)	-32.28† (-36.13, -28.42)
Week 12 (CI)	-25.97 (-30.02, -21.92)	-31.33 (-35.42, - 27.24)	-30.41 (-34.47, -30.41)	-32.70* (-36.81, -32.70)
WOMAC OA, Stiffness¶				
Baseline Mean	4.84	4.87	4.91	4.73
LSM change				
Week 2 (CI)	-0.78 (-0.98, -0.57)	-1.03 (-1.24, - 0.82)	-1.20† (-1.41, -0.99)	-1.24† (-1.45, -1.03)
Week 6 (CI)	-1.04 (-1.27, -0.82)	-1.25 (-1.48, - 1.02)	-1.42* (-1.65, -1.20)	-1.43* (-1.66, -1.20)
Week 12 (CI)	-1.12 (-1.36, -0.89)	-1.33 (-1.57, - 1.09)	-1.41 (-1.65, -1.17)	-1.46* (-1.70, -1.22)
WOMAC OA, Composite#				
Baseline Mean	53.49	53.03	54.73	53.42
LSM change				
Week 2 (CI)	-10.13 (-12.28, -7.99)	-13.26* (-15.42, - 11.09)	-15.05‡ (-17.20, -12.90)	-15.44‡ (-17.63, -13.32)
Week 6 (CI)	-12.98 (-15.45, -10.51)	-15.47 (-17.97, - 12.98)	-16.74* (-19.22, -14.26)	-17.33* (-19.48, -14.51)
Week 12 (CI)	-13.48 (-16.07, -10.89)	-16.84 (-19.46, - 14.23)	-17.34* (-19.93, -14.74)	-17.22* (-20.64, -15.44)
*P < .05 vs placebo, significant.				
† P < .01 vs placebo, significant.				
‡ P < .001 vs placebo, significant.				
§ Scale = 1 (very good) to 5 (very poor).				
£ Scale = 0 mm (no pain) to 100 mm (most severe pain).				
¶ Scale = 0 (no symptoms) to 8 (worse symptoms).				
# Scale = 0 (no symptoms) to 96 (worse symptoms).				
CI, 95% confidence interval; LSM, least square mean; PAAP, Patient's Assessment of Arthritis Pain; PhGAA, Physician's Global Assessment of Arthritis; QD, once daily; WOMAC OA, Western Ontario and McMaster's Universities Osteoarthritis Index.				

**This information was pulled directly from Kivitz et al[5]

Makarowski et al[6] had a total of 467 patients randomized in the ITT population, 209 of which withdrew before the end of the study period.[6] Withdrawal due to treatment failure in the Valdecoxib 5mg & 10mg groups was significantly lower than placebo where $p \leq 0.05$. It is also noted that withdrawal from the placebo group occurred at a faster rate than any of the treatment groups.[6] This study design was very similar to the one described in Kivitz et al, so the assessment tools and indices were using the same scales as stated above.

In assessment of efficacy, it was shown that Valdecoxib 5mg QD & 10mg QD were significantly superior to placebo for all assessments.[6] The only exception to this was in the PAAP-VAS week 12 assessment where only Valdecoxib 10mg QD was statistically superior to placebo.[6] A summary of the data from Makarowski et al can be found in Tables 3 and 4. This study included all continuous data that could not be converted to dichotomous data.

Table 3: Makarowski et al[6] least square mean changes from baseline for PaGAA, PhGAA, PAAP-VAS.

	Placebo (N=117)	**Valdecoxib 5mg QD** (N=120)	**Valdecoxib 10mg QD** (N=111)
PaGAA ‡			
Baseline mean	4.1	4.1	4.1
LSM change			
Week 2	-0.72	-1.10**†	-1.26***†
Week 6	-0.82	-1.11*†	-1.29***†
Week 12	-0.87	-1.20*†	-1.29***†
PhGAA‡			
Baseline mean	4.1	4.1	4.1
LSM change			
Week 2	-0.72	-1.10**†	-1.22***†
Week 6	-0.84	-1.17*†	-1.25**†
Week 12	-0.88	-1.18*	-1.25*
PAAP-VAS§			
Baseline mean	71.2	72.3	73.4
LSM change			
Week 2	-14.4	-21.0*	-24.6**
Week 6	-16.0	-23.3*	-25.8**
Week 12	-15.2	-21.3	-23.2*

Statistically significant *$P \leq 0.05$ vs placebo, **$P \leq 0.01$ vs placebo, ***$P < 0.001$ vs placebo.
†Statistically significantly different from placebo in pairwise comparisons.
‡Scale ranged from 1 (very good) to 5 (very poor).
§Scale ranged from 0–100 mm, with 0=no pain and 100=most severe pain.

*Information was pulled directly from Makarowski et al[6]

Table 4: Makarowski et al[6] least square mean changes from baseline for WOMAC indices.

	Placebo (N=117)	**Valdecoxib 5mg QD** (N=120)	**Valdecoxib 10mg QD** (N=111)
Pain index§			
Baseline mean	10.8	11.2	10.8
LSM change			
Week 2	-0.90	-2.48***‡	-2.56***‡
Week 6	-1.09	-2.76***‡	-3.23***‡
Week 12	-1.25	-2.54*‡	-2.83**‡
Composite index¶			
Baseline mean	52.6	54.7	52.8

LSM change			
Week 2	-4.31	-10.8**	-12.6***
Week 6	-5.07	-12.3**	-14.7***
Week 12	-5.28	-12.0**	-14.0***
Statistically significant *$P \leq 0.05$ vs placebo, **$P \leq 0.01$ vs placebo, ***$P < 0.001$ vs placebo. ‡Statistically significantly different from placebo in pairwise comparisons according to Hochberg's procedure. §Scale ranged from 0 to 20, with lower score as better. ¶Scale ranged from 0 to 96, with lower score as better.			

*Information was pulled directly from Makarowski et al[6]

The study design for Moskowitz et al[7] was still looking at efficacy of Valdecoxib, but not as a long term treatment. They were assessing the quickness of onset of analgesia during acute pain flare. In order to be included in the ITT population, patients were screened according to inclusion and exclusion data described in Table 1 and then randomized and given at least one study medication.[7] The ITT population included 435 patients, but 95 patients were then excluded from the per protocol (PP) cohort due to various reasons described in the study.[7]

Pain intensity difference (PID) VAS scores were significantly greater in the Valdecoxib treatment group at 4 hours versus placebo.[7] Median time to first onset of analgesia in the PP cohort was also significantly shorter for Valdecoxib as compared to placebo. Also, Valdecoxib had significantly improved Summed PID (SPID) scores in the first 6 hours compared to placebo.[7] Analgesic onset in the ITT population showed a significant percentage of patients with onset of analgesia from 4hrs to 6hrs, shown in Table 5.[7] This study included some dichotomous data that could be calculated to show that the NNT for Valdecoxib 10mg was 7; meaning that 7 patients need to be treated with this medication in order to have a positive impact on one. This data is shown in Table 6.

Table 5: Percent incidence of onset of analgesia during the first 6hrs in ITT population[7]

Time (h)	**Valdecoxib 10mg QD** (n=212)	**Placebo** (n=110)
1.0	29	28
2.0	46	39
3.0	50	41

4.0	55*	40
5.0	56*	42
6.0	58*	43
*P < 0.05		

*Information pulled directly from Moskowitz et al[7]

Table 6: Calculated data for treatment using dichotomous data

		Relative benefit increase (RBI)	**Absolute Benefit increase (ABI)**	**Number Needed to treat (NNT)**
CER	EER	$\frac{\text{EER-CER}}{\text{CER}}$	EER-CER	1/ABI
40%	55%	0.375	0.15	7
Where p-value ≤ 0.05 vs placebo				

DISCUSSION

The populations studied in each article were relatively similar, with mean age ranging from 59.7 years to 63.9 years old. All studies had similar inclusion and exclusion criteria, assuring that all patients were considered to have significant disease before the studies were done. There were similar results as far as efficacy of Valdecoxib, showing it to be significant to placebo at doses equal to and greater than 10mg QD. Kivitz et al did not find Valdecoxib 5mg QD to be significant to placebo, requiring further evaluation of a proper daily dosage.[5]

One aspect of this drug that has been evaluated in other studies is its safety. The original thought behind COX-2 inhibitors was to improve GI safety compared to NSAIDS, but drugs like Valdecoxib have displayed safety issues in other areas like cardiovascular events.[8] As part of the sulfonamide class, Valdecoxib already carries increased risk for reactions including TEN, SJS, and erythema multiforme.[8]

CONCLUSION

Based on the information provided in these three studies, it has been concluded that Valdecoxib is an effective treatment for pain in patients with Osteoarthritis of the hip or knee compared to placebo at doses of 10mg and higher; however, there are several issues with these studies that would require further examination. One main concern is the withdrawal

rates for all three articles were very high, reducing the validity of each of them significantly. Although it was shown by Kivitz et al[5] and Makarowski et al[6] that withdrawal number and rates were higher in placebo than treatment groups, there was still a significant amount of participants withdrawing from experimental groups due to treatment failure.

The second issue with Valdecoxib in general is that in recent studies, safety has been evaluated leading the FDA to take Valdecoxib off the market completely in 2005.[8] Further studies have clearly showed that the risks outweighed the benefits of Valdecoxib in the treatment of Osteoarthritis; however there are still many COX-2 inhibitors on the market to treat Osteoarthritis that did not have the cardiovascular events that Valdecoxib did. By researching Valdecoxib or other failed treatment options we can provide insight to future prospects in pain management for Osteoarthritis.

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