572
APPA PROVIDES SYMPTOM RELIEF IN CLINICAL CANINE OSTEOARTHRITIS

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Purpose: Lameness due to osteoarthritis (OA) is common in aged dogs and altered weight bearing can be objectively quantified. Oral APPA (apocynin and paeonol), and underwater treadmill therapy (UTW) were evaluated in client-owned dogs with OA, for normalization of weight bearing utilizing force-plate measurements, pre and post 4 weeks of treatment.
Methods: OA was diagnosed in client-owned dogs by physical examination and confirmed by radiography. Thirty-two dogs were enrolled with half having elbow and half hip OA. Treatment consisted of either 50 mg/kg BID oral APPA or twice weekly sessions of underwater treadmill (UWT) therapy for 4 weeks with all dogs receiving both treatments, with a wash-out period of 3 weeks in-between. Half the animals received APPA first, and half the animals received UWT first. Force plate measures were obtained before and after each treatment at a consistent treadmill speed for each dog (average of 0.6 ± 0.09 m/s). No other pain medications, including nutraceuticals, were administered to any of the dogs for the duration of the study. Ground reaction force (GRF) measures from 5 strides were used to calculate peak vertical force (PFz), mean vertical force (MFz), and vertical impulse (IFz). Symmetry indices (SI) for the limb pairs (left and right forelimbs for dogs with elbow OA, left and right hindlimbs for dogs with hip OA) were calculated for each of the three measurements, with a high SI indicating more asymmetry (or lameness), and absolute symmetry giving a SI of zero. Individual dog pre- and post-treatment SI values were compared with Wilcoxon matched pairs non-parametric test.
Results: The dogs enrolled in the study were middle to older-aged and mid-large sized (6 ± 4 years and 30 ± 9 kg). Two dogs in the initial UWT group were withdrawn from the study, with one requiring NSAID therapy for pain, and the other had a cardiac tumor. The UWT was well tolerated and the duration of each twice-weekly session steadily increased from 5 ± 2 min to 21 ± 7 min over the 4 week treatment period. Twice daily oral APPA was well tolerated for 4 weeks in all but one of the 32 dogs who was removed from the study following mild gastrointestinal signs (vomiting following dosing). A total of 29 dogs completed the study and received the two, 4-week treatments, with a total study length of 11 weeks (including the 3 week wash-out interval). APPA decreased Peak Vertical Force SI when compared to pre-treatment levels ($p < 0.02$, Wilcoxon test), decreased Mean Vertical Force SI ($p = 0.0001$), and decreased Vertical Impulse SI ($p < 0.0001$). Gait symmetry indices following both APPA and UWT approached those obtained historically from healthy dogs.
Conclusions: APPA and UWT therapy were well-tolerated in client-owned dogs and normalized gait asymmetry, as measured with an objective force plate system. APPA normalized gait symmetry indices without the need for UWT equipment or specialized supervision. APPA has also demonstrated decreased disease progression in a rat meniscal tear model of OA, but disease progression was not examined in this dog study. APPA is being further investigated for its ability to decrease pain, clinically in human and veterinary patients, and to decrease cartilage destruction in preclinical models.

573
A RANDOMIZED CONTROLLED STUDY FOR THE COMPARISON OF EFFICACY AND SAFETY ASSESSMENT OF INTRA-ARTICULAR INJECTION OF HIGH MOLECULAR WEIGHT HYALURONIC ACID AND ORAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS FOR JAPANESE PATIENTS WITH KNEE OSTEOARTHRITIS (UMIN000001026)

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Purpose: Among the pharmacological treatment for knee osteoarthritis (OA), oral non-steroidal anti-inflammatory drugs (NSAIDs) are recommended to be used in OARSI recommendations for the management of OA. Although intra-articular injections of hyaluronic acid (IA-HA) are also recommended, there was very considerable heterogeneity of outcomes between trials. IA-HA is more common in clinical medicine in Japan. However, there is no direct comparison in terms of the efficacy and safety of these two treatments in Japanese patients with knee OA. The aim of this multicenter randomized controlled head-to-head comparison study was to clarify that IA-HA was not inferior to NSAID for the treatment of Japanese patients with knee OA.
Methods: A total of 200 patients with knee OA (K/L grade 1 to 3) were registered from nineteen hospitals and randomized to NSAID (loxoprofen sodium, Loxonin®) or IA-HA (High molecular weight 2,700 kDa HA, Suvenyl®). For patients treated with NSAID, they used NSAID 3 tablets (180 mg)/day for five weeks. For patients treated with IA-HA, intra-articular injection of high molecular weight HA was conducted for 5 times with one week interval. The trial was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before enrollment in this trial. The protocol was reviewed by the institutional review board of each institution. The primary endpoint was the percent changes of Japanese Knee Osteoarthritis Measure (JKOM), which is a patient-oriented outcome measure for Japanese patients with knee OA, during 5 weeks observation. The secondary endpoint was the percent differences of pain visual analogue scale (VAS) score. The authors analyzed the full analysis set (FAS) as the primary analysis, based on the concept of intention-to-treat (ITT) and the per protocol set (PPS) as the secondary analysis. As the results obtained by FAS were similar to those by PPS analysis, data obtained from FAS analysis will be presented.
Results: During the 5 weeks of examination, while 20.4% of patients with NSAID were withdrawn, 9.2% of patients with IA-HA were withdrawn. These differences for the frequency of withdrawal between NSAID and IA-HA were statistically significant ($p=0.02$). The frequency for adverse events in patients with NSAID and IA-HA was 10.8% and 1.0%, respectively. These differences for the frequency of adverse events between NSAID and IA-HA were statistically significant ($p=0.003$). No significant changes of JKOM sc ore were observed in patients with either NSAID or IA-HA by the treatment ($p=0.18$ and 0.55, respectively). The difference of percent changes of JKOM score between the two intervention arms (primary outcome measure) was -1.34% (90%CI; -7.68 to 5.01), and IA-HA was non-inferior
to NSAID. Pain VAS scores of the patients with NSAID (56.1) and IA-HA (58.9) at baseline were significantly reduced in comparison to those after the treatment (31.0 and 30.3) ($p<0.001$), respectively. The differences of the secondary outcome measure (% change of pain VAS score) between two intervention arms was -5.74% (90%CI; -23.6 to 12.1), and IA-HA was non-inferior to NSAID for pain. In addition, when the patients were divided into two groups (responder or non-responder) by OMERACT-OARSI response criteria, 51.5% of the patients with IA-HA were classified into "responder", while 49.5% of those with NSAID were "responder". Again, there were no significant differences of the frequency of "responder" between these two groups. Logistic regression analysis for odds of responders also revealed that the patients with IA-HA were not inferior to those with NSAID (OR 1.00 (95%CI; 0.56-1.78, $p=0.99$)).
Conclusions: This study showed that the efficacy of IA-HA was not inferior in comparison to that of NSAID, and the safety of IA-HA was superior in comparison to that of NSAID for Japanese patients with knee OA.

574
EXPLORATORY ANALYSIS OF OSTEOARTHRITIS PROGRESSION AMONG MEDICATION USERS: DATA FROM THE OSTEOARTHRITIS INITIATIVE

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Purpose: There has been limited success exploring disease modifying interventions for knee osteoarthritis (OA) and it would be cost prohibitive to explore a large number of pharmacological interventions in randomized clinical trials. Therefore, we conducted an exploratory analysis of OA

progression among medication users in the Osteoarthritis Initiative (OAI) to identify interventions or pathways that may be of interest for future clinical trials.

Methods: An exploratory analysis was conducted using OAI participants with annual medication inventory form data between baseline and the 36-month (mo) follow-up visit (n = 2,938). *Consistent medication users* were defined for each medication classification (class) as a participant reporting at every annual visit that they were regularly using an oral prescription medication at the time of the clinic visit. Two definitions of *consistent medication nonuser* were assessed: 1) **definite nonuser**: participants never reported the prescription medication, and 2) **probable nonuser**: participants never reported regularly using an oral prescription medication at the time of the clinic visit. The exploratory analysis focused on medication classes with $\geq$ 40 users. Key outcome measures were 12-mo quantitative joint space width at x = 0.250 (JSW250), JSW250 change (12-mo to 36-mo visits), 12-mo WOMAC pain score, and WOMAC pain score change (12-mo to 36-mo visits). Change was calculated as follow-up minus baseline. Each medication class was analyzed separately. We explored five sets of comparisons including three with nonusers matched to users based on OAI cohort, race, gender, age ($\pm$ 5 years), and body mass index ($\pm$ 5 kg/m^2): 1) no matching: users to all definite nonusers, 2) matched: users to definite nonusers, 3) matched and restricted to only participants with JSW250 data: users to definite nonusers, 4) no matching: users to all probable nonusers, and 5) matched: users to probable nonusers. A Cohen effect size was generated for each medication class in each set of comparisons (d= [user mean-nonuser mean] divided by pooled standard deviation). Medication classes with 4 out of 5 effect sizes for JSW250 change $>$ 0.10 or $<$ -0.10 for WOMAC pain change were further explored with box plots to determine if the median change of matched definite nonusers was beyond interquartile range (IQR) of users.

Results: Twenty-six medication classes were eligible for screening (Table 1). Table 1 contains sample sizes and effect sizes for each medication class. Anti-estrogen, anticonvulsants, antineoplastic agents, progestogens, antidepressants, hypoglycemics, and ACE inhibitors were further explored with box plots for JSW250 change. Anti-estrogen users' IQR included less JSW250 change than the median for nonusers. Progestogens also had a potential signal but the other medications had clear overlap between users and nonusers. For symptom modification, alpha-adrenergic blockers and diuretics were further explored with box plots of WOMAC pain change. Alpha-adrenergic users' IQR included greater improvement in WOMAC pain scores than the median for nonusers but diuretic users and nonusers had clear overlap.

Conclusions: A hormonal pathway, theoretically associated with bone turnover, may be an area for further focus since anti-estrogen and progestogen users had evidence of slower JSW change while bisphosphonate users had greater JSW change. Furthermore, weak but consistent evidence suggested that central nervous system agents may deserve further research since anticonvulsants and antidepressant users had slower JSW change while anxiolytics users had greater JSW change. Alpha-adrenergic users had signal for improved symptoms but no other medications had complimentary signals.

Table. Summary of Sample Sizes for Consistent Medication User and Nonusers as well as Cohen Effect Sizes (median [range]) Based on Joint Space Width (JSW x = 0.250) and WOMAC Pain Analyzed Among the Five Sets of Comparisons

	Overall Sample Size (m)		Smallest Sample Size (m)				JSW250 Change Ranking Potential Benefit	WOMAC Pain 12-mo Visit	WOMAC Pain Change (12 to 36 mo)	WOMAC Pain Change Ranking Potential Benefit
Medication	users	nonusers	users	nonusers	JSW250 at 12-mo Visit	JSW250 Change (12 to 36 mo)				
Anti-estrogen	61	2837	16	15	-0.20 (-0.23, 0.19)	0.66 (0.63, 0.81)	1	0.04 (-0.03, 0.26)	-0.02 (-0.47, -0.01)	5
Anticonvulsants	67	2742	18	18	0.15 (-0.15, 0.30)	0.24 (0.15, 0.43)	2	0.33 (0.16, 0.45)	-0.04 (-0.16, 0.22)	18
Antineoplastic Agents	48	2767	11	8	-0.45 (-0.69, -0.05)	0.30 (0.01, 0.45)	3	-0.06 (-0.09, 0.31)	0.07 (-0.43, 0.26)	7
Progestogens	56	2802	19	13	0.36 (0.07, 0.66)	0.20 (0.18, 0.36)	4	-0.14 (-0.17, 0.17)	0.14 (-0.20, 0.39)	24
Antidepressants	360	2259	102	102	0.06 (-0.15, 0.12)	0.18 (0.16, 0.28)	5	0.16 (0.10, 0.16)	-0.02 (-0.05, 0.07)	15
Hypoglycemics (oral)	143	2685	57	43	-0.12 (-0.38, -0.10)	0.11 (0.05, 0.34)	6	0.32 (0.17, 0.47)	-0.05 (-0.23, -0.05)	3
ACE Inhibitors	404	2230	138	127	-0.03 (-0.06, 0.05)	0.10 (0.08, 0.22)	7	0.07 (0.02, 0.12)	-0.04 (-0.08, -0.03)	11
Anti-gout	59	2852	24	22	-0.08 (-0.33, -0.06)	0.07 (0.00, 0.41)	8	-0.04 (-0.14, 0.16)	0.07 (-0.16, 0.10)	17
Beta-adrenergic Blockers	476	2159	146	140	-0.17 (-0.18, -0.03)	0.13 (-0.04, 0.18)	9	0.01 (-0.08, 0.12)	-0.03 (-0.10, -0.01)	8
Statins	839	1544	255	255	0.06 (0.03, 0.11)	0.07 (0.07, 0.17)	10	-0.03 (-0.04, -0.02)	-0.05 (-0.08, -0.04)	9
Alpha-adrenergic Blockers	92	2720	26	26	0.17 (0.07, 0.40)	-0.05 (-0.06, 0.03)	11	0.05 (-0.02, 0.34)	-0.15 (-0.63, -0.14)	1
Antilipemic Agents	925	1440	270	270	0.05 (0.01, 0.05)	0.04 (0.02, 0.05)	12	-0.01 (-0.03, 0.00)	-0.03 (-0.06, -0.01)	10
Sulfonylureas	70	2803	27	25	0.13 (0.10, 0.26)	0.07 (-0.07, 0.07)	13	0.49 (0.47, 0.53)	0.13 (0.06, 0.30)	23
Ca Channel Blockers	307	2397	101	101	-0.23 (-0.38, -0.17)	-0.08 (-0.14, 0.12)	14	0.20 (0.07, 0.32)	0.07 (0.04, 0.09)	14
NSAIDs	81	2493	33	27	0.12 (-0.18, 0.15)	-0.02 (-0.23, 0.16)	15	0.24 (0.18, 0.45)	0.02 (0.01, 0.18)	21
Diuretics	525	1917	160	157	-0.19 (-0.25, -0.12)	0.02 (-0.13, 0.13)	16	0.15 (-0.02, 0.19)	-0.16 (-0.35, -0.10)	2
Estrogen	137	2647	40	40	0.14 (0.06, 0.35)	0.06 (-0.12, 0.13)	17	-0.01 (-0.03, 0.06)	0.03 (-0.08, 0.15)	16
Thyroid Agents	420	2427	145	122	-0.06 (-0.06, 0.04)	-0.01 (-0.14, 0.07)	18	0.06 (-0.01, 0.07)	-0.04 (-0.23, 0.04)	6
Vitamin B Complex	2769	49	16	12	-0.30 (-0.40, -0.24)	0.05 (-0.26, 0.15)	19	0.04 (0.03, 0.34)	0.01 (-0.11, 0.52)	19
Anticulcer Agents	357	2152	108	108	-0.11 (-0.12, -0.04)	-0.18 (-0.28, -0.09)	20	0.13 (-0.09, 0.17)	0.00 (-0.06, 0.08)	13
Antihistamines	108	2589	35	35	0.29 (0.07, 0.38)	-0.12 (-0.29, 0.09)	21	0.19 (0.03, 0.22)	0.04 (0.03, 0.23)	20
Anticoagulants	69	2742	28	19	0.08 (-0.03, 0.32)	-0.18 (-0.32, 0.14)	22	-0.07 (-0.12, -0.02)	-0.04 (-0.14, 0.06)	4
Angiotensin II R Ant.	279	2392	79	79	-0.12 (-0.19, -0.08)	-0.14 (-0.38, -0.06)	23	0.08 (0.02, 0.10)	0.00 (-0.01, 0.05)	12
Anxiolytics	42	2746	13	9	0.20 (0.14, 0.77)	-0.20 (-0.46, 0.10)	24	0.01 (-0.37, 0.14)	0.17 (0.14, 0.44)	26
Bisphosphonates	265	2406	70	69	-0.32 (-0.32, 0.07)	-0.18 (-0.37, -0.10)	25	-0.22 (-0.29, -0.05)	0.02 (0.00, 0.12)	22
COX-2 Inhibitors	52	2670	14	14	-0.46 (-0.67, -0.04)	-0.46 (-1.00, -0.36)	26	0.21 (0.17, 0.25)	0.12 (0.03, 0.24)	25

JSW250 = joint space width at x = 0.250, Mo = month, Ca = calcium, NSAIDs = nonsteroidal anti-inflammatory drugs, Ant = antagonist. Rankings are based on the distribution of effect sizes defined as beneficial (JSW250 change d $\geq$ 0.20, WOMAC pain change d $\leq$ -0.20) less beneficial (JSW250 change d = 0.10 to 0.19, WOMAC pain change d = -0.19 to -0.10), no effect (d = -0.10 to 0.10), less adverse effect size (JSW250 change d = -0.19 to -0.10, WOMAC pain change d = 0.10 to 0.19), and adverse effect size (JSW250 change d $\leq$ -0.20, WOMAC pain change d $\geq$ 0.20).

575

LONGITUDINAL EVALUATION OF VISCOSUPPLEMENTATION THERAPY ON OA PATIENTS USING T1(RHO) MRI

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Purpose: To quantify changes to articular cartilage in patients following viscosupplementation therapy with mild to moderate osteoarthritis using T1ρ MRI.

Methods: Following IRB guidelines, 10 subjects (mean age, 56 $\pm$ 10 yrs) with Kellgren-Lawrence Grades 1 and 2 OA, and who never had prior VS or knee surgery, were scanned at baseline, 6 weeks post-, and 3 months post-VS using Hylan G-F 20 (3T, Siemens Medical Solutions, Malvern, PA). T1-weighted isotropic MPRAGE images were acquired for segmentation of cartilage, and T1ρ-weighted 3D TrueFISP images were acquired to calculate spatial T1ρ relaxation maps. Sixteen T1ρ-weighted slices were acquired in each aspect to allow for volumetric analysis. Image acquisition parameters have been described previously. Isotropic sagittal MPRAGE images were re-sliced along coronal and axial views and interpolated to match the resolution of T1ρ- weighted images. Inter- and intra-scan motion was corrected 3D rigid-body co-registration algorithms (Analyze, AnalyzeDirect, Inc., KS). Femoral and tibial images were co-registered separately due to discrepancies in flexion angle between imaging sessions. ROI analysis was performed on the same locations for three time points to accurately quantify changes in T1ρ through mean compartmental analysis and percent change maps from baseline images. Cartilage was segmented using the SliceOMatic (Tomovision, Quebec, CA) software package. Co-registered T1ρ-weighted images were fit pixelwise to the linearized, mono-exponential signal decay equation $\ln(S) = -TSL/T1\rho + \ln(S0)$. Volumetric T1ρ means were calculated by layer depth (superficial, middle, deep) as well as by region (medial and lateral patella, femoral condyles, and tibial plateau). Statistical analysis was performed using a one-tailed paired t-test between time points. Additional data to be analyzed but not present for this abstract include the visual analog pain, WOMAC, and IKDC subjective scores before injection and at the time of follow-up MRI. WORMS scoring for each patient is currently being performed and will be correlated to quantitative findings. Statistical significance was accepted when $p<0.05$.

There were significant differences in volumetric T1ρ scores in both the medial and lateral compartments of the superficial patella ($p< 0.05$) 6 weeks following but not after three months (Med. - $p<0.1$, Lat. - p 20% across the entire patella while Figure 2 has no significant difference in average between two following time points. There is a large region across the middle of the lateral facet with an average T1ρ score $<$ 20% versus the volumetric mean. This trend of non-uniform spatial changes to T1ρ following VS regiments is prevalent among all patients.

Conclusions: These data suggest that VS has a quantifiable physiological effect on knee articular cartilage. This effect is greater in the superficial layers than in the deep layers. Intuitively, direct contact between VS and cartilage occurs at the superficial layer, and there may be a subsequent physical mechanism of action for VS. Interestingly, the greatest effects were observed in the patella-femoral compartment which may be due to lower load-bearing activities and increased cartilage thickness. Future work will assess methods to predict homo- or heterogeneous changes within the articular cartilage through correlation analysis with WORMS, WOMAC, and other qualitative assessments. While some patients responded positively to the VS, as calculated through lower T1ρ scores, there were some who did not or had higher T1ρ values. There may be both placebo effects as well as anti-inflammatory mechanisms associated with the VS which allowed patients to push through pain more than before thereby causing increased damage to the cartilage tissue.