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THU0465

PHARMACOKINETICS AND TOXICOKINETICS STUDIES OF A SUSTAINED RELEASE LIPOSOMAL FORMULATION OF DEXAMETHASONE SODIUM PHOSPHATE (TLC599) FOLLOWING INTRA-ARTICULAR INJECTION IN DOGS

Tzung-Ju Wu, Wan-Ni Yu, Ming-Ju Wu, Po-Chun Chang, Sheue-Fang Shih.
Taiwan Liposome Company, Taipei, Taiwan, Republic of China

Background: Osteoarthritis (OA) is a degenerative joint disorder with limited long-lasting treatment options. Various steroid formulations on the market are effective but required frequent intra-articular (IA) injections due to short-term symptomatic relief. IA steroids have been shown to increase cartilage loss in knee and the rapid absorption into systemic circulation could cause adverse side effects, limiting their effectiveness [1]. To circumvent these issues, TLC599, a novel sustained-release liposome formulation of dexamethasone sodium phosphate (DSP) was developed to provide a sustained OA pain management over an extended period with reduced side effects and toxicity. TLC599 resulted in sustained presence in the synovial fluid without significant local and systemic side effects from OA treatments following IA injection.

Objectives: To evaluate pharmacokinetics (PK) and toxicokinetics (TK) of TLC599 following IA injection in dogs.

Methods: In two studies, the dexamethasone phosphate (DP) and dexamethasone (DEX) concentration was quantified and the PK/TK profile of TLC599 was evaluated in dogs following IA injection. DSP is the sodium salt form of DP and DEX is the active form of DSP. Study#8351851: TLC599 was administered as a single- or multiple-dose injection (once every 13 weeks for total of four times) at 18 mg/knee (36 mg/animal). Synovial fluid was collected at 2.5, 48, 96, 168 and 360 hours post-dose from 4 animals/time point, and plasma was collected at 0.25, 0.75, 1.25, 2, 4, 6, 24, 48, 96 and 168 hours post-dose from 8 animals/time point. Study#8388198: TLC599 was administered as a single-dose injection at 18 mg/knee. The synovial fluid was collected at 15, 30, 45, 90, and 120 days post-dose from 4 animals/time point.

Results: Study#8351851: Following a single-dose IA injection of TLC599, DP concentration declined gradually after 2.5 hr but remained detectable through 360 hr, demonstrating the prolonged local exposure in the joint (Figure 1). The PK parameters of DP and DEX in dog plasma were assessed in the multiple-dose group. The mean C_{max} and AUC_{0-24} values of DP and DEX were comparable between the first dose (Day 1) and the fourth dose (Day 274) (Table 1), indicating there was no accumulation of systemic exposure of DP and DEX following four repeated IA injections of TLC599. By evaluating the effect on cartilage, it was also shown that the local safety profiles were similar between multiple-dose and single-dose TLC599 injections.

Abstract THU465 – Figure 1. Mean Concentration of DP in Dog Synovial Fluid.

Abstract THU465 – Table 1. Summary of Mean C_{max} and AUC_{0-24} of DP and DEX in Dog Plasma.

Analyte	Dose #	Dose Level (mg/animal)	C_{max} (ng/mL)	AUC_{0-24} (hour*ng/mL)
Dexamethasone Phosphate	First Dose (Day 1)	36	450	419
	Fourth Dose (Day 274)	36	522	505
Dexamethasone	First Dose (Day 1)	36	498	6385
	Fourth Dose (Day 274)	36	427	5955

Study#8388198: Following a single-dose IA injection of TLC599, DP concentration declined after 15 days but remained at similar level from 30 days to 120 days post-dose. Overall, the prolonged 120-day residence time of TLC599 in synovial joint was observed (Figure 2).

Abstract THU465 – Figure 2. Mean Concentration of DP in Dog Synovial Fluid.

Conclusion: TLC599, a novel extended-release liposome formulation of DSP, showed a long-lasting profile up to 120 days in synovial joint after a single IA injection in a preclinical dog study. In addition, no significant systemic exposure and accumulation of DP and DEX in dog plasma was observed following multiple-dose administration of TLC599. Animal studies indicate that TLC599 may be an effective and superior chronic treatment for OA.

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THU0466

THE EVALUATION OF THE EFFECTIVENESS OF INTRA-ARTICULAR STEROID, TENOXICAM AND COMBINED STEROID-TENOXICAM INJECTIONS IN THE TREATMENT OF PATIENTS WITH KNEE OSTEOARTHRITIS

YILMAZ Ebru . Korfez Government Hospital, Physical Therapy and Rehabilitation, Kocaeli, Turkey

Background: Intra-articular corticosteroid injections are widely applied in the treatment of symptomatic knee osteoarthritis (OA). There is an evidence of short-term effects of intra-articular corticosteroid injection (up to 3-4 weeks), however there is no consensus for the long-term benefit of this treatment yet (1). Tenoxicam is an effective analgesic and anti-inflammatory drug for symptomatic treatment of OA. Additionally, apart from oral use, tenoxicam is also applied as an intra-articular treatment option to minimize gastrointestinal side effects of NSAIDs (2). Clinical evidence suggests that the combined use of NSAIDs and corticosteroids is synergistic (especially macular edema after cataract surgery in ophthalmology) (3).

Objectives: The aim of this study is to compare the effectiveness of intra-articular administration of these treatments and their combination and determine whether the combination of intraarticular steroid and tenoxicam was more effective for a long period rather than only tenoxicam and steroid injection alone in OA treatment.

Methods: 90 patients (56 female, 34 male) with diagnosis of knee osteoarthritis were randomly divided into three groups (30 patients per group): Group 1 were treated by intra-articular injection of tenoxicam. Group 2 were treated by intra-articular injection of triamcinolone hexacetonide. Group 3 were treated by intra-articular injection of triamcinolone hexacetonide combined with tenoxicam. The estimation of the severity of pain by the visual analog scale (VAS) were enrolled at baseline and 1, 3, 6 months post-injection. Additionally, the Western Ontario and McMaster Universities Index (WOMAC) was used to determine the outcome measures of pain, stiffness and physical functioning at baseline and 1, 3, 6 months post-injection.

Results: The mean age of patients was 65.97±9.29 years. In tenoxicam group, median pre- and post-treatment (at 1, 3 and 6 months) VAS/WOMAC scores were 7.00/32.00, 2.00/10.00, 7.00/32.00 and 7.00/32.00, respectively. In steroid group, median pre- and post-treatment (at 1, 3 and 6 months) VAS/WOMAC scores were 8.00/34.00, 1.00/8.00, 8.00/34.00 and 8.00/34.00, respectively. In steroid plus tenoxicam group, median pre- and post-treatment (at 1, 3 and 6 months) VAS/WOMAC scores were 7.00/34.00, 0.00/6.00, 1.00/8.00 and 2.00/10.00, respectively. VAS and WOMAC scores in 1 month after the injection significantly decreased in both groups compared to baseline ($p<0.01$). However, there was a pronounced improvement in only steroid plus tenoxicam group at 3 and 6 months post-injection ($p<0.01$). Steroid plus tenoxicam group showed significantly improved VAS and WOMAC scores when compared to only steroid and tenoxicam group at follow-up 3 and 6 months ($p<0.01$).

Abstract THU0466 –Table 1.

Table 1. Patients characteristics			
Variables	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)
Age (mean)	65.97±9.29	65.97±9.29	65.97±9.29
Sex			
Male	16 (53.3%)	16 (53.3%)	16 (53.3%)
Female	14 (46.7%)	14 (46.7%)	14 (46.7%)
Duration of osteoarthritis (months)	10.00±10.00	10.00±10.00	10.00±10.00
Medications			
Paracetamol	10 (33.3%)	10 (33.3%)	10 (33.3%)
NSAIDs	10 (33.3%)	10 (33.3%)	10 (33.3%)
Glucocorticoids	10 (33.3%)	10 (33.3%)	10 (33.3%)
Other	10 (33.3%)	10 (33.3%)	10 (33.3%)
Baseline WOMAC (mean)	32.00±10.00	32.00±10.00	32.00±10.00
Follow-up			
1 month	2.00±1.00	2.00±1.00	2.00±1.00
3 months	7.00±3.00	7.00±3.00	7.00±3.00
6 months	7.00±3.00	7.00±3.00	7.00±3.00
Statistical significance (p-value)			
Group 1 vs Group 2	0.001*	0.001*	0.001*
Group 1 vs Group 3	0.001*	0.001*	0.001*
Group 2 vs Group 3	0.001*	0.001*	0.001*

All values are expressed as mean (SD). *p<0.05, significant.

Abstract THU0466 –Table 2.

Table 2. Changes in VAS in before injection and 1, 3 and 6 months after the injection in group 1, 2 and 3.			
Variables	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)
Before injection	7.00 (7.00-8.00)	8.00 (7.00-8.00)	7.00 (7.00-8.00)
1 month after the injection	2.00 (1.00-3.00)	1.00 (0.00-2.25)	0.00 (0.00-1.00)
3 months after the injection	7.00 (7.00-8.00)	8.00 (7.00-8.00)	1.00 (0.00-2.00)
6 months after the injection	7.00 (7.00-8.00)	8.00 (7.00-8.00)	2.00 (1.00-3.00)
P	<0.001*	<0.001*	<0.001*

All values are expressed as mean (SD). *p<0.05, significant.

Conclusion: The combination of corticosteroids and tenoxicam seems to produce a more effective result than alone therapy in reducing pain and improving functional recovery.

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THU0467

DOES GENERALISED PAIN AND LOCALISED PAIN SEVERITY INCREASE RISK OF PREVALENT AND INCIDENT FRACTURES IN OLDER ADULTS?

Feng Pan¹, Jing Tian¹, Dawn Aitken¹, Flavia Cicuttini², Graeme Jones¹. ¹University of Tasmania, Menzies Institute for Medical Research, Hobart, Australia; ²Monash University Medical School, Department of Epidemiology and Preventive Medicine, Melbourne, Australia

Background: Musculoskeletal pain is common particularly in the elderly and typically occurs in multiple sites. Pain has been linked to falls risk; however, whether increased risk of falls related to pain can subsequently increase fracture risks remains unclear.

Objectives: To describe the associations of localised pain severity and generalised pain (number of painful sites) with incident fractures, and to explore whether their associations are independent of falls risk, bone mineral density (BMD) and potential confounders.

Methods: Data from a longitudinal population-based study of older adults (mean age 63 years, 51% female) were utilised. A mean follow-up was performed at 2.6, 5.1 and 10.7 years later, respectively. Pain severity in the knee was measured by the Western Ontario and McMaster Universities Osteoarthritis Index pain questionnaire. Presence/absence of pain at the neck, back, hands, shoulders, hips, knees and feet was assessed by questionnaire at baseline. Fractures were self-reported at each time-point. BMD was measured by Dual-energy X-ray absorptiometry (DXA). Falls risk was calculated based on the short form Physiological Profile Assessment.

Results: A total of 455 fractures at baseline and 154 new fractures were reported during follow-up. In multivariable analyses, both pain severity and number of painful sites were associated with prevalent fractures at any site. Pain severity was associated with prevalent vertebral fractures, while number of painful sites was associated with prevalent fractures at non-vertebral and hip sites. Furthermore, pain severity was associated with an increased risk of incident fractures at any site [relative risk (RR) 1.04, 95%CI 1.02-1.06], major (including the femur, radius, ulnar, vertebral, rib and humerus) (RR 1.10, 95%CI 1.05-1.15) and vertebral (RR 1.04, 95%CI 1.01-1.08). Similarly, number of painful sites was also associated with increased risk of incident fractures at any site [RR 1.69, 95%CI 1.13-2.53], major (RR 2.17, 95%CI 1.12-4.22) and vertebral (RR 6.44, 95%CI 1.64-25.33). There was a dose-response relationship between number of painful sites and risk of incident fractures. These associations remained significant after further adjustment for falls risk and BMD. No significant associations were found for fractures occurring at non-vertebral and hip sites.

Conclusion: Both pain severity and generalised pain are associated with increased risk of prevalent and incident fractures, which is independent of falls risk, BMD and potential confounders, suggesting that pain may be an independent marker of fracture risk. Improved pain management may have the potential to prevent fractures in older adults.

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Fibromyalgia

THU0468

THE INTERACTIONS OF PHYSICAL ACTIVITY LEVELS WITH THE SODIUM CHANNEL PROTEIN TYPE 9 SUBUNIT ALPHA AND METHYLENE TETRAHYDROFOLATE REDUCTASE GENES ARE ASSOCIATED WITH FATIGUE IN WOMEN WITH FIBROMYALGIA

Fernando Estevez-Lopez^{1,2,3}, Diego Salazar-Tortosa², Blanca Gavilán Carrera², Virginia A Aparicio², Pedro Acosta-Manzano², Víctor Segura-Jiménez⁴, Inmaculada C Alvarez-Gallardo⁴, Ana Carbonell-Baeza⁴, Diego Munguía-Izquierdo⁵, Rinie Geenen¹, Eliana Lacerda⁶, Manuel Delgado-Fernández², Luis J Martínez-González⁷, Jonatan R Ruiz², María J Álvarez-Cubero^{2,7}. ¹Utrecht University, Utrecht, Netherlands; ²University of Granada, Granada, Spain; ³Ulster University, Belfast, United Kingdom; ⁴University of Cádiz, Cádiz, Spain; ⁵Universidad Pablo de Olavide, Seville, Spain; ⁶The London School of Hygiene and Tropical Medicine, London, Spain; ⁷Liquid biopsy and metastasis research group and Genomic Unit, GENYO (Pfizer-University of Granada-Andalusian Government Centre for Genomics and Oncological Research), Granada, Spain

Background: People with fibromyalgia identify fatigue as one of the main symptoms of the disease [1]. It is hypothesised that the pathogenesis of fibromyalgia involves a genetic susceptibility that is modulated by environmental factors [2]