Nutraceuticals for canine osteoarthritis: scientific evidence of an innovative "disease-modifying" approach

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INTRODUCTION

Nowadays, increased knowledge about etiology and pathophysiology of canine osteoarthritis (OA) are underpinning the importance of the so-called "combined therapy". It is a balanced multimodal treatment programme in which both pharmacological and non pharmacological conservative (medical) measures as well as surgical treatment options – tailored to the age and the lifestyle of the patient and to the clinical findings and severity of its OA – are simultaneously or consecutively performed, in order to counteract causes, mechanisms and symptoms of the disease (Mortellaro and Miolo, 2004; Aragon et al, 2007; Johnston et al, 2008; Rychel, 2010; Fox, 2010). Non pharmacological medical OA treatment includes weight management, modification of exercise level and physical rehabilitation (Marshall et al, 2009; Millis, 2009). The pharmacological management of OA is achieved both with a "pain-oriented" multimodal analgesia (i.e. NSAIDs, corticosteroids, opioids) and a "disease-modifying" approach, named chondroprotection, able to exert structural and symptomatic long-term anti-OA effects by controlling the main pathogenetic osteoarthritic mechanisms (i.e. chondrodegeneration, inflammation and oxidative stress) (McLaughlin, 2000; Boothe, 2001; Beale, 2004; Fox, 2010). Since the 1990s, a wide variety of compounds with different chemical structures, bioavailabilities, mechanisms of action and degree of purity have been proposed in Veterinary Orthopaedics as "chondroprotectants", i.e. substances specifically aimed to rebalance the metabolism of degenerating cartilage, boosting the synthesis and reconstruction processes (pro-anabolic effects) and inhibiting degradation processes (anti-catabolic effects) (McNamara et al, 1997; McLaughlin 2000; Beale, 2004). Among these, anti-OA nutraceuticals are a variety of heterogeneous substances administered by oral route, sharing the peculiarity to be isolated and purified from food sources and meeting specific metabolic needs of the OA joint. In particular, they not only support or enhance the articular intrinsic repair capability (chondroprotection *sensu strictu*), but also exert anti-inflammatory and analgesic effects and rebalance the intrarticular oxidative stress (Beale, 2004; Henrotin et al, 2005; Aragon, 2007). The aim of this lecture is to present the clinical and experimental data about the functional principles of a nutraceutical commonly used in Italy within the combined management of canine OA [Condrostress®3.0, Innovet Italia Srl].

Presented at the 1st VEPRA Conference "Physical therapy of the stifle", Faculty of Veterinary Medicine, University of Zagreb (Croatia), May 15th-16th, 2010 www.vepra.eu

Chondroitin sulfate: NSCS fraction 5/20

Normo-sulfated chondroitin sulfate fraction 5/20 (NSCS 5/20) is an original, highly qualified, patented fraction of low molecular weight chondroitin sulfate (CS), which possesses three essential features as a guarantee for a high level of chondroprotective efficacy and safety:

1- low molecular weight: NSCS 5/20 has an average molecular weight (MW) of between 5 and 20 kiloDaltons (kD). NSCS 5/20 therefore does not contain fractions with a high MW, which are hard to absorb, or fractions lower than 3kD, which have an undesirable collagenolytic effect. Orally administered, this specific fraction of CS is absorbed in significant amounts (70%) in the dog (Conte et al, 1995), displays significant accumulation upon multiple dosing (Adebowale et al, 2002) and it is rapidly distributed into tissues, with a preferential tropism for articular cartilage (Volpi, 2004).

2- physiological degree of sulfation: the degree of sulfation of NSCS 5/20 is between 0.75 and 1. This is called "normosulfation", because the CS normally present in the joint tissues has 1 sulfate unit per disaccharide unit. It has been demonstrated that the closer to 1 the degree of sulfation comes, the more CS is absorbed after oral administration (Volpi, 2002).

3- high degree of purity: NSCS 5/20 is a pure fraction of CS, because it possesses a high degree of purity (>98%). In other words, it is free of protein "impurities" and other inactive or undefined compounds which compromise both the absorption and chondroprotective effects of this molecule (Tat et al, 2010)

Finally, the pro-anabolic (e.g. increase in proteoglycan and collagen synthesis) and anti-catabolic (e.g. inhibition of matrix proteases and pro-inflammatory cytokines) effects of low molecular weight CS, especially when combined with glucosamine, have been confirmed by several *in vitro* and *in vivo* studies, as far as by systematic reviews or metanalyses both in humans and dogs (Henrotin et al, 2005; Aragon et al, 2007; Sanderson et al, 2009).

Glupamid® (N-palmitoyl-D-glucosamine)

Glupamid® is the name of an original form of glucosamine (N-palmitoyl-D-glucosamine), which is both a substance with an autacoid local injury antagonism effect (ALIA effect) and an innovative system to provide slow-release glucosamine in the intracellular environment. Chemically, Glupamid® is the amide of a monocarboxylic acid (palmitic acid) with the aminosugar glucosamine. It is taken up within the cell, where as a result of the action of a specific enzyme (FAAH, *fatty-acid amide hydrolase*) it releases slow-acting glucosamine with the well-known chondroprotective activities. In view of its structure and mechanism of action, Glupamid® belongs to the class of aliamides: synthetic analogues of endogenous compounds, of which the parent molecule is palmitoylethanolamide (PEA). Aliamides accumulate in peripheral tissues exposed to various damages, in order to prevent the excessive propagation of the inflammatory response, regulate pain sensitivity and consequently modulate in a "nature-like" manner the tissue hyper-reactivity (Lambert et al, 2002; Re et al, 2007). The proved anti-inflammatory and analgesic effects of PEA both in experimental (Costa et al, 2008; De Filippis et al, 2010) and clinical studies (Re et al, 2007) are, at least in part, mediated by the down-modulation of local mast cells release (degranulation) of biological mediators, directly involved in inflammation and pain, both of inflammatory and neuropathic nature (Costa et al, 2009; Cerrato et al, 2010). Similarly, Glupamid® has proved to be active in inhibiting the release of vasoactive and nociceptive mediators (i.e. serotonin) by a well-established in vitro model of mast cell degranulation (Rat basophilic-leukemia cells, RBL-2H3).

Indeed, the percentage inhibition of serotonin release increases in a dose-dependent manner from 60% (for 0.01 microM Glupamid®) to 103% (1 microM Glupamid®) (Miolo et al, 2006). In conclusion, Glupamid®, being an aliamide also able to release slow-acting glucosamine, combines chondroprotective and anti-inflammatory/painkilling properties in a single molecule. This strengthens its potential therapeutic use in the combined "disease-oriented" approach for canine OA .

Quercetin

The bioflavonoid quercetin can be found in a great variety of plants, fruits and vegetables and has recently referred to as a "nutraceutical for OA", owing to its multiple anti-oxidant, anti-inflammatory and anti-degenerative activities on several cell lines (e.g. chondrocytes, synovial mast cells, macrophages, synoviocytes and fibroblasts) present in the joints (Teixeira, 2002; Matsuno et al, 2009). In particular, the chondroprotective and antioxidant effects of quercetin have been demonstrated specifically on canine chondrocytes (Fabris et al, 2002). Indeed, two-hour exposure to an oxidant stimulus (hydrogen peroxide) causes 70% chondrocyte death, whereas combined exposure to hydrogen peroxide and quercetin results in a significant increase in the percentage of viable cells. This represents the first important evidence of the cytoprotective and antioxidant efficacy of quercetin, specifically referring to canine chondrocytes.

Clinical trial

The efficacy of the anti-OA nutraceutical containing NSCS 5/20, Glupamid® and quercetin [Condrostress®3.0, Innovet Italia Srl] has been tested with an open-label controlled clinical study, enrolling ten dogs with diagnosis of rupture of the cranial cruciate ligament (CCLr), one of the most frequent causes of OA and lameness of the rear limb in the dog (Crovace et al, 2006). The purpose of this clinical trial was to evaluate the efficacy of associating the anti-OA nutraceutical with surgical treatment of spontaneous CCLr by means of spectroscopic analysis (proton NMR spectroscopy) of the synovial fluid, taken by arthrocentesis from all animals at start of the study (T0), at T60 and T90. All dogs underwent surgical reconstruction of CCL (modified "over the top" intrarticular fascial graft procedure), but only five dogs received also the anti-OA nutraceutical for 60 days, starting on the day after surgery. The trend over time of the synovial concentration of four metabolites (lactate, alanine, acetyl groups of N-acetylated sugars on glycoproteins and alpha-anomers of glucose) was found to differ to a statistically significant extent between the two groups, suggesting that the nutraceutical studied produces an intra-articular metabolic rebalance. In conclusion, the results of this clinical study suggest that the studied anti-OA nutraceutical : a) modulates *in vivo* not only chondrodegeneration, but also produces an intra-articular metabolic improvement, by rebalancing inflammatory and oxidative synovial metabolites; b) is useful in the combined management (surgery) of OA secondary to CCLr.

Conclusions

The current scientific data indicate the beneficial effects of the functional principles of the studied nutraceutical in the long term combined management of canine OA, thanks to their ability to control all together the pathogenic OA mechanisms, such as chondrodegeneration, inflammation and oxidative stress.

REFERENCES

Adebowale A, Du J, Liang Z, leslie JL, Eddington ND. The bioavailability and pharmacokinetics of glucosamine hydrochloride and low molecular weight chondroitin sulfate after single and multiple doses to beagle dogs. Biopharm Drug Disp 2002; 23: 217-25

Aragon CL, Hofmeister EH, Budsberg SC. Systematic review of clinical trials of treatments for osteoarthritis in dogs. J Am Vet Med Assoc. 2007; 230(4):514-21

Beale BS. Use of nutraceuticals and chondroprotectants in osteoarthritic dogs and cats. Vet Clin North Am Small Anim Pract 2004; 34(1):271-89,

Boothe DM. Anti-inflammatory drugs. In: Small animal clinical pharmacology and therapeutics. WB Saunders Company, Philadelphia, 2001, pp. 281-311

Cerrato S, Brazis P, della Valle MF et al. Effects of palmitoylethanolamide on immunological induced histamine, PGD2 and TNFα release from canine skin mast cells. Vet Immunol Immunopathol 2010; 133(1): 9-15

Conte A, Volpi N, Palmieri L, Bahous I, Ronca G. Biochemical and pharmacokinetic aspects of oral treatment with chondroitin sulfate, ArzneimittelForschung, 1995: 45: 918-25

Costa B, Comelli F, Bettoni I et al. The endogenous fatty acid amide palmitoylethanolamide has anti-allodynic and anti-hyperalgesic effects in a murine model of neuropathic pain: involvement of CB1, TRPV1 and PPARgamma receptors and neurotrophic factors. Pain, 2008; 139(3): 541-50

Costa B, Comelli F, Bettoni I et al. Targeting mast cells in neuropathic pain with the endogenous modulator palmitoylethanolamide. J Periph Nerv Syst 2009; 14(suppl.1): 10

Crovace A, Lacitignola L, Miolo A. Surgery plus chondroprotection for canine cranial cruciate ligament (CCL) rupture. A proton-NMR study. Vet Comp Orthop Traumatol, 2006; 19 (4):239-245

De Filippis D, D'Amico A, Cipriano M et al. Levels of endocannabinoids and palmitoylethanolamide and their pharmacological manipulation in chronic granulomatous inflammation in rats. Pharmacol Res. 2010; 61(4):321-8

Fabris M, Dalle Carbonare M, Leon A et al. Quercetin protects canine articular chondrocytes from oxidative damage. Proceedings 1st World Orthopaedic Veterinary Congress ESVOT-VOS, Munich, September 5th-8th 2002, p. 69

Fox S. Multimodal management of canine osteoarthritis. In: Chronic pain in small animal medicine, Fox SM ed. Manson Publishing LTd, 2010, pp. 189-201

Henrotin Y, Sanchez C, Balligand M. Pharmaceutical and nutraceutical management of canine osteoarthritis: present and future perspectives, Vet J, 2005: 170: 113-123

Johnston SA, McLaughlin RM, Budsberg SC. Non surgical management of osteoarthritis in dogs. Vet Clin North Am Small Anim Pract 2008; 38(6):1449-70

Lambert DM, Vandevoorde S, Jonsson KO, Fowler CJ. The palmitoylethanolamide family: a new class of anti-inflammatory agents? Curr Med Chem 2002; 9(6): 663-74

Marshall W, Bockstahler B, Hulse D, Carmichael S. A review of osteoarthritis and obesity: current understanding of the relationship and benefit of obesity treatment and prevention in the dog. Vet Comp Orthop Traumatol 2009; 22(5): 339-45

Matsuno H, Nakamura H, Katayama K et al. Effects of an oral administration of glucosamine-chondroitin-quercetin glucoside on the synovial fluid properties in patients with osteoarthritis and rheumatoid arthritis. Biosci. Biotechnol. Biochem. 2009; 73(2): 288-292

McLaughlin R. Management of chronic osteoarthritic pain. Vet Clin North Am Small Anim Pract 2000; 30(4):933-49

McNamara PS, Johnston SA, Todhunter RJ. Slow-acting, disease-modifying osteoarthritis agents. Vet Clin North Am Small Anim Pract 1997; 27: 863-81

Millis DL. Physical therapy and rehabilitation in dogs. In: Handbook of veterinary pain management, Gaynor JS, Muir WW eds., Mosby Elsevier, Second edition, 2009, pp.507-37

Miolo A, Badino P, Barbero R, Re G. Glupamid: a novel nutraceutical approach to canine and feline osteoarthritis. J Vet Pharmacol Ther. 2006; 29 Suppl 1:202-3

Mortellaro CM, Miolo A. Approccio medico combinato all'artrosi del cane. Veterinaria 18(3): 9-19

Re G, Barbero R, Miolo A, Di Marzo V. Palmitoylethanolamide, endocannabinoids and related cannabimimetic compounds in protection against tissue inflammation and pain: Potential use in companion animals. Vet J. 2007; 173(1):23-32

Rychel JK. Diagnosis and treatment of osteoarthritis. Top Companion Anim Med. 2010; 25(1):20-5

Sanderson RO, Beata C, Flipo RM, Genevois JP, Macias C, Tacke S, Vezzoni A, Innes JF. Systematic review of the management of canine osteoarthritis. Vet Rec. 2009; 164(14):418-24

Tat SK, Pelletier JP, Mineau F et al. Variable effects of 3 different chondroitin sulfate compounds on human osteoarthritic cartilage/chondrocytes: relevance of purity and production process. J Rheumatol 2010; 37(3): 656-664

Teixeira S. Bioflavonoids: proanthocyanidins and quercetin and their potential roles in treating musculoskeletal conditions. J Orthop Sports Phys Ther 2002; 32: 357-63

Volpi N. Influence of charge density, sulfate group position and molecular mass on adsorption of chondoritin sulfate onto coral. Biomaterials 2002; 23(14): 3015-22

Volpi N. The pathobiology of osteoarthritis and the rationale for using the chondroitin sul fate for its treatment. Current Drug Targets – Immune, Endocrine & Metabolic Disorders,2004, 4: 119-127