OSTEOARTHRITIS: THE CHALLENGE OF ESTABLISHING A PERSONALISED TREATMENT

Summary of Presentations from the TRB Chemedica-Sponsored Satellite Symposium held at the Annual European Congress of Rheumatology - EULAR, Paris, France, on 11th June 2014

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MEETING SUMMARY

The symposium, co-chaired by Prof Johanne Martel-Pelletier and Prof Antonello Pietrangelo, opened with a discussion of metabolic syndrome-associated osteoarthritis (OA) and a brief overview of treatment options by Prof Francis Berenbaum. Prof Jean-Pierre Pelletier then discussed the use of symptomatic slow-acting drugs for OA (SYSADOA) for knee OA within the context of the new European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) recommendations. Finally, Dr Burkhard Leeb concluded the session by discussing the indications, contraindications, and side-effect management of diacerein.

Metabolic Syndrome-Associated OA: A New Phenotype for Targeted Management

Professor Francis Berenbaum

OA is a consequence of the build-up of cartilage degradation products that move to and inflame the synovial membrane.[1] The synovial membrane responds by releasing several mediators including proinflammatory factors such as tumour necrosis factor (TNF) and interleukins ([IL]-1, IL-6, IL-8, etc.) and matrix metalloproteinases (MMPs) (Figure 1). These mediators further degrade the cartilage creating a vicious cycle. Moreover, soluble mediators are also released at the interface between subchondral bone and cartilage leading to degradation in the deep layer of cartilage.

Currently, OA phenotypes are location based, for instance in the knee, hip, hand, and spine. However, there is an emerging paradigm to consider OA phenotypes based on their risk-factors, therefore offering the potential for targeted therapies. These phenotypes include (not exhaustively) post-traumatic OA, metabolic syndrome (MetS)-associated OA, and age-related OA.[2] Typically a post-traumatic OA patient is aged <45 years with OA in the knee, hip, ankle, or shoulder caused by repetitive mechanical stresses or by a unique acute joint trauma (joint fracture, meniscectomy, etc.). Appropriate interventions include joint protection and stabilisation, prevention of falls, and surgery. The typical MetS-OA patient is aged between 45–65 years with generalised OA, overweight or obese, with at least one of the component of the MetS (diabetes mellitus, hypertension, dyslipidemia). Adipokines, insulin resistance, systemic low-grade inflammation, and lipid toxicity are suggested as triggers for initiation of the OA process. Interventions include weight loss, glycaemia, or lipid control, as appropriate. Age-related OA affects patients >65 years in the hip, knee, or hand without any history of trauma or MetS. It could be due to the accumulation of advanced glycation end products (AGEs) or to chondrocyte senescence. There are no specific interventions; however, soluble receptor for AGE (sRAGE)/AGE breakers may be a potential target.

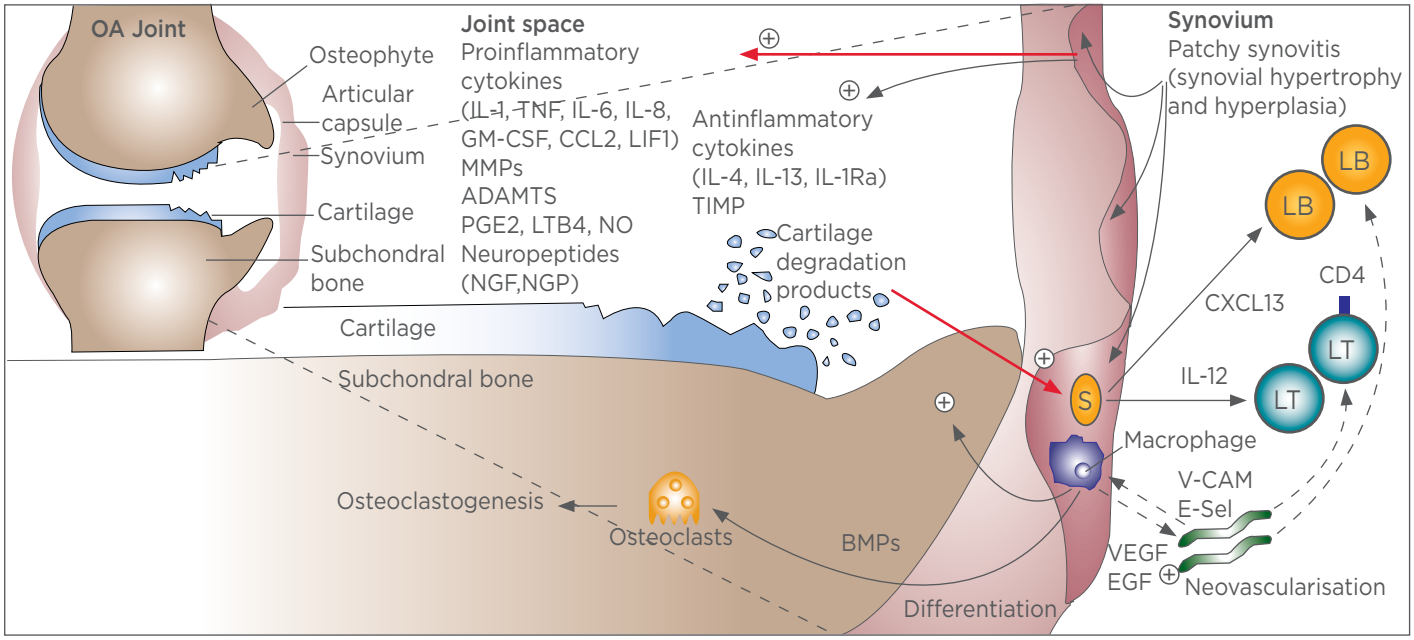

Figure 1: The pathophysiology of osteoarthritis.

ADAMTS: a disintegrin and metalloproteinase with thrombospondin motifs; BMP: bone morphogenetic protein; CCL2: CC-chemokine ligand 2; CXCL13: CXC-chemokine ligand 13; EGF: endothelial growth factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; IL: interleukin; IL-1Ra: IL-1 receptor antagonist; LIF: leukaemia inhibitory factor; MMP: matrix metalloproteinase; NGF: nerve growth factor; NO: nitrous oxide; OA: osteoarthritis; PGE2: prostaglandin E2; TNF: tumour necrosis factor; vCAM: vascular cell adhesion molecule; vEGF: vascular endothelial growth factor.

Modified from Sellam J et al.[1]

Obesity conveys a variable risk of OA depending on the area affected. The relative risk (RR) for the incidence of OA in the knee of a patient with a body mass index (BMI) of 30–35 kg/m^2 versus a BMI <25 kg/m^2 is 2.4 (95% CI 1.0–5.8), and the RR of progression in a patient with a BMI >25 kg/m^2 versus <22 kg/m^2 is 2.6 (95% CI 1.0–6.8). The RR for the incidence of OA in the hip of a patient with a BMI >28 kg/m^2 versus <24 kg/m^2 is 1.9 (95% CI 1.1–3.3).[3-5] OA in the hand is also more frequent in obese patients with a RR of 1.9,[6] despite the mechanical stresses of obesity on the weight-bearing joints, suggesting an alternative mechanism is at play. Adipokines are thought to circulate and accumulate in the joints, causing cartilage degeneration. This phenotype is termed obesity-related or obesity-induced OA. Recent research not only implicates obesity but also metabolic components. MetS is defined as an obese patient having two or more of the following: raised triglycerides (≥150 mg/dL [1.7 mmol/L]); reduced HDL cholesterol (<40 mg/dL [1.03 mmol/L] in males and <50 mg/dL [1.29 mmol/L] in females); raised blood pressure (systolic ≥130 mmHg, diastolic ≥85 mmHg); or raised fasting plasma glucose (≥100 mg/dL [5.6 mmol/L]). The Research on Osteoarthritis Against Disability (ROAD) study followed 1,384 patients for 3 years and showed that the risk of occurrence and progression of knee OA increased in line with the number of MetS components,[7] as did the incidence of knee replacements in 13,753 patients from the Australian Orthopaedic Association National Joint Replacement Registry, even after controlling for weight.[8]

Over 50% of metabolic OA patients suffer from hypertension suggesting that, in addition to insulin resistance, hypertension of the vessels in the subchondral bone, possibly combined with lipid abnormalities of the subchondral bone or the synovial membrane, may increase the risk of OA. Data from the third National Health and Nutrition Examination Survey (NHANES III) show that 28% of OA patients receiving medication for hypertension have diabetes, 12% have angina, 12% have congestive heart failure, 11% had a previous cardiovascular (CV) accident, and 26% have coronary heart disease.[9] Such comorbid CV problems complicate treatment with non-steroidal anti-inflammatory drugs (NSAIDs) as they increase blood pressure by between 3 and 5 mmHg.[10] Since blood pressure is a surrogate marker for ischaemic heart disease,[11] increases such as those caused by NSAIDs increase the risk for CV events. The relationship between myocardial infarction (MI) and NSAID use was investigated in the Taiwanese national health insurance claim database.[12] The risk of an NSAID-induced MI was higher in patients with a prior hypertension diagnosis (n=3,672) than those without (n=4,682). The adjusted odds ratio (OR) was 1.56 (95% CI 1.36–1.79) versus 1.32 (95% CI 1.15–1.51) for oral NSAIDs and 3.43 (95% CI 2.30–5.13) versus 3.18 (95% CI 2.08–4.87) for parenteral NSAIDs. Studies such as these form the basis of the FDA and EMEA special warnings governing NSAID use in patients with, or at risk of, CV disease.

Paracetamol (acetaminophen) is a widely used alternative to NSAIDs and it is now known to raise blood pressure in patients with coronary artery disease after 2 weeks of treatment at a dose of 3 g per day.[13] Opioid analgesics offer another alternative but they are poorly tolerated in older patients with OA as they can cause dizziness, which can, in turn, cause more severe adverse events (AEs). For instance, the risk of fracture is increased by 4.47 (95% CI 3.12–6.41) compared to NSAIDs,[14] which can lead to death in older patients. Therefore, the use of paracetamol and opioids should be considered carefully in OA.

There are many unmet needs in MetS-OA; 63% of patients and 73% of general practitioners are dissatisfied with current treatments.[15] Multiple agents are often required and 53% of OA patients switch to a second NSAID within the first 2 months.[16] Lack of efficacy is the most common reason (33%) with 13% switching due to AEs.[17] There is indeed a critical need for safer treatments in this particular and frequent OA phenotype for which SYSADOA may be an alternative.

Looking to the future, data from the ongoing TRB Chemedica-sponsored DIGItal Cohort Osteoarthritis Design study (DIGICOD) will provide valuable information on risk-based OA phenotypes. DIGICOD will study as many as 500 hand OA patients using radiography and clinical follow-up for 6 years.

Use of SYSADOA in the Treatment of OA. Who to Treat and How?

Professor Jean-Pierre Pelletier

OA is one of the most common chronic diseases, affecting 9.6% of men and 18.0% of women over

the age of 60. The main symptom is pain, with joint tenderness and stiffness being accompanied by limitation of movement. Problems arise due to the large number of patients requiring long-term disease management using a limited number of therapeutic options. Management of OA is complicated by the nature of disease, the severity and number of joints involved, the age of patients, and the fact that pain levels are not always related to structural changes. Furthermore, concomitant disease may influence levels of symptoms. There is also a high variability of both response to treatment and side-effects, and many patients require combined therapy.

OA treatment guidelines have been proposed by the EULAR,[18] the American College of Rheumatology (ACR),[19] the Osteoarthritis Research Society International (OARSI),[20] and the National Institute for Health and Care Excellence (NICE);[21] however, most do not prioritise intervention sequence, are not 'user-friendly', and offer no provision for combined treatment. The ACR guidelines do not make 'strong recommendations' for any particular pharmacological intervention as many of the drugs listed in Europe are not available in the US.[19] The OARSI 2014 guidelines are considered restrictive compared with previous versions and most interventions are classified as uncertain.[22] The recommendations for patients with comorbidities are limited to topical NSAIDs and intra-articular steroids combined with biomechanical interventions, but these are suboptimal for most patients.

Recently, ESCEO formed a working group to propose new guidelines for the treatment of knee OA.[23] The main objective of these new guidelines was the development of a comprehensive, user-friendly OA treatment algorithm allowing prioritisation of interventions using a stepwise approach. The working group consisted of ten rheumatologists, two clinical epidemiologists, and a clinical scientist experienced in OA randomised controlled trial (RCT) design, analysis, and interpretation. The group performed a comprehensive literature search of all interventions considered by current guidelines until February 2014. A draft algorithm recommendation was made in a one-day meeting and a final consensus was reached after three rounds of electronic consultation. The basic principles consist of the need for a combined pharmacological and non-pharmacological treatment, with a core set of initial measures, including patient information access and education, weight loss if necessary, and an appropriate exercise programme.

Four multimodal steps are then established. Step 1 consists of either non-pharmacological or pharmacological background therapy. Non-pharmacological approaches include referral to a physical therapist for realignment treatment if needed and sequential introduction of further physical interventions initially, and at any time thereafter. Pharmacological interventions consist of paracetamol on a regular basis or chronic SYSADOA (e.g. prescription glucosamine sulphate and/or chondroitin sulphate) with paracetamol as needed; topical NSAIDs or capsaicin are added in the still symptomatic patient. Step 2 consists of advanced pharmacological management in the persistent symptomatic patient and centres on the use of cycles of oral COX-2 selective or non-selective NSAIDs, chosen based on concomitant CV, gastrointestinal (GI) or renal risk factors,[20] with intra-articular corticosteroids or hyaluronate used for further symptom relief, if required. There are no age restrictions on the use of NSAIDs as many patients over the age of 75 still benefit from their use in a controlled environment. In Step 3, the last pharmacological attempts before surgery are represented by weak opioids and other central analgesics such as duloxetine. Finally, if symptoms are severely impacting on quality of life, Step 4 consists of end-stage disease management and surgery, with classical opioids as an alternative when surgery is contraindicated. However, the risks of CV events, falls, and fractures leading to increased mortality,[14] discussed above, mean that opioids and narcotics should only be used in knee OA if all other therapeutic options have been exhausted.

The SYSADOA diacerein is recommended by both the EULAR[18] and OARSI[20] guidelines. The OARSI guidelines conclude that diacerein provides a small, but statistically significant, benefit on pain versus placebo (effect size [ES =0.24, 95% CI 0.08–0.39), which compares favourably to the ES versus placebo for paracetamol and NSAIDs of 0.14 (95% CI 0.05–0.22) and 0.29 (95% CI 0.22–0.35), respectively.[20] However, despite a significant risk of diarrhoea (RR=3.5), the guidelines conclude that diacerein is a safer alternative to NSAIDs.[20] Furthermore, the efficacy of diacerein for the treatment of OA symptoms and improvement of function has been demonstrated in four major

meta-analyses that also noted a therapeutic carry-over effect for up to 2-3 months after the cessation of medication.[24-27]

A study of 168 knee OA patients clearly demonstrated the clinical relevance of diacerein using OMERACT-OARSI 2004 responder criteria,[28] which are particularly meaningful for patients as they require ≥20% improvement and absolute change ≥10% in at least two of the three following areas: pain, function, and patient's global assessment. A post-hoc analysis of five major clinical trials[28-32] has assessed the clinical relevance of diacerein using the Minimum Clinically Important Improvement (MCII) and Patient Acceptable Symptom State (PASS) scales.[33] All trials demonstrated an increase in mean pain improvement (MCII) and all but one, a dose-finding study,[32] demonstrated a reduction in mean pain level (PASS).

The carry-over effect was demonstrated in a 16-week study, comparing diacerein with piroxicam 20 mg/day in knee OA patients.[34] Both groups achieved around an 80% reduction in pain by week 16. However, in the 2 months following the cessation of treatment, pain increased in the piroxicam group but was still 30% of baseline levels, whereas, in the diacerein group the pain levels remained lower at about 80% of baseline levels ($p<0.0001$). In the 16-month observational PEGASE study of knee OA, patients treated with NSAIDs plus SYSADOAs experienced a significant reduction in pain 4-8 months after starting treatment (OR 0.72, 95% CI 0.56–0.92) and a significant improvement in function after 8 months of starting treatment (OR 0.77, 95% CI 0.60–0.99).[35]

In summary, diacerein is superior to placebo; it has significant clinical benefits similar to NSAIDs and provides a good alternative to these drugs with a carry-over effect. SYSADOAs improve pain and function and represent the most useful and logical drug treatment for symptomatic OA.

Diacerein: New Recommendations for Treatment Optimisation

Doctor Burkhard Leeb

The EMA and the Pharmacovigilance Risk Assessment Committee (PRAC) recently reviewed data on diacerein and confirmed the safety profile established in 1997 by the French Medicines Agency. To improve the benefit/risk ratio of diacerein, PRAC recommended that treatment with diacerein should be initiated by an experienced OA physician. They also recommended that diacerein should be indicated for patients with OA of the hip or knee where the most data have been generated, but it is not recommended for patients with rapidly progressive hip OA as they may respond only weakly to diacerein. According to the EULAR recommendations, a diagnosis of knee OA can be made based on observations of typical symptoms without the need of costly examinations, laboratory tests, or imaging.[36]

As mentioned by the previous speaker, the efficacy and carry-over effect of diacerein treatment was demonstrated in several well-designed controlled clinical studies and meta-analyses.[24,26,28] The Bartels meta-analysis concluded that diacerein could be an alternative therapy for OA patients who cannot take paracetamol or NSAIDs because of AEs such as CV or GI disorders.[26] Soft stools and diarrhoea are the most frequent side-effect of diacerein and usually occur during the first 2-4 weeks of treatment but abate with continued use. To minimise the risk of diarrhoea, PRAC advise starting treatment with a single 50 mg dose daily for the first 2-4 weeks, after which the recommended dose is 50 mg twice daily. Furthermore, PRAC advise that diacerein should no longer be recommended in patients >65 years of age because they are more vulnerable to complications associated with severe diarrhoea. However, if diacerein is prescribed in these patients without problem, no change in the usual recommended dose is necessary. In cases of unusually frequent liquid or watery stools, diacerein should be stopped and alternative treatments discussed with the prescribing physician. Diacerein is contraindicated in patients with inflammatory intestinal disease (ulcerative colitis or Crohn's disease), intestinal obstruction or pseudo-obstruction, and painful abdominal syndromes of undetermined cause. Patients should avoid laxatives and those who need them should be strictly monitored. Care should be exercised with patients taking diuretics and those with low potassium levels.

Although very rare, hepatic disorders may occur during treatment with diacerein. During clinical trials these disorders were infrequent (0.5%), mostly mild, and usually were reversible transaminase increases. Of note, drug-induced liver injury was rare (0.03%). Since the launch of diacerein in

1994, there has been one documented case of acute hepatitis in a 65-year-old woman who recovered after diacerein treatment was stopped and one case of fatal hepatitis in a 68-year-old man also taking NSAIDs and other undocumented drugs.[37,38] The incidence of liver disorders is approximately 1.68 liver disorders per 100,000 patient-years of treatment (PY-T), which compares favourably with data for NSAIDs and paracetamol. Data for NSAIDs show incidences of 10.0 clinically apparent liver injuries and 23.4 liver injuries resulting in hospitalisation per 100,000 PY-T.[39,40] The rate of transplantation due to paracetamol-induced acute liver failure is 0.33 per 100,000 PY-T.[41] Nevertheless, patients should limit their alcohol intake when taking diacerein. Another recommendation is that diacerein is contraindicated in people with past or present liver disease and patients should be screened for major causes of active hepatic disease. Care should be taken when prescribing other drugs known to cause hepatotoxicity. To manage the risks of hepatotoxicity, patients should be taught to recognise the symptoms and contact their physician immediately if they occur. Signs of hepatic injury should be monitored and treatment stopped if elevated hepatic enzymes or suspected signs or symptoms of liver damage are detected.

Diacerein has been marketed in Austria since 2004 where between 2,500-3,000 patients are treated each year with an average treatment duration of 4-5 months. In this period, three unexpected AEs were reported: one case of severe cramps in the calf muscle and foot pain without electrolyte imbalance, one case of vaginal discharge, and one case of loss of consciousness which was not related to diacerein or any drug.

In conclusion, diacerein is indicated for the symptomatic treatment of OA of the hip or knee. Its onset of efficacy is between 2-4 weeks after treatment start. During this time, paracetamol or NSAIDs may be co-prescribed to provide more immediate pain relief. Diacerein is contraindicated in liver disease and monitoring of liver function is recommended. Treatment should be started with a single daily dose of 50 mg, increasing to a twice-daily dose (100 mg daily). Due to the risks of dehydration associated with severe diarrhoea in elderly people, diacerein is no longer recommended in patients over 65 years. Risks and benefits should be considered for each patient and therapy should be individualised wherever possible. Patients with symptomatic hip or knee OA, who are refractory to paracetamol and for whom NSAIDs are contraindicated or ineffective, are ideal candidates for treatment with SYSADOAs, particularly diacerein.

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