on whether MTX can be considered a disease-modifying antirheumatic drug (DMARD).

According to Prof. Kingsley, the aim of DMARD therapy is to improve long-term outcomes, not just symptoms. However, definitive demonstration of DMARD efficacy is difficult to confirm outside of placebo-controlled, randomized, controlled trials.

The MTX in Psoriatic Arthritis (MIPA) Trial [Kingsley et al. *Rheumatology*. In Press 2011] was a 6-month RCT that compared MTX with placebo to test the hypothesis that the drug improves disease activity and function in PsA. Key findings from the study indicate that MTX improves self-reported symptoms but has no effect on objective joint counts or acute phase reactants, which classifies it as a "symptom-modifying agent" rather than a DMARD. Prof. Kingsley recommends a reconsideration of current guidelines, based on new data [Baranauskaite A et al. *Ann Rheum Dis* 2011; Lie E et al. *Ann Rheum Dis* 2009; Kingsley GH et al. *Rheumatology*. In press 2011].

Reactive Arthritis: Clinical Insights and Treatment Options

Reactive arthritis (ReA) occurs 1 to 6 weeks after exposure to a causative organism, either postdysentery or postvenereal. John D. Carter, MD, University of South Florida, Tampa, Florida, USA, discussed the epidemiology of ReA and the pathophysiology, treatments, and outcomes of *Chlamydia trachomatis*-induced ReA (CiReA) [Carter JD et al. *Arthritis Rheum* 2009].

In the United States, the incidence of ReA is underestimated and underdiagnosed. Dr. Carter concluded that *Chlamydia* might be a common cause of undifferentiated spondyloarthropathies; that ocular serovars appear to be uniquely capable of causing ReA [Gerard HC et al. *Microb Pathog* 2010]; that ReA is a Th2-predominant disease; and that combination antibiotics show promise in the amelioration of CiReA symptoms and the elimination of the persistent state of *Chlamydia*.

Pain, the Brain, and Osteoarthritis

Written by Maria Vinall

Data that were presented by Apkar Vania Apkarian, PhD, Northwestern University, Chicago, Illinois, USA, appear to demonstrate that chronic pain imparts a specific signature on the brain that is associated with functional, behavioral, and chemical changes in the cerebral cortex. The specificity of this pain signature for different clinical conditions may provide the opportunity to develop targeted therapies for osteoarthritis and other chronic painful conditions.

Dr. Apkarian reviewed a study that was conducted at Northwestern University in which painful pressure stimuli were applied to the knee of osteoarthritis (OA) patients and healthy controls and ratings of evoked pain and related brain activity were subsequently examined. In this study, the psychophysical pressure pain ratings and brain activation patterns of evoked pain were essentially the same between OA patients and healthy subjects and between knees with better and worse OA. In addition, the location of brain activity for evoked pain did not overlap the areas that were associated with continuous pain. However, brain activity that was related to pain scoring systems, such as the Western Ontario and McMaster Universities Osteoarthritis Index and the McGill Pain Questionnaire, mainly overlapped areas that were identified for chronic pain [Parks EL et al. *Eur J Pain* 2011].

Regional gray matter density studies indicate decreases in grey matter in specific regions of brain that are associated with chronic OA pain. There was also evidence for reversibility, whereby treatment may potentially undo grey matter decreases. In a recent, yet-to-be published study, Dr. Apkarian's group also examined brain anatomical changes in healthy patients compared with those who have chronic back pain, complex regional pain syndrome, or OA. Using Voxel-wise Voxel-based morphometry, the group examined how the brain reorganizes regionally in response to pain. They identified unique morphological signatures that are associated with the different types of chronic pain. Areas of brain interaction increased in chronic pain subjects, destroying spatial relationships. This was not apparent in healthy subjects. Whether pain was chronic versus acute determined the amount of time the brain required to reorganize into its new anatomical state.

Specificity of this signature for each clinical condition provides the opportunity to develop targeted therapies. In a double-blind, placebo-controlled brain imaging study in which chronic back pain subjects were treated with a 5% lidocaine patch or placebo, no difference in pain perception or brain activity was noted between the two groups at 2 weeks. However, when the subjects were regrouped into persisting pain (nonresponders) and decreasing pain (responders), it was possible to identify at baseline two functional connections in the brain that distinguish between persisting and decreasing chronic

back pain and which can be used to predict which patients will respond to placebo. A pure placebo and brain imaging study found the same results in OA patients.

Using brain coordinates from a chronic back pain study, the investigators were able to identify a prefrontal circuit that differentiates and predicts placebo responders from nonresponders with >95% accuracy. Thus, there is a brain circuit that indicates which patients will be placebo responders. "The brain predicts the future, and this may be a critical tool for future decisions about the patient," Dr. Apkarian concluded.

N-3 Fatty Acids at the Intersection of RA and CV Morbidity

Written by Rita Buckley

A meta-analysis of 17 randomized, controlled trials suggests that supplementation with oral n-3 fatty acids improves patient-assessed pain, duration of morning stiffness, and number of painful and/or tender joints in patients with rheumatoid arthritis (RA) [Bahadori B et al. *JPEN J Parenter Enteral Nutr* 2010; Kremer JM. *Am J Clin Nutr* 2007; Goldberg RJ, Katz J. *Pain* 2007]. Joel M. Kremer, MD, Albany Medical College and the Center for Rheumatology, Albany, New York, USA, reviewed studies on the efficacy of fish oil in the treatment of RA and its cardiovascular (CV) benefits.

A 24-week, prospective, double-blind, randomized trial of high and low doses of fish oil and olive oil showed significant improvements from baseline in the number of tender joints (p=0.05 for the high dose; p=0.04 with the low dose) and morning stiffness (p≤0.01) and significant decreases in leukotriene B4 and macrophage IL-1 production, especially in the high-dose n-3 fatty acid group [Kremer JM et al. *Arthritis Rheum* 1990].

A 12-month, double-blind, randomized study [Geusens P et al. *Arthritis Rheum* 1994] compared supplementation with either 2.6 mg of n-3 fatty acids or 1.3 gm of n-3 fatty acids+3 gm of olive oil. Findings indicated that 2.6 gm/day of n-3 fatty acids led to significant clinical benefit and may have reduced the need for concomitant antirheumatic medication.

According to Dr. Kremer, more than 20 peer-reviewed, blinded studies have demonstrated a consistent amelioration of tender joints in patients who have been given n-3 fatty acids versus controls of corn or olive oil. All but two studies added n-3 fatty acids to existing RA treatment regimens.

The minimal effective dose of n-3 fatty acids per day appears to be 3 to 5 g, or at least 10 capsules per day of most over-the-counter fish oil supplements. These contain about 300 mg of n-3, but "high-potency" capsules with 500 to 950 mg of n-3 are now available.

The finding that fish oil decreases CV risk is well established [Mozaffarian D. *Am J Clin Nutr* 2008; Albert CM et al. *N Engl J Med* 2002]. A protective effect seems evident at doses of long-chain n-3 fats >250 mg, much lower than those needed for symptomatic relief in RA [James M. *Proc Nutr Soc* 2010].

Fish oil may reduce CV events in RA via direct myocardial and, possibly, antithrombotic actions [Cleland LG et al. *J Rheumatol* 2006] and may also induce a favorable vascular response to ischemia [DiGiacomo RA et al. *Am J Med* 1989].

In a double-blind prospective study, 32 patients with primary or secondary Raynaud phenomenon were randomly assigned to olive oil placebo or fish oil groups. Data indicated that the ingestion of fish oil improved tolerance to cold exposure and delayed the onset of vasospasm in patients with primary (p=0.05), but not secondary, Raynaud phenomenon. The improvements were associated with significantly increased digital systolic blood pressures in cold temperatures [DiGiacomo RA et al. *Am J Med* 1989].

Dr. Kremer recommended three high-potency fish oil capsules (approximately 3 g n-3/day) in young patients with primary Raynaud, with at least 6 weeks of observation. He noted that the potential of n-3 fatty acids in the amelioration of CV comorbidity in inflammatory diseases, like RA, is worthy of further study.

Calcium, Bone Health, and CVD

Written by Rita Buckley

The benefits of calcium intake for bone health are very clear, but the risks—cardiovascular (CV), in particular—have become controversial. Richard Bockman, MD, PhD, Weill Cornell Medical College and Hospital for Special Surgery, New York, New York, USA, discussed calcium metabolism and the results of recent studies on calcium supplementation and CV health.