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ANGIOTENSIN II TYPE 2 RECEPTOR ANTAGONIST FOR POST-HERPETIC NEURALGIA

Findings from earlier studies have demonstrated that the Angiotensin II, type 2 receptor (AT_2R) is expressed in human sensory neurons. As studies have demonstrated that EMA401, a highly selective AT_2R antagonist, has analgesic properties, this study was designed to further determine the analgesic efficacy, tolerability, safety and kinetics of this compound for patients with post- herpetic neuralgia.

This multicenter, double-blind, placebo-controlled trial included participants from 29 sites in six countries. All patients had a diagnosis of post-herpetic neuralgia, and were randomized to receive either the study drug, at 100 mg, or a placebo, administered twice per day. After randomization, the subjects completed efficacy endpoint patient outcome measures, and were given a diary card to record their daily pain intensity and the time of study drug administration. All were assessed for efficacy, safety and pharmacokinetics. The primary endpoint was the change in mean pain intensity from baseline to the final week of dosing.

A total of 183 patients were assessed, with 92 receiving the study drugs and 91 the placebo. The changes in mean pain intensity between baseline and final weeks of treatment were 2.29 for the treatment group and 1.6 for the placebo group (p=0.0066). The difference between the groups in mean pain intensity first reached significance at week three. No significant treatment related side effects were noted in the treatment group.

Conclusion: This study of patients with post-herpetic neuralgia found that EMA401, a highly selective angiotensin II type 2 receptor antagonist, significantly reduced the pain symptoms of this condition.

Rice, A., et al. EMA401, on Orally Administered, Highly Selective Angiotensin II Type 2 Receptor Antagonist, as a Novel Treatment for Post-Herpetic Neuralgia: A Randomized, Double-Blind, Placebo - Controlled, Phase 2 Clinical Trial. **Lancet.** 2014**,** May 10-16: 1637-1647.

AUTOLOGOUS CHONDROCYTE IMPLANTATION AT THE PATELLA

Cartilage defects are present in more than 50% of patients undergoing knee arthroscopy. The articular surface of the patella is affected in 11 to 36% of the cases. However, cartilage repair at the patella has demonstrated relatively poor results. This study assessed the effect of treatment with autologous chondrocyte implantation (ACI) for cartilage defects of the patella.

Patients presenting for repair of cartilage defects in the patella underwent chondrocyte harvesting, with chondrocytes expanded in cell culture. The cells were then implanted at the site of the defects. Postoperative rehabilitation included the use of a locked brace for ambulation, with weight bearing as tolerated for those with isolated ACI. The patients were followed prospectively, with questionnaires used to assess function, activity level and satisfaction.

A total of 110 patients were followed post-surgery for an average of 90 months. The average size of the patella defect was 5.4 cm^2. Nine were considered treatment failures and were revised. Overall, the Short Form–12 Physical Component Subscale demonstrated an increase from 38.6 to 44.1 (p=0.001). Significant improvements were also noted in the International Knee Documentation Committee (IKDC) scores ($p < 0.0001$) , the modified Cincinnati score ($p < 0.0001$), the Knee Society knee score, and the Knee Society function score, ($p < 0.0001$). The WOMAC score improved from 50.4 to 28.6, with 75% of patients exceeding a commonly accepted threshold for MCIDs. Of the 93 patients asked to rate their knee, 86% rated their knee function as good or excellent.

Conclusion: This study of patients with cartilage defects in the patella found that autologous chondrocyte implantation can produce significant and clinically meaningful improvements in pain and function.

Gomoll, A., et al. Autologous Chondrocyte Implantation in the Patella: A Multicenter Experience. **Am J Sports Med.** 2014, May; 42 (5): 1074-1081.

ENERGY EXPENDITURE DURING RESISTIVE TRAINING ACTIVITY

To date, few studies have addressed the energy expenditure of resistance training. This study assessed the energy expenditure of resistance training using two separate methods.

Subjects included twelve healthy men, with a mean age of 23.6 years. The subjects completed each individual resistive training exercise for a maximum of 60 seconds or until fatigue degraded the proper form. After completing each exercise, the subject was rested. Traditional calorimetry was used to measure oxygen uptake continuously throughout the trial, including during the recovery period between exercises. The average energy expenditure was calculated using a traditional calculation as well as a recovery calculation.

Based upon the traditional calculation, the kilocalories-per-

minute expenditure was 4.31 for push-ups, 4.09 for curl-ups, 5.28 for lunges and 4.03 for pull-ups. However, using the recovery calculation, the kilocalories-per- minute were 8.56 for push-ups, 7.29 for curl-ups, 9.33 for lunges and 9.95 for pull-ups. After converting the mean values for each exercise to METS, all were classified as being of moderate intensity when using the traditional method, while when using the recovery calculation, all but the curl-ups were classified as vigorous.

Conclusion: This study of energy expenditure during resistive training found that traditional measures of energy expenditure may underestimate energy consumed during these activities, with the authors suggesting that the recovery time method of estimation may be more accurate.

Vezina, J., et al. An Examination of the Differences between Two Methods of Estimating Energy Expenditure in Resistive Training Activities. **J Strength Cond Res.** 2014, April; 28(4): 1026-1031.

EXERCISE INTERVENTIONS TO PREVENT SPORTS INJURY

As management of sports injuries is difficult and time-consuming, prevention of these injuries is of particular interest. This meta-analysis was designed to better understand the effect of physical activity exercises as a means to prevent injuries.

Data were reviewed from several databases, searched through January of 2013. Those studies included focused on primary prevention,subjects free of injury at inclusion, sports/physical activity injuries, randomized controlled trials, appropriate controls and publication in peer reviewed journals.

Twenty-five trials were selected for inclusion, including data from 26,610 individuals with 3,464 injuries. Injury prevention strategies were assessed. As a group, the relative risk of injury, using the prevention strategies was 0.632, with significant findings for both adults and adolescents. The pooled effect of strength training, including four studies, resulted in a relative risk of 0.315. The pooled effect of proprioceptive training resulted in a relative risk of 0.55. No significant effect was found for stretching.

Conclusion: This review and meta-analysis of injury prevention programs found that, while stretching has no beneficial effect, multiple exposure programs, proprioceptive training and strength training are effective strategies. Strength training was found to reduce injury risk to less than one third.

Lauersen, J., et al. The Effectiveness of Exercise Interventions to Prevent Sports Injuries: A Systematic Review and Meta-Analysis of Randomized, Controlled Trials. **Br J Sports Med.** 2014, June; 48(11): 871-877.

FACTORS PREDICTING ROTATOR CUFF RETEARS

After rotator cuff tears, the rate of retears is estimated to be between 11 and 57%. Factors that contribute to rotator cuff retears remain unclear. Thus, this study was designed to better understand risk factor for retears.

This retrospective study included 1,000 consecutive patients who had undergone a primary rotator cuff repair. Preoperatively, all patients completed a questionnaire grading the frequency of pain during activity and at rest, as well as the frequency of extreme shoulder pain and stiffness. Questions also focused on employment and sport related activity. All patients underwent a preoperative clinical examination. During surgery, measurements were made of the tear. Six months after surgery, all participants underwent ultrasound examination to determine the integrity of the surgical site.

At surgery, 561 full thickness and 393 partial thickness tears were noted. At follow-up, retears were seen in 174 patients, corresponding to an overall rate of 17%. Independent factors predicting rotator cuff retears, ranked by strength of predictive value, included anterior posterior tear lengths ($p<0.001$), age at surgery $p<0.001$), tear size area ($p<0.001$), mediolateral tear length ($p<0.001$), tear thickness ($p=0.022$) and operative time ($p=0.036$).Using these, the authors provide an equation for estimating the risk for retear.

Conclusion: This retrospective analysis of 1,000 consecutive rotator cuff retears found that initial tear dimensions and advanced age were significantly related to the risk of retear at six months.

Le, B., et al. Factors Predicting Rotator Cuff Retears. An Analysis of 1,000 Consecutive Rotator Cuff Repairs. **Am J Sports Med**. 2014, May; 42(5): 1134-1142.

FRACTURE AFTER ALENDRONATE DISCONTINUATION

The Fracture Intervention Trial Long-Term Extension (FLEX) trial demonstrated that, among older postmenopausal women who have used alendronate for five years, those who discontinue treatment have similar fracture rates to those who receive an additional five years of treatment. However, the rate of symptomatic vertebral fractures is lower among those who continue therapy. This post-hoc analysis was designed to test methods of predicting fractures among women who have discontinued alendronate therapy.

Data were obtained from the FLEX trial, which randomized postmenopausal women to receive either alendronate sodium or placebo for five years. Bone mineral density (BMD) was measured at the hip and lumbar spine at baseline, and at the 36-month follow-up visit. In addition, bone turnover biochemical markers were assessed at baseline and at 12- month and 36-month visits. The primary outcome variable was the incidence of clinical fractures, defined as either new, non -spine fracture or new clinical

vertebral fracture, during the FLEX follow-up period.

Of the 437 participants randomized to receive placebo, 22% experienced one or more clinical fractures during follow-up. Older age and lower hip BMD at the time of medication discontinuation were strong predictors of fracture risk after discontinuation. However, neither the one-year change in hip bone mineral density, nor the one- or three-year change in biochemical markers of bone turnover, were associated with the risk of fracture after discontinuation.

Conclusion: This study of postmenopausal women, all treated with alendronate therapy for five years, found that age and bone mineral density at the time of discontinuation of medication were useful for predicting clinical fractures during the subsequent five years.

Bauer, D., et al. Fracture Prediction after Discontinuation of Four to Five Years of Alendronate Therapy. The Flex Study. **JAMA Internal Med**. 2014; doi:10.1001jamainternmed. 2014.1232

HAND OSTEOARTHRITIS AND FENOFIBRATE

Fibrates are agonists of the peroxisome proliferator activated receptor alpha. These medications have long been used for dyslipidemia and have also demonstrated benefits for reducing systemic and synovial inflammation, inhibit chondrocyte inflammatory response and exert anti -nociceptive properties. This study was designed to determine the effects of fenofibrate for the treatment of patients with erosive hand osteoarthritis (EHOA).

This single center non-controlled open label study included 15 patients over the age of 45 years with a diagnosis of HOA. The patients received treatment with 145 mg of fenofibrate per day for 12 weeks. Clinical evaluations were made at baseline and at weeks four, eight, and 12. These included assessment of disease activity, pain, and laboratory tests of inflammatory markers. Response to treatment was assessed in accordance with Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society criteria.

Fourteen women were enrolled in the study. Fenofibrate treatment resulted in significant decreases in pain scores, total joint count, the duration of morning stiffness, as well as the patient's assessment of disease activity and global health. An improvement of hand function was noted by improvements in the Cochin index. Significant reductions were noted in levels of ESR, while no change was noted in several other inflammatory markers.

Conclusion: This pilot, non-controlled study of patients with erosive hand osteoarthritis found that fenofibrate, an agonist of the peroxisome proliferator activated receptor alpha, may be helpful for reducing pain, and improving hand function.

Shirinsky, I et al. Treatment of Erosive Osteoarthritis with Peroxisome Proliferator – Activated Receptor Alpha Agonist Fenofibrate: A Pilot Study. **Rheum International** 2014, May. 34(5):613-616.

MEMORY CONSOLIDATION WITH CAFFEINE

Caffeine has been shown to have positive effects on attention, processing speed and, in some cases, working memory. However, most studies have administered caffeine before learning, causing the effects on memory to be impossible to dissociate from other effects of the caffeine. This study assessed the effect of caffeine administered after a learning task.

This randomized, double-blind, placebo-controlled trial included caffeine naïve participants. A hippocampal memory-dependent task included two phases. During the incidental encoding phase, participants viewed pictures of objects and decided whether the picture depicted an indoor or an outdoor item. The subjects were then given either a placebo or 200 mg of caffeine. Twenty-four hours after the study session, the participants were evaluated for recognition performance, with researchers presenting items from the previous day (targets), new items(foils) and items that were similar but not identical to previously shown pictures (lures). For each image, they were instructed to decide whether the image was ”old”, ”new” or ”similar”.

Participants who received caffeine were more likely to call lure items “similar”, rather than “old”, as compared to those who received placebo. No difference was found between groups in rates of target hits or foil rejections, suggesting that basic recognition was not altered. Calculating a lure discrimination index, as *P* (”similar”/lure) minus *P* (”similar”/foil) to correct for response bias, a significant difference was found between groups (p=0.05). The authors note that this finding suggests that caffeine enhanced consolidation of the initial study session, such that discrimination during retrieval was improved. Reviewing multiple caffeine doses, it was determined that a dose of at least 200 mg was required to produce the enhancing effect of caffeine on consolidation of memory.

Conclusion: This study found that caffeine, administered after information encoding, improved the patients’ ability to consolidate memories.

Borota, D., et al. Post- Study Caffeine Administration Enhances Memory Consolidation in Humans. **Nature Neurosci.** 2014, February; 17(2): 201-203.

MESENCHYMAL STEM CELLS FOR OSTEOARTHRITIC KNEES

Cartilage regeneration procedures have become the focus of increased interest due to their potential to provide pain relief and alter the progression of osteoarthritis (OA). While mesenchymal stem cells (MSCs) can be derived from a number of tissues, some have suggested that those derived from adipose have the highest chondrogenic potential. This study investigated outcomes of adipose derived MSC implantation in patients with OA of the knees

This retrospective review included the records of 56 consecutive patients treated with MSC implantation for cartilage regeneration. All had isolated, full-thickness articular cartilage lesions in OA knees. The mean size of the cartilage lesions was 5.4 cm^2. The subjects originally had MSCs aspirated from adipose tissue from their buttock fat pad, with the stem cells introduced to the cartilage lesion under arthroscopic guidance. The knees were then immobilized for two weeks, with weight bearing initiated at two weeks, progressing to full weight- bearing at four weeks. Clinical outcomes were evaluated using the International Knee Documentation Committee (IKDC)

score and Tegner activity scale. For those agreeing to a second look arthroscopic assessment, cartilage repair was assessed using International Cartilage Repair Society (ICRS) grading.

At final follow-up, the mean IKDC and Tegner activity scale scores had both improved significantly ($p<0.001$). The patients reported that satisfaction with the procedure was excellent in 63%, and good in 31%, of the cases. However, at second look arthroscopy, two of the 37 lesions (five percent) had grade I (normal), seven (19%) had grade II (near normal), 20 (54%) had grade III (abnormal) and eight (22%) had grade IV (severely abnormal) lesions. Those patients with lesions larger than 5.4 cm^2 had significantly worse outcomes than did those with smaller lesions.

Conclusion: This study of patients with osteoarthritis of the knee found that autologous mesenchymal stem cell implantation, derived from adipose, can produce significant functional gains.

Koh, Y., et al. Second Look Arthroscopic Evaluation of Cartilage Lesions after Mesenchymal Stem Cell Implantation in Osteoarthritic Knees. **Am J Sports Med**. 2014, doi:10.1177/0363546514529641

NSAIDS AFTER ROTATOR CUFF TENDON REPAIR

While nonsteroidal anti-inflammatory drugs (NSAIDs) have been found to affect bone metabolism and fracture healing, little evidence exists concerning their effect on tendon healing. This animal study assessed the effect of a selective COX-2 inhibitor on tendon-bone healing.

Using an animal rotator cuff model, surgery was performed on 39 rats to detach and repair the supraspinatus tendon insertion sites. After surgery, 13 rats received daily injections of meloxicam for 10 days (group A), while 13 rats received injections of meloxicam starting at postoperative day 11 (group B). A third group of 13 rats received saline injections (group C). Tendon specimens of each group were used for gross inspection, histopathology evaluation and biomechanical testing. Biomechanical testing was completed at 21 days post-surgery, using parameters including load to failure, stiffness and displacement.

Maximal loads in group B were significantly lower than those for both the C and A groups. Stiffness was lower in group B than in group A ($p=0.05$). Histological examination revealed less organized collagen at the tendon bone interface in group B than in the other two groups.

Conclusion: This animal study found that, after a rotator cuff repair, delayed (days 11 to 20) use of nonsteroidal anti-inflammatory drugs, during the proliferative phase of healing may negatively impact tendon strength and collagen formation.

Chechik, O., et al. Timing Matters: NSAIDs Interfere with the Late Proliferation Stage of the Repaired Rotator Cuff Tendon Healing in Rats. **Arch Orthop Trauma Surg**. 2014, April; 134(4): 515-520.

OSTEOARTHRITIS AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

Estimates of the prevalence of osteoarthritis (OA) following anterior cruciate ligament (ACL) reconstruction range from 10% to 90%. Some have reported that meniscus injuries requiring repair increase this risk. However, randomized trials are sparse. This study was designed to better understand the prevalence of radiological OA after ACL reconstruction.

This randomized, controlled trial included 164 patients, treated between 1995 and 1997. Each had a traumatic ACL injury. The participants were randomized to receive either a bone tendon bone graft or a semitendinosus graft. Fourteen years after reconstruction, 135 were contacted and agreed to participate in this follow-up study. All subjects underwent radiological examinations of both knees to determine the grade of OA, and all also underwent knee function assessment using a visual analogue scale and the Knee Injury and Osteoarthritis Outcomes Score (KOOS). Osteoarthritis was defined as a Kellgren-Lawrence grade 2 or greater.

Osteoarthritis was more frequent in the reconstructed knee than in the contralateral knee. OA of the medial compartment was most frequent, occurring in 57% of OA cases in the reconstructed knee, and in 18% in the contralateral knee ($p<0.001$). Univariable analysis revealed that the risk of OA did not differ between those with, versus without medial meniscal injury. Patients with a resected medial meniscus were at increased risk relative to those with a repaired medial meniscus ($p=0.03$).

Conclusion: This prospective study found a three-fold increase in osteoarthritis after an anterior cruciate ligament injury, treated with reconstruction, as compared to the contralateral uninjured knee.

Barenius, B., et al. Increased Risk of Osteoarthritis after Anterior Cruciate Ligament Reconstruction. A 14-Year, Follow-up Study of a Randomized, Controlled Trial. **Am J Sports Med**. 2014, May; 42(5): 1049-1057.

PSOAS TENDINOPATHY INTERVENTIONS

Psoas tendinopathy, or internal snapping hip syndrome, occurs predominantly as an overuse injury. Pain is thought to originate from the friction of the iliopsoas tendon sheath over the iliopectineal ridge or the iliacus tendon. Operative interventions include step cutting the iliopsoas and releasing the iliopsoas tendon. This study assessed the efficacy of surgery as well as tendon and bursa hip injections over time.

Patients with primary psoas tendinopathy were seen by a hip specialist and referred for musculoskeletal ultrasound and plain film radiographs. If snapping was visualized, triamcinolone and anesthetic were placed in the tendon sheath and bursa. Six to eight weeks post-injection, the subjects were reassessed for psoas related pain. Those with no pain relief were removed from the study. Those with temporary benefit were offered the choice of further injections or surgical intervention. All were administered questionnaires, the nonarthritic hip score (NAHS) and a study questionnaire, which queried the patient concerning hip function activity and pain over the previous 48 hours.

From 1997 to 2011, 37 hips were identified with primary iliopsoas tendinitis. Of those, 13 hips were injected, with no pain improvement. Twenty-six hips, (70%) were treated surgically with psoas tenotomy, and 11 (30%) were treated by steroid injection alone. The average follow-up period for those patients treated by surgical release was 49 months, while the average for those treated

with steroid injection was 52 months. The average NAHS score after surgery and injection were 68 and 86, respectively ($p<0.05$). Improvements in pain were similar between the surgery and injection groups, though neither group noted increased activity.

Conclusion: This study of patients with primary psoas tendinopathy found that local steroid injections can provide long-term pain relief. For patients with only temporary relief from injections, psoas tenotomy can provide good long term pain relief.

Garala, K., et al. Medium Term and Long-Term Outcomes of Interventions for Primary Psoas Tendinopathy. **Clin J of Sports Med.** 2014, May; 24(3): 205-210.

STEM CELLS FOR ROTATOR CUFF HEALING

Rotator cuff tears occur in more than 50% of individuals over the age of 60 years. However, approximately 50% of surgically repaired rotator cuffs do not heal properly. As stem cell therapies for tissue regeneration and repair represent a new avenue for investigation, this study was designed to determine whether healing after a rotator cuff repair can be accelerated through the use of autologous stem cells.

This animal study included 40 white male rabbits. All underwent bilateral subscapularis (SSC) rupture. After six weeks the rabbits were randomly divided into five groups. These included adipose-derived stem cells (ADSCs) plus repair, saline plus repair, ADSCs only, saline only and a control. Animals then underwent electromyographic, biomechanical and histologic analysis six weeks after the secondary procedures. All tendons in the ADSC only and saline groups failed to heal. Biomechanically, the load to failure of the ADSC plus repair group was 87.02 N, and that of the saline plus repair group was 59.85 N ($p=0.085$). Histologically, the mean proportion of fatty infiltration in the SSC muscles was lowest in the ADSC plus repair group ($p<0.001$).

Conclusion: This study, using an animal model for rotator cuff tears, found that locally administered adipose derived stem cells may have a positive benefit on tendon-to-bone healing and fatty infiltration.

Oh, J., et al. 2013 Neer Award: Effect of the Adipose Derived Stem Cell for the Improvement of Fatty Degeneration and Rotator Cuff Healing in a Rabbit Model. **J Shoulder Elbow Surg**. 2014, April; 23(4): 445-456.

STRETCHING TECHNIQUES AND VERTICAL JUMPING PERFORMANCE

Many coaches believe that static stretching before competition improves performance, prevents injuries and increases flexibility. Recent studies have suggested, in fact, that static stretching may negatively impact athletic performance, and that the effect of stretching on performance depends upon the type of stretching. This study evaluated three different stretching techniques with regard to their effect on vertical jumping performance.

One hundred, physically active, male athletes volunteered for participation in this study. All subjects underwent pre-jump performance assessments, including flexibility measurement. The volunteers were divided into three groups, according to flexibility and pre-jump performances. After warm-up, the participants were asked to perform one of three stretching techniques. Those techniques included ballistic stretching (BS), proprioceptive neuromuscular facilitation stretching plus ballistic stretching (PNF plus BS) and proprioceptive neuromuscular facilitation stretching plus static stretching (PNF plus SS). Each stretching technique was applied bilaterally, with four sets of each performed. The subjects were then assessed by countermovement jump, and were asked to jump as high as possible while extending the legs. The jump was repeated three times.

For the entire group, BS increased vertical jump performance, and also improved the performance of those in the low average flexibility and poor pre-jumping performance groups. PNF plus BS improved performance among those with high flexibility.

Proprioceptive neuromuscular facilitation plus SS decreased performance in the whole group, as well as among those in the high flexibility, moderately high pre-jumping performance groups.

Conclusion: This study, comparing pre-performance stretching techniques, found that combining proprioceptive neuromuscular facilitation with static stretching can degrade jumping performance. The results suggested that ballistic stretching is more suitable, resulting in enhanced performance.

Kirmizigil, B., et al. Effects of Three Different Stretching Techniques on Vertical Jumping Performance. **J Strength Cond Res.** 2014, May; 28 (5): 1263-1271.

TENNIS-RELATED INJURIES

Tennis is among the fastest growing sports in the United States, with a 46% increase in participants over the past decade. Most data concerning tennis injuries are based upon elite or professional, rather than amateur, player data. This study was designed to determine patterns of injury among all tennis players seen for injury in emergency departments in the United States.

Data were obtained from the National Electronic Injury Surveillance System (NEISS), with data collected from 100 hospitals, representing a stratified probability sample of 5,400 hospitals. The data were reviewed for mechanism of injury and reviewed by age categories. Injury diagnoses and locations were identified.

From 1990 through 2011, 492,002 patients were treated in United States emergency departments for tennis- related injuries. The number of tennis related injuries decrease by 41.4% during the years 1990 to 2011. Children five to eighteen years of age accounted for 29.2% of those injuries, and patients 19 to 45 years accounted for 27.3% of the cases. Most patients were treated and released (96.2%). Among the patients admitted to a hospital, 65.6% were 56 years of age or older.

The most commonly injured body regions were lower extremities, representing 42.2% of the injuries, with injuries to the ankles representing 47.2% of lower extremity injuries. The wrist represented 34.8% of upper extremity injuries. Strains and sprains were the modal injury, at 44.1%, followed by fractures, at 14.6%, and soft tissue injuries, at 13.9%.

Conclusion: This study demonstrates that tennis-related injuries have decreased over the past 20 years. More than 40% of all injuries involved the lower extremities.

Gaw, C., et al. Tennis Related Injuries Treated in the United States Emergency Departments, 1990 to 2011. Clin J Sport Med. 2014, May; 24(3): 226-232.

ADALIMUMAB AND JOINT DAMAGE IN EARLY RHEUMATOID ARTHRITIS

Given the significant impact that biologic therapies have on rheumatoid arthritis (RA), some have advocated for the earlier use of these medications. The efficacy and safety of the tumor necrosis factor-alpha inhibitor, Adalimumab, has been well established as a monotherapy or combined with methyltrexate (MTX). This study compared the efficacy and safety of early intervention with adalimumab plus MTX versus MTX alone for inhibiting radiographic progression in MTX-naive Japanese patients with RA.

This study included patients at least 20 years of age, all diagnosed with RA. The subjects were randomized to receive either subcutaneous adalimumab, 40 mg, or a placebo every other week in combination with oral MTX at 6 mg/wk or MTX alone at up to 8 mg/wk. All participants were assessed by radiographs of the hands and feet and scored by two independent readers held blind to the treatment assignment.

A total of 171 patients received the combination medications and 163 received MTX alone. Radiographic progression was significantly more reduced in the combination group at 26 weeks than in the MTX group alone ($p<0.001$).

Conclusion: This study of patients with rheumatoid arthritis found that a combination of methyltrexate and adalimumab is superior to methyltrexate alone in preventing joint deterioration.

Takeuchi, T., et al. Adalimumab , a Human Anti-TNF Monoclonal Antibody, Outcome Study for the Prevention of Joint Damage in Japanese Patients with Early Rheumatoid Arthritis: The HOPEFUL 1 Study. **Ann Rheum Dis.** 2014, March; 73: 536-543.

ADALIMUMAB FOR ACTIVE ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is characterized by inflammation of the axial skeleton, and can cause considerable disability and pain. Anti - tumor necrosis factor therapy is recommended for those who do not respond to conventional therapies. This study was designed to determine the safety and efficacy of adalimumab for the treatment of AS in Chinese patients.

Eligible patients were between 18 and 65 years of age, all diagnosed with AS. Following screening, the subjects were randomized to receive either adalimumab at 40 mg or a matching placebo subcutaneously every other week. A 12-week, double - blind phase was followed by a 12-week open label phase in which all patients received the treatment medication. Efficacy and safety of the treatment and placebo were assessed at weeks zero, two and four, and then every four weeks thereafter. The primary efficacy endpoint was the percentage of patients achieving the ASAS20 response criteria at week 12, defined as an improvement of ≥20% and an absolute improvement of ≥10 units from baseline in at least three of four domains.

One hundred fifteen patients were randomized to the placebo group and 229 to the treatment group. A total of 67.2% of the treatment group and 30.4% of the placebo group achieved the ASAS20 response at week 12 ($p<0.001$). The ASAS20 rates were significantly different as early as week two. At week 12, the efficacy of the treatment was demonstrated for several secondary efficacy variables, including chest expansion.

Conclusion: This study of Chinese patients with ankylosing spondylitis found that adalimumab can provide significant improvement in symptoms, physical function and quality of life, as compared with placebo.

Huang, F., et al. Efficacy and Safety of Adalimumab in Chinese Adults with Active Ankylosing Spondylitis: Results of a Randomized, Controlled Trial. **Ann Rheum Dis**. 2014, March; 73(3): 587-594.

CORONARY ARTERY BYPASS GRAFTING VERSUS PERCUTANEOUS CORONARY INTERVENTION

Coronary artery disease is a leading cause of death worldwide. Noting that recent trials comparing coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) have been under-powered, the authors of this study employed a meta-analysis of randomized trials to better understand the difference in outcomes between these surgical techniques.

A systematic search of the medical literature was completed, reviewing randomized, controlled trials which paired CABG and PCI. All studies had dedicated CABG and PCI arms, had an average follow-up duration of at least one year, used arterial grafting and used stents in at least 70% of the PCI arm.

Of the trials reviewed, six were included in the analysis, for a total of 6,055 patients. The analysis revealed a 27% greater reduction in total mortality with the use of CABG, as compared with PCI ($p=0.001$). In addition, a 42% greater reduction was found in myocardial infarction among those treated with CABG as compared with PCI ($p<0.001$). The analysis revealed an insignificant trend towards excess strokes among those treated with CABG as compared with PCI ($p=0.06$). Repeat revascularizations ($p<0.001$) and major, adverse cardiac and cerebrovascular events were significantly more reduced with CABG than with PCI ($p<0.001$).

Conclusion: This meta-analysis of randomized, controlled trials found that, among patients with multivessel coronary disease, coronary artery bypass grafting significantly reduces long-term, all-cause mortality and myocardial infarctions as compared with percutaneous coronary intervention.

Sipahi, I., et al. Coronary Artery Bypass Grafting versus Percutaneous Coronary Intervention and Long-Term Mortality and Morbidity in Multivessel Disease: Meta-Analysis of Randomized Clinical Trials of the Arterial Grafting

and Stenting Era. **JAMA Intern Med.** 2014, February; 174(2): 223-230.

IMMEDIATE BLOOD PRESSURE REDUCTION AFTER ACUTE ISCHEMIC STROKE

Clinical trials have documented that lowering blood pressure reduces the risk of stroke in hypertensive and normotensive patients with a history of stroke or transient ischemic attack. However, the effect of immediate antihypertensive treatment in patients with acute ischemic stroke who present with elevated blood pressure is much less certain. This multicenter, randomized, controlled trial tested whether moderate lowering of blood pressure within the first 48 hours after the onset of acute ischemic stroke can reduce death and major disability.

This randomized, controlled trial was conducted in 26 hospitals across China. Eligible patients had an ischemic stroke with systolic blood pressure elevated between 140mmHg and 220mmHg. The participants were randomly assigned to receive antihypertensives aimed at lowering blood pressure 10 -25% within the first 24 hours and achieving blood pressure less than 140/90mmHg within seven days, or to a control group discontinuing all antihypertensive medications during their hospitalization. The primary outcome measure was the combination of death and major disability at 14 days or hospital discharge.

Of the 4,071 patients eligible, 2,038 were assigned to receive antihypertensive treatment and 2,033 to the control group. At 14 days or hospital discharge, 33.6% in the treatment group and 33.6% in the control group experienced death or major disability. The odds of a higher modified Rankin scale score were not associated with antihypertensive treatment. At three months, 25.2% in the treatment group had died or had experienced major disability, as compared with 25.3% in the control group. The median modified Rankin scale score, death rate and vascular disease events were similar between the two groups. None of the differences were statistically significant.

Conclusion: This study of patients with acute ischemic stroke found that blood pressure reduction during hospitalization does not reduce the likelihood of death or major disability at 14 days.

He, J., et al. Effects of Immediate Blood Pressure Reduction on Death and Major Disability in Patients with Acute Ischemic Stroke: The CATIS Randomized Clinical Trial. **JAMA**. 2014, February 5; 311(5): 479-489.

INITIATING PHYSICAL ACTIVITY IN LATER LIFE AND HEALTHY AGING

Emerging evidence suggests that regular physical exercise is among the most important lifestyle factors for the maintenance of good health as one ages. This study examined the association between physical activity and healthy aging over an eight-year follow-up in the English Longitudinal Study of Ageing (ELSA).

The ELSA cohort consists of men and women born before February 1952. This prospective study of community dwelling older adults measured self-reported physical activity, assessed at baseline, 2002 to 2003. The subjects were reassessed every two years, and then for healthy aging at eight years. With repeated questionnaires, researchers were able to determine new onset activity. Healthy aging was defined as surviving without major chronic disease, depressive symptoms or physical or cognitive impairment. Physical activity was measured as the frequency and regularity of exercise routinely practiced.

The final sample comprised 3,454 individuals with an average age of 63.7 years at baseline. A dose response association was found between baseline physical activity and healthy aging after eight years, with those reporting moderate or vigorous activity 3.1 fold and 4.3 fold, respectively, more likely to be healthy agers as compared with inactive participants. Of those who became active during the study period, this activity was associated with improved healthy aging as compared with those who remained inactive.

Conclusion: This study of community-based individuals found that remaining active, or beginning active exercise in later life, is associated with healthier aging.

Hamer, M., et al. Taking up Physical Activity in Later Life and Healthy Ageing: The English Longitudinal Study of Ageing. **Br J Sports Med**. 2014, February; 48(3): 239-243.

LEVODOPA INTESTINAL GEL FOR PARKINSON'S DISEASE

Over time, patients with Parkinson's disease (PD) receiving long-term oral levodopa treatment experience a duration of response that becomes shorter, with motor fluctuations and dyskinesias developing. Levodopa/carbidopa intestinal gel (LCIG) has been found to produce a more stable plasma concentration of levodopa in patients with advanced PD. This prospective study assessed the efficacy of LCIG on patients' symptoms and subjective response.

The subjects were 59 patients with advanced PD, with optimized oral medication, but with continued fluctuations in motor symptoms and dyskinesias. The study medication, LCIG, was initially administered by a temporary naso-duodenal tube for three to four days, followed by permanent percutaneous endoscopic gastrostomy (PEG). The patients were assessed for motor complications, gait disorders, dysphagia, dysarthria, quality-of-life (QOL) and clinical global improvement. After seven years, 41 patients remained in the study.

The perceived QOL improved in all patients, with 44% noting great improvement. Autonomy was rated as greatly improved in 30% and moderately improved in 51%. Clinical global improvement was found to be greatly improved in 62% and moderately improved in 28%. The majority of patients (54%) reported improvement in gait, whereas dysphagia improved in only 33% and dysarthria in only 18%.

Conclusion: This study of patients with advanced Parkinson's disease found that the use of levodopa/carbidopa intestinal gel results in improvement in quality-of-life, autonomy and global status.

Zibetti, M., et al. Levodopa/ Carbidopa Intestinal Gel Infusion and Advanced Parkinson's Disease: A Seven-Year Experience. **Euro J Neurol.** 2014, February; 21(2): 312-318.

PHYSICAL ACTIVITY, COGNITION AND WALKING IN MULTIPLE SCLEROSIS

Slowed cognitive processing speed (CPS) is common among patients with multiple sclerosis (MS). While evidence exists of a coupling between walking performance and CPS among those with MS, no randomized trials have directly studied this effect. This study examined the efficacy of physical activity behavioral intervention for improving CPS and walking performance among patients with MS.

Eighty-two patients with MS who were randomly allocated to an intervention or a wait list control group. Over a six-month period, those in the intervention group visited a study website, wore a Yamax SW-401 Digiwalker pedometer, completed a log book, used Goal Tracker software and participated in one-on- one video coaching sessions. All were assessed for CPS using the Symbol Digit Modalities Test (SDMT), for walk performance using the six- minute walk test (6MW), for physical activity with the Physical Activity Questionnaire (IPAQ) and for disability using the Patient- Determined Disease Steps (PDDS) scale.

A total of 39 patients were included in the wait list control group and 37 in the testing group. The overall compliance with the behavioral intervention was 80.6% in the treatment group. The intervention increased walking performance as measured by the 6MW regardless of disability status, while deterioration was seen in the control group. Using a mixed model analysis of variance, a time by condition by disability group interaction was noted for SDMT test scores, with a significant time by condition action seen in 6MW distance, as compared with the control group.

Conclusion: This study of patients with multiple sclerosis found that cognitive scores improve with physical activity intervention.

Sandroff, B., et al. Randomized, Controlled Trial of Physical Activity, Cognition, and Walking in Multiple Sclerosis. J Neurol. 2014, February; 261(2): 363-372.

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