

Bulletin Board

Collagenase clostridium histolyticum effective in the nonsurgical treatment of Dupuytren's contracture

Results from the Collagenase Option for the Reduction of Dupuytren's (CORD II) study have been published in *The Journal of Hand Surgery*, demonstrating the beneficial role of collagenase clostridium histolyticum (Xiaflex[®], Auxilium Pharmaceuticals Inc., PA, USA) in the nonsurgical treatment for Dupuytren's contracture.

Collagenase Option for the Reduction of Dupuytren's II, was a prospective, multicenter, Phase III study that investigated the efficacy and safety of injectable collagenase clostridium histolyticum in patients with Dupuytren's contracture, estimated to affect up to 13% of the population in Europe. The 12-month study involved two phases: a 90-day randomized, double-blind, placebo-controlled phase and a 9-month open-label phase. It involved a total of 66 patients, with Dupuytren's cords from either metacarpophalangeal or proximal interphalangeal joints injected with collagenase clostridium histolyticum.

The mean percentage decrease in degree of joint contracture from baseline to 30 days after last injection was $70.5 \pm 29.2\%$ in the collagenase group and $13.6 \pm 26.1\%$ in the placebo group ($p < 0.001$), with a significantly greater mean increase in range of motion in the collagenase group, compared with the placebo group.

Chris Bainbridge, consultant hand and nerve surgeon, Pulvertaft Hand Centre, Royal Derby Hospital (Derby, UK), commented, "Collagenase clostridium histolyticum treatment significantly improved patient outcomes compared with placebo. Patients usually have to wait for their condition to become advanced before receiving treatment, often leaving them unable to carry on with their day-to-day lives".

Collagenase clostridium histolyticum was also shown to be generally well tolerated, with most treatment-related adverse

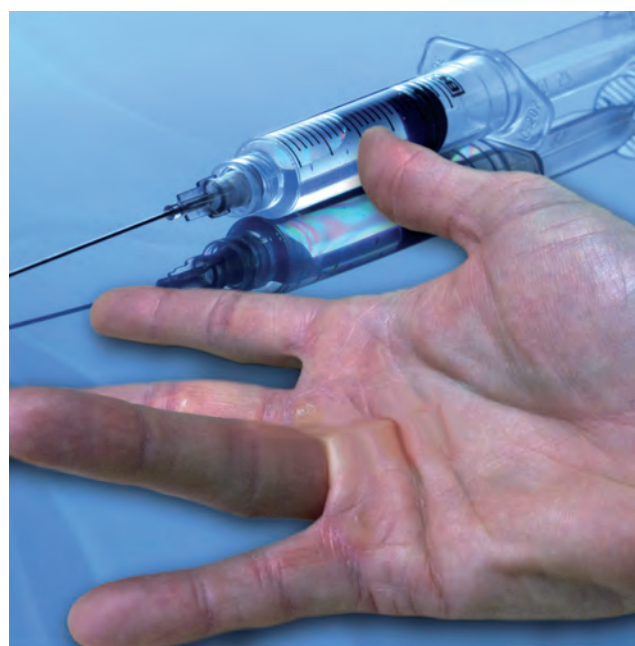
events mild or moderate in intensity and resolved within a median of 8–10 days with limited or no medical intervention. All patients who received the collagenase injection in the double-blind phase reported at least one adverse event, compared with 38.1% in the placebo group, with rates of peripheral edema, contusion, extremity pain, injection-site hemorrhage, injection-site pain and lymphadenopathy significantly higher in the collagenase group. A total of three serious adverse events were reported across the 12-month study, with one patient suffering a flexion pulley rupture of the little finger and one patient with both cord proliferation and sensory abnormality in the treated hand.

Dupuytren's contracture is a progressive disease that can lead to major difficulties in performing everyday tasks with the affected hand. At present, it is treated primarily by surgical therapies, which whilst effective, are highly invasive with a significant risk of complications such as tendon rupture, nerve and artery injury and infection. The disease will also eventually recur after surgery, with each reoperation often becoming more challenging, increasing the risk of complications.

At the time of the 12-month follow-up, none of the 20 successfully treated cords from the double-blind phase or 48 successfully treated cords from the open-label phase

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had experienced a recurrence, making collagenase clostridium histolyticum appearing an attractive alternative to current surgical approaches.

“The results for both metacarpophalangeal and proximal interphalangeal joints that were treated with Xiaflex are compelling and compare favorably to surgery from both an efficacy and safety point of view”, said David Gilpin, surgeon at the Brisbane Hand and Upper Limb Clinic

(Brisbane, Australia) and study investigator. “The investigators believe that the limited long-term efficacy and the potential for numerous complications associated with percutaneous needle aponeurotomy, and the serious complications and prolonged recovery associated with surgery, underscore the need for a simpler, less-invasive treatment option that is effective, safe and causes minimal convalescence and rehabilitation. I believe that Xiaflex, as a

new nonsurgical treatment, addresses these needs and could become the standard of care for Dupuytren’s contracture”.

Source: <http://ir.auxilium.com/phoenix.zhtml?c=142125&p=irol-newsArticle&ID=1504435&highlight=>

Gilpin D, Coleman S, Hall S, Houston A, Karrasch J, Jones N: Injectable collagenase clostridium histolyticum: a new nonsurgical treatment for Dupuytren’s disease. *J. Hand Surg. Am.* 35(12) 2027–2038.e1 (2010).

Smoking accounts for more than one third of severe rheumatoid arthritis cases

Results published in the *Annals of the Rheumatic Diseases* have suggested that smoking is a major risk factor associated with severe rheumatoid arthritis (RA) and is responsible for over one third of cases. Furthermore, patients who are genetically susceptible to the disease are at even greater risk, with over half of cases attributable to smoking.

“...smoking is a preventable risk factor for RA and the increased risk due to smoking depends on both the levels of smoking and the individual’s genetic susceptibility.”

Previous studies have shown that smoking and genetic factors interact to increase the risk of RA, but little is known on how smoking contributes to the disease in the context of genetic variability and

what proportion of RA cases are caused by smoking. This latest study, carried out at the Institute of Environmental Medicine, Karolinska Institutet (Stockholm, Sweden), investigated the association between the amount of smoking and the risk of RA, in the context of different HLA-DRB1 shared epitope alleles and tried to quantify the proportion of RA cases caused by smoking.

A total of 1204 people with RA and 871 people matched for age and sex, but free of the disease took part in the study and blood samples were taken in all participants to assess both their genetic susceptibility to RA and the severity of their case, by measuring their antibody levels. Testing positive for anticitrullinated protein/peptide antibody was considered indicative of severe RA and occurred in 61% of patients with the disease. Those who were classified as the heaviest smokers (>20 cigarettes per day for over 20 years)

in brief...

Rituximab improved physical function and quality of life in patients with rheumatoid arthritis naive to methotrexate (IMAGE study). Rigby W, Ferraccioli G, Greenwald M *et al.*: *Arthritis Care Res. (Hoboken)* (2010) (Epub ahead of print).

The effect of rituximab plus methotrexate (MTX) has been compared with MTX alone in patients with early active rheumatoid arthritis previously untreated with MTX in a 52-week study involving 748 patients. Patients were randomized to either MTX plus placebo, MTX plus rituximab 500 mg or MTX plus rituximab 1000 mg. At week 52, patients in both rituximab groups showed significant improvements in Health Assessment Questionnaire Disability Index (-0.905 and -0.916 in the rituximab 500 mg and 1000 mg plus MTX groups, respectively) compared with MTX alone (-0.628). Both doses of rituximab plus MTX were also associated with significant reductions in patients’ global assessment of disease activity and pain, as well as a significantly higher improvement in fatigue scores from baseline to week 52. Therefore, rituximab plus MTX is associated with significant improvements in health-related quality of life, as well as physical function, in early rheumatoid arthritis, MTX-naive patients.

Tocilizumab in refractory adult Still’s disease. Puéchal X, Debandt M, Berthelot JM *et al.*: *Arthritis Care Res. (Hoboken)* 63(1), 155–159 (2011).

Treatment with the anti-IL6 receptor antibody tocilizumab led to a rapid improvement in arthritis and systemic symptoms in a French study involving adult Still’s disease (ASD) patients. A total of 14 patients were involved in this first series of patients with ASD treated with tocilizumab, with the European League against Rheumatism (EULAR) improvement criteria and resolution of systemic symptoms at 3 and 6 months the main outcome measures. Tocilizumab was administered at 5–8 mg/kg every 2 or 4 weeks and 11 patients successfully completed the 6-month study. A good EULAR response was observed in nine out of the 14 patients (64%) at 3 months and EULAR remission was observed in eight patients (57%) at 6 months. Of the seven patients with systemic symptoms, six (86%) appeared to have their symptoms resolved after 3 months. Although the study size was small, they provide encouraging results for the potential role of tocilizumab in ASD patients.

were more than 2.5-times more likely to test positive for anticitrullinated protein/peptide antibody, with the risk falling the longer ex-smokers had given up smoking. The risk still remained high for the heaviest smokers, however, even if they had not smoked in over 20 years.

Based on these values, the researchers calculated that smoking accounted for 35% of severe RA cases and 20% of all RA cases. For each HLA-DRB1 shared epitope genotype, smoking was dose-dependently associated with an increased risk of severe RA and in participants carrying two copies of the HLA-DRB1 shared epitope, 55% of severe RA could be attributed to smoking.

The researchers concluded that smoking is a preventable risk factor for RA and the increased risk due to smoking depends on both the levels of smoking and the individual's genetic susceptibility. While the risk is not as high as for lung cancer, where smoking is responsible for 90% of cases, it is similar to that for coronary artery heart disease and the researchers urge those with a family history of RA to give up smoking.

Source: Källberg H, Ding B, Padyukov L *et al.*: Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. *Ann. Rheum. Dis.* (2010) (Epub ahead of print).

Investigational anti-inflammatory drug demonstrates promising data in hip osteoarthritis

A recent randomized study examining the use of the investigational anti-inflammatory drug naproxcinod demonstrated improvements in pain and functioning in patients with hip osteoarthritis. The study was a double-blind, parallel-group, 13-week, multicenter study that was intended to examine the efficacy of naproxcinod compared with placebo and to assess the safety of naproxcinod and its effects on a patient's blood pressure.

Naproxcinod is part of the cyclooxygenase-inhibiting nitric oxide donator family of drugs; it was developed to attenuate the adverse effects that can hamper the long-term use of many nonsteroidal anti-inflammatory drugs.

In the trial, 810 patients were randomized to receive naproxcinod 750 mg twice daily, placebo or naproxen 500 mg twice daily. The primary efficacy analysis utilized in the study was a covariance of three coprimary end points; the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function subscales and patients' overall rating of

disease status. The occurrence of adverse events and blood pressure measurements were used to examine the safety of naproxcinod.

At the end of the study it was found that, in patients receiving naproxcinod, pain scores decreased from a mean score of 66.25 out of 100 by a least squares mean of -25.81, compared with a change in the placebo group of -17.97; this change was statistically significant ($p < 0.0001$). The decrease in pain scores for naproxcinod was found to be similar to that of naproxen. Naproxcinod and naproxen were found to have similar safety profiles and adverse event rates, and the study's authors concluded that, "Naproxcinod was well tolerated, with effects on systolic blood pressure similar to those of placebo".

Source: Baerwald C, Verdecchia P, Duquesroix B, Frayssinet H, Ferreira T: Efficacy, safety, and effects on blood pressure of naproxcinod 750 mg twice daily compared with placebo and naproxen 500 mg twice daily in patients with osteoarthritis of the hip: a randomized, double-blind, parallel-group, multicenter study. *Arthritis Rheum.* 62(12), 3635–3644 (2010).

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of rheumatology. If you have newsworthy information, please contact:

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Garlic may offer protection against hip osteoarthritis

Researchers from King's College London and the University of East Anglia, UK, have discovered that a diet high in allium vegetables, such as garlic and onions, resulted in lower levels of hip osteoarthritis (OA) in women. Furthermore, the researchers also highlight the potential use of compounds found within garlic as a treatment option for the condition.

While a relationship between bodyweight and OA has been previously recognized, it is not fully understood and this new study investigated further the possible effects of dietary patterns and its effect on OA.

The study, funded by Arthritis Research UK, the Wellcome Trust and Dunhill Medical Trust, involved over 1000 healthy, female twins, many of whom did not display any symptoms of arthritis. The researchers

assessed the twins' dietary patterns, as well as taking x-ray images of the hip, knee and spine to record the extent of early OA in these regions. There was less evidence of early OA in the hip found in those that consumed a diet high in fruit and vegetables, in particular the alliums, such as garlic.

“...the compound diallyl disulfide limits the amount of cartilage-damaging enzymes when introduced to a human cartilage cell line in the laboratory...”

The researchers then went on to further investigate any potential protective effect of allium vegetables, by studying compounds found in garlic. They found

that that the compound diallyl disulfide limits the amount of cartilage-damaging enzymes when introduced to a human cartilage cell line in the laboratory, opening up the possibility that it could be used in future as a treatment option for hip OA.

Dr Frances Williams, Department of Twin Research, King's College London and lead author of the study, comments “While we don't yet know if eating garlic will lead to high levels of this component in the joint, these findings may point the way towards future treatments and prevention of hip osteoarthritis”.

Source: Williams FM, Skinner J, Spector TD *et al.*: Dietary garlic and hip osteoarthritis: evidence of a protective effect and putative mechanism of action. *BMC Musculoskelet. Disord.* 11(1), 280 (2010).

Increasing physical activity helps osteoarthritis of the knee

A large, prospective study has demonstrated that increasing physical activity over a 2-year period can improve the function and walking speed in adults with osteoarthritis (OA) of the knee.

The ongoing cohort study involves 2589 patients, aged between 45 and 79 years, with OA of the knee and categorizes patients into physical activity quartiles based on their Physical Activity Scale for the Elderly (PASE) scores, a 26-question assessment of activities such as housework, outdoor walking and sports. Researchers found that the baseline average gait speed, which is an objective measure of functional performance, was 4, 4.2, 4.3 and 4.5 feet/s among the quartile groups with increasing physical activity.

According to the researchers from Northwestern University, Chicago, IL

USA, who have reported current results in *Arthritis & Rheumatism*, a walking speed of 4 feet/s considered to be the minimum speed necessary to cross streets with timed traffic lights. Maintaining that level of functionality is an important goal for the 27 million adults with OA in the USA alone.

In the lowest quartile of activity group, 51% of patients were unable to walk 4 feet/s, compared with 37, 29 and 19% in the increasingly higher quartiles, respectively. At 2-year follow-up, after controlling for demographic and health factors such as age, sex, knee pain and comorbidities, average gait speeds in the four quartiles remained the same as the baseline values, which the researchers suggest demonstrates a strong relationship between physical activity and function in OA of the knee.

“These prospective data indicate a consistent graded relationship between physical activity level and better performance in adults with knee OA”, write the investigators. The researchers believe that given the large and diverse nature of the study, it provides strong evidence that OA of the knee patients should increase their physical activity levels in order to help alleviate their symptoms. “These findings support guidelines that encourage patients with arthritis who cannot attain minimum recommended physical activity to be as active as possible”, they conclude.

Source: Dunlop DD, Song J, Semanik PA, Sharma L, Chang RW: Physical activity levels and functional performance in the osteoarthritis initiative: a graded relationship. *Arthritis Rheum.* 63(1), 127–136 (2011).