A subgroup of patients suffering from moderate-to-severe osteoarthritic knee pain benefited exclusively from glucosamine and chondroitin sulfate supplements, compared with placebo

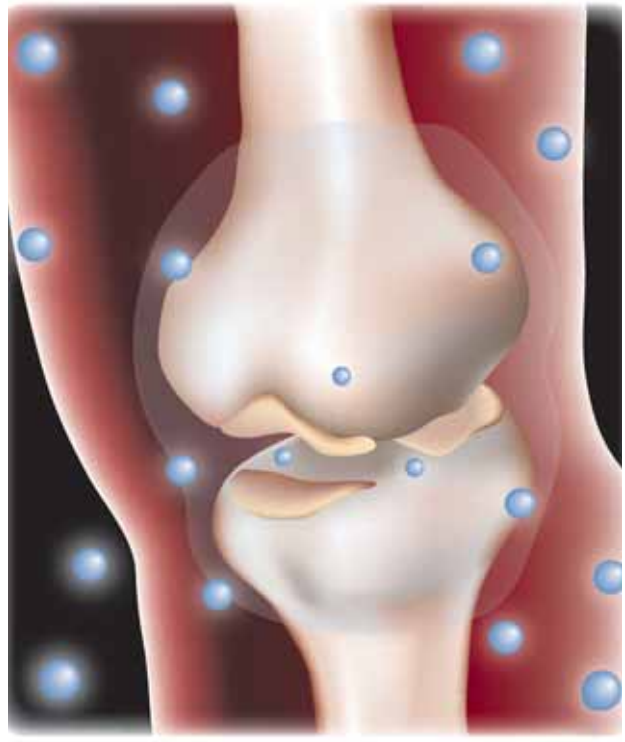
Efficacy of glucosamine and chondroitin sulfate linked to degree of pain

Results from the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) confirmed earlier data from the study that glucosamine and chondroitin sulfate are little better than placebo for the treatment of osteoarthritic knee pain. However, on closer analysis, the results showed that patients with moderate-to-severe knee pain did find the supplements to be effective in providing pain relief.

'In this group of patients, the benefits of a combination of supplements were greater than those of celecoxib...'

Glucosamine is an amino sugar produced and distributed in connective tissue, whereas chondroitin sulfate is a complex carbohydrate that helps cartilage to retain water. Both have become increasingly popular dietary supplements over the last 20 years or so. Despite their popularity among osteoarthritis (OA) patients, these supplements have previously had mainly anecdotal support for their pain-relieving properties.

In the study, led by Daniel O Clegg (University of Utah School of Medicine, UT, USA), 1583 patients were randomly assigned to receive glucosamine (1500 mg/day), chondroitin sulfate (1200 mg/day), a combination of both supplements, celecoxib (200 mg/day) or placebo for 24 weeks. Celecoxib served as a positive control as an approved OA pain drug. 78% of patients were classified as suffering from mild pain and the remaining 22% from moderate-to-severe pain (defined as a Western Ontario and McMaster OA index [WOMAC] pain score of 301–400). Knee pain was assessed using the WOMAC score at baseline and at weeks 4, 8, 16 and 24. A positive treatment response was defined as a 20% or greater decrease in knee pain, compared with the start of the study. Patients had to have both pain and x-ray evidence of arthritis to be enrolled in GAIT.



Clegg stated that, "For the study population as a whole, supplements were found to be ineffective". Not surprisingly, celecoxib was shown to be the most effective, providing significant pain relief for 70% of that subgroup. Glucosamine and chondroitin sulfate response rates were 64 and 65%, respectively. In combination the positive response rate was 66% and 60% in the placebo subgroup. Adverse events were mild, and distributed evenly among the different groups.

However, the researchers undertook an exploratory analysis and found that these results differed when only patients with moderate-to-severe pain were considered. In this group of patients, the benefits of a combination of glucosamine and chondroitin sulfate were greater than those of celecoxib (positive response rates of 79 and 69%, respectively). The placebo subgroup also experienced less pain relief than when all patients were taken into account, with only 54% positive responders.

The authors caution that, as only 22% of the total number of patients suffered from moderate-to-severe knee pain, the sample size was small and these results should be considered preliminary. Thus, further trials investigating this group of people are necessary.

'For the study population as a whole, supplements were found to be ineffective.'

A second part to this study is already planned, with researchers tracking the effects of glucosamine and chondroitin sulfate (both alone and in combination) on OA progression. Knee x-rays were taken at the start of the GAIT trial of all participants of this second stage. These will be repeated at 1 and 2 years and evaluated regarding whether the supplements have structure-modifying effects. The results from this stage are expected later this year. It remains to be seen whether these negative results will have any impact on the popularity of glucosamine and chondroitin sulfate with OA patients.

Priority Paper Alerts

Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study.

van Riel PL, Taggart AJ, Sany J *et al.*: *Ann. Rheum. Dis.* Feb 7 (2006) (Epub ahead of print).

The efficacy and safety of etanercept monotherapy, compared with combination etanercept and methotrexate therapy, in patients with rheumatoid arthritis (RA) who have not responded adequately to methotrexate were evaluated. RA patients who had been taking methotrexate for at least 3 months were randomly assigned to receive either etanercept plus methotrexate or etanercept monotherapy. Both substitution and addition of etanercept to methotrexate gave noticeable improvement in clinical signs and symptoms in this patient group.

Denosumab in postmenopausal women with low bone mineral density.

McClung MR, Lewiecki EM, Cohen SB *et al.*: *N. Engl. J. Med.* 354(8), 821–831 (2006).

This study evaluated the efficacy and safety of denosumab administered subcutaneously over a 12-month period. A total of 412 postmenopausal women were randomly assigned to receive denosumab every 3 or 6 months, open-label alendronate once a week or placebo. The primary end point was the percentage change in bone mineral density (BMD) of the lumbar spine. Changes in bone turnover were also assessed. An increase in BMD of 3–6.7% was seen in the denosumab-treated groups, compared with 4.6% with alendronate and a loss of 0.8% with placebo. Bone turnover was also suppressed in an apparently dose-dependent manner.

Moderate and severe neutropenia in patients with systemic lupus erythematosus.

Martinez-Banos D, Crispin JC, Lazo-Langner A, Sanchez-Guerrero J: *Rheumatology* Feb 16 (2006) (Epub ahead of print).

Cases of neutropenia in systemic lupus erythematosus (SLE) were reviewed to investigate predisposing factors, clinical outcomes and related prognostic factors. Medical charts of 98 SLE patients were reviewed, which included 33 cases of neutropenia and 65 age- and sex-matched controls. Baseline characteristics were similar in both groups. An increased risk of developing neutropenia was found to be associated with concomitant medication with immunosuppressive drug use and a history of thrombocytopenia and CNS involvement. Mortality rates did not differ between the groups.

First B-cell targeted therapy for rheumatoid arthritis approved by the FDA

FDA approval of rituximab provides an alternative therapeutic option for rheumatoid arthritis sufferers who do not respond adequately to anti-TNF therapy

Rituximab (Rituxan®, Genentech, Inc., CA, USA and Biogen Idec, Inc., MA, USA) has been approved by the US FDA for treatment of moderate-to-severe rheumatoid arthritis (RA). This is the first RA treatment that specifically targets B cells, which are believed to contribute significantly to the initiation and development of RA. It is hoped that patients who are inadequate responders to tumor necrosis factor (TNF) antagonist therapies will benefit from the unique action of the drug.

RA affects approximately 1% of the world's population. While many sufferers respond well to anti-TNF therapy, there remains a significant proportion who do not respond adequately to previously available disease-modifying agents (e.g., TNF inhibitors or methotrexate). While RA has traditionally been thought of as a T-cell-mediated disease, recent research has highlighted the role of B cells (and other immune cells) in joint inflammation and has led to RA trials of rituximab.

Rituximab was approved originally for the treatment of non-Hodgkin's lymphoma in the USA in 1997 and Europe in 1998, under the trade name MabThera® (Roche). It is an antibody that selectively targets $CD20^+$ B cells. For the treatment of RA, rituximab is administered every 6 months as two 100-mg intravenous infusions given 2 weeks apart, in combination with a stable dose of methotrexate. Other studies are also being conducted into the effectiveness of rituximab in other autoimmune disease, such as systemic lupus erythematosus, lupus nephritis and multiple sclerosis.

Results from the Phase III Randomized Evaluation oF Long-term Efficacy of rituXimab (REFLEX) trial showed a higher percentage of patients with American College of Rheumatology (ACR) 20, 50 and 70 response rates when treated with rituximab compared with placebo. At 24 weeks, 51% of patients in the rituximab group achieved ACR20 versus 18% in the placebo-treated group (27% achieved ACR50 vs 5% with placebo; 12% achieved ACR70 vs 1% with placebo). "In clinical trials, rituximab demonstrated significant improvement in joint pain, inflammation and physical function from a single course of therapy in this difficult-to-treat patient population", said Stephen Paget (Hospital for Special Surgery, NY, USA).

Adverse events in RA patients were similar to those observed in non-Hodgkin's lymphoma patients, the most common being infusion reactions and infections. A total of 7% of patients administered with rituximab and methotrexate suffered from serious adverse events, compared with 10% of patients treated with placebo and methotrexate. Serious infections occurred in 2% of rituximab-treated patients and 1% of those treated with placebo.

Rituxan is currently one of the world's most lucrative cancer drugs. With treatment now available for RA patients who have not responded to one or more TNF inhibitors, the drug has moved onto a new market, which could boost sales by another $1 billion. For RA sufferers, it offers an entirely new alternative to conventional disease-modifying antirheumatic drugs and TNF-inhibitor therapy.

Celecoxib increases the risk of cardiac events

An article published recently in the *Journal of the Royal Society of Medicine* claims that celecoxib, the most commonly used cyclooxygenase (COX)-2 inhibitor, increases the risk of myocardial infarction (MI) and has a similar risk profile to rofecoxib. These most recent results add further concerns to the use of this class of drug.

Current guidelines from the European Medicines Agency state that patients with heart disease or stroke should not be taking celecoxib and that doctors should use the lowest dose for the shortest duration possible. Researchers from the Medical Research Institute of New Zealand conducted two meta-analyses to investigate whether the risk of cardiovascular events seen with rofecoxib is indicative of the COX-2 class of drugs. The first analysis looked at four placebo-controlled trials including

A meta-analysis finds that the cyclooxygenase-2 inhibitor celecoxib doubles a patient's risk of myocardial infarction

4422 patients. To be included in the analysis, studies had to be randomized, double-blind, placebo-controlled, at least 6 weeks in length and report serious cardiovascular thromboembolic events. The use of celecoxib was found to increase the risk of MI by 2.26 times, compared with placebo.

A second meta-analysis also included two further studies, where celecoxib was compared with nonsteroidal anti-inflammatory drugs or acetaminophen/paracetamol, rather than placebo. The total number of patients involved was 12,780 and a 1.18-fold increased risk of MI was found. However, unlike rofecoxib, no corresponding increased risk of cerebrovascular events was noted.

Richard Beasely (New Zealand Medical Research Institute, Wellington), lead author of this study, is confident that the data demonstrate risks associated with celecoxib. Spokesmen from Pfizer, who manufacture celecoxib as Celebrex, have accused the authors of selectively choosing studies to include in the analysis. For their part, the authors posit that including studies that did not meet their criteria (outlined previously), such as trials in which serious cardiovascular events were not reported, would be flawed. Pfizer have conducted a similar systematic review including 44 trials and 40,000 patients; this did not find the strong association between celecoxib and MI that Beasely and colleagues reported.

If at first you don't succeed…

Methotrexate is taken by many patients with RA, although not all respond to the treatment. A study published recently in *Arthritis Research and Therapy* has recommended that, for these patients, a second course of methotrexate may prove beneficial.

Methotrexate is one of the most commonly used disease-modifying antirheumatic drugs (DMARDs). Reconsidering methotrexate therapy may be a viable option for many patients who do not initially respond to the treatment, on the condition that there was no major toxicity during the initial course.

Over 6400 years of patient data were included in this observational study. Patients who were administered with a second course of methotrexate, following a previous course of at least one other DMARD, were identified. Termination of treatment owing to inefficacy was found to be lower in the second course, compared with the original. The main limitation of the study is its observational nature, which may have led to bias by indication. However, feasibility of a randomized clinical trial into these effects is low, leaving these the best currently available data.

Re-employment of methotrexate was effective in almost a half of patients who intially showed no response. It was twice as likely to be effective if the intial dose had been low and was even successful when the second dose was lower than that originally prescribed. In the study, the authors conclude, "This therapeutic option may be valuable in patients in whom other therapies, especially biologics, cannot be used or have proven insufficiently effective."

Natalizumab found to be safe

A clinical and laboratory study of people treated with natalizumab (Tysabri®) found no new cases of progressive multifocal leukoencephalopathy (PML). Patients had been administered with natalizumab, an immune system-modifying drug, for RA, Crohn's disease and multiple sclerosis. A previous clinical trial of natalizumab in relapsing–remitting multiple sclerosis was halted when two cases of PML were diagnosed. A Crohn's disease patient was also diagnosed with the disease. The drug was subsequently withdrawn from the market and clinical trials.

Detailed clinical histories, physical examinations and brain magnetic resonance imaging scans were taken of over 3000 people who had been exposed to natalizumab and only the three previously known cases of PML were confirmed. This is good news, not only for natalizumab, but also for similar drugs now in development.