Osteoarthritis drug withdrawn from the UK market following hepatotoxicity fears

Following advice from the Commission on Human Medicines, the Medicines and Healthcare products Regulatory Agency has halted the sale of the osteoarthritis drug lumiracoxib (marketed as Prexige®) in the UK. The move was prompted by concerns over the association between treatment with lumiracoxib and severe liver damage.

'…the drug has been restricted or banned altogether in Australia, New Zealand, Turkey, Canada, Germany and Austria after reports of severe liver reactions…'

Lumiracoxib is a member of a class of drugs known as COX-2 inhibitors, a drug group developed as an alternative to NSAIDs for the treatment of arthritic pain. Both NSAIDs and COX-2 inhibitors work by inhibiting prostanoid biosynthesis by targeting the enzyme COX. There are two isoforms of the enzyme, COX-1, which is associated with gastrointestinal effects, and COX-2, which is linked to inflammation. NSAIDs such as ibuprofen inhibit both isoforms, and therefore, while they do act as anti-inflammatory compounds, they are also associated with gastrointestinal side effects such as ulcers and bleeding. As a result, compounds were sought that targeted COX-2 only, providing pain relief without the associated side effects. This lead to the development of a number of COX-2-specific inhibitors.

Following its introduction in Brazil in 2005, lumuiracoxib has been marketed in more than 30 countries worldwide. However, starting in August 2007, use of the drug has been restricted or banned altogether in Australia, New Zealand, Turkey, Canada, Germany and Austria after reports of severe liver reactions; usually following daily doses higher than those licensed. It did not receive initial approval at all in the USA.

However, recently, several cases of hepatotoxicity have been reported in patients receiving the relatively low 100-mg daily dosage over a short period of time, prompting the move to withdraw the drug altogether in the UK. In total, as of October 2007, there had been 159 spontaneous reports of suspected adverse liver reactions to lumiracoxib worldwide, of which 91 were considered serious. Three of these patients required liver transplants, two reactions were fatal. A Europe-wide review of lumiracoxib that will dictate the long-term future of the drug is to be launched.

This development comes at a bad time for COX-2 inhibitors. In November 2007, the drug manufacturer Merck & Co. paid a US$4.85 billion settlement to claimants who had been given the COX-2 inhibitor Vioxx® (rofecoxib). Findings published in 2004 showed that the risk of myocardial infarction and ischemic stroke was more than doubled in those receiving the drug for more than 18 months, prompting the initiation of between 45,000 and 50,000 personal-injury lawsuits. Despite the settlement, Merck & Co. has not admitted liability; Kenneth Frazier, Merck's executive vice-president, said: "Without this settlement, the litigation might very well stretch on for years".

'…there had been 159 spontaneous reports of suspected adverse liver reactions to lumiracoxib worldwide, of which 91 were considered serious.'

Those claiming from the settlement must meet a number of criteria, including medical proof of heart attack or stroke, proof that at least 30 Vioxx pills were taken and that they received enough pills to support a presumption that they were ingested within 2 weeks before problems developed. These qualifications represent a substantial concession by Merck, who initially claimed that complications could arise after no less than 18 months of use.

Sources:
http://business.timesonline.co.uk/tol/business/industry_sectors/health/article2843943.ece;
www.timesonline.co.uk/tol/life_and_style/health/article2903645.ece;
www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2033073&ssTargetNodeId=221;
www.merck.com/newsroom/press_releases/corporate/2007_1109.html

Priority Paper Alerts

Associations of erosive arthritis with anticyclic citrullinated peptide antibodies and MHC class II alleles in systemic lupus erythematosus.

Chan MT, Owen P, Dunphy J *et al.*: *J. Rheumatol.* 35(1), 77–83 (2008).

This study sought to find a correlation between erosive arthritis (EA) in systemic lupus erythymatosus (SLE) and anticyclic citrullinated peptide (anti-CCP) antibodies and MHC II alleles. SLE patients were examined and classified based on their degree of arthritis. Serum from the patients and 130 controls was taken and tested for anti-CCP antibodies and rheumatoid factor. The patients and 117 genetic controls were genotyped for *HLA–DRB1* and *HLA–DQB1* and the data analyzed using a χ^2 test and odds ratio with 95% confidence intervals (CIs). Among patients with synovitis, EA was associated with anti-CCP (OR: 28.5; 95% CI: 4.7–173.8; p = 0.001), with a weaker association for rheumatoid factor (p = 0.3). Four out of six patients with EA, major erosions and signs of rheumatoid arthritis were anti-CCP positive. *HLA–DQB1*0302* was associated with EA (p = 0.01), and similarly, for *HLA–DRB1*0401*. Patients with SLE are more likely to have EA if anti-CCP positive; therefore, being anti-CCP positive may serve as a useful marker for EA in patients with synovitis. Anti-CCP antibodies may have a pathogenic role in bone erosion, resulting in the clinical overlap seen between SLE and rheumatoid arthritis.

Anti-TNF-α therapy induces a distinct regulatory T-cell population in patients with rheumatoid arthritis via TGF-β.

Nadkarni S, Mauri C, Ehrenstein MR: *J. Exp. Med.* 204(1), 33–39 (2007).

This work follows previous studies showing that $CD4^+CD25^{hi}$ regulatory T cells (Tregs) isolated from patients with active rheumatoid arthritis (RA) have a defect in their ability to suppress proinflammatory cytokine production by $CD4^+CD25^-$ T cells, and that this failure to suppress can be overcome following anti-TNF-α antibody (infliximab) therapy. This paper demonstrates that infliximab therapy gives rise to a distinct Treg subset ($CD4^+CD25^{hi}FoxP3^+$), which lacks CD62L expression and is able to mediate suppression through TGF-β and IL-10. Despite the suppression capacity displayed by this $CD62L^-$ Treg population, $CD62L^+$ Treg cells remained defective in infliximab-treated patients, suggesting that anti-TNF therapy generates a newly differentiated population of Tregs, which compensates for the defective natural Tregs. It is therefore hoped that a therapy that restores tolerance through the induction of this unique Treg population can be developed.

Human trials begin for rheumatoid arthritis drug

Rigel Pharmaceuticals Inc. has announced that Phase I clinical trials are underway for a new drug aimed at treating a range of autoimmune conditions including rheumatoid arthritis.

The placebo-controlled, double-blind study will provide information on the safety, tolerability and pharmokinetics of R348, an orally administered inhibitor of JAK3. JAK3 is a cytoplasmic tyrosine kinase expressed in many cells of the immune system. As part of the signal transduction cascade for a number of growth factors involved in lymphocyte activation, it plays a central role in the differentiation and proliferation of white blood cells. As such it is hoped that JAK3 will provide the ideal target for suppression of the overactive immune response responsible for diseases such as rheumatoid and psoriatic arthritis. Results from the preliminary studies are expected in mid 2008.

"These drug candidates may provide a new, additional method of immunosuppression, and may result in a safer and more desirable protocol for preventing transplant rejection and treating other T-cell-mediated diseases", said Donald Payan, executive vice-president and chief scientific officer at Rigel.

Source: http://ir.rigel.com/phoenix.zhtml?c=120936&p=irol-newsArticle&ID=1093801&highlight=

Report concludes that science at the US FDA is highly inadequate

A recent internal review of science within the US FDA has concluded that the standard of science within the FDA is inadequate, and this is having a detrimental impact on the agency's ability to fulfil its role.

The FDA is responsible for licensing drugs, vaccines and medical devices in the USA, where many new drugs are developed. As such, it plays a central role in the health of the USA, which has a significant knock-on impact on the rest of the world.

The report, entitled *FDA Science and Mission at Risk*, found that "The FDA cannot fulfill its mission because its scientific base has eroded and its scientific organizational structure is weak", and that its "scientific workforce does not have sufficient capacity and capability".

These problems are a result of soaring demands, without the required increase in resources, resulting in an infrastructure that is stretched to breaking point.

Of particular interest, the report notes that the FDA is floundering when it comes to 'new sciences' such as genomics, and recommends the formation of a specific team within the FDA composed of renowned academics to identify emerging technologies and advise the FDA accordingly.

However, the authors warn that "there is a long history of excellent reviews of the FDA that have been followed by little to no action taken to achieve the recommendations" and so call for a comprehensive plan outlining how and when the FDA will respond to the findings of the report.

Source: www.fda.gov/ohrms/dockets/AC/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf

Exercise program may help alleviate arthritis

The first randomized, controlled trial to evaluate the Arthritis Foundation Exercise Program has been completed, demonstrating that regular exercise can alleviate arthritis.

The Program, a variety of range-of-motion and low-resistance exercises, is aimed at improving flexibility and muscle strength. Scientists surveyed 346 arthritis patients, half of whom were assigned to the program and half of whom were controls, to determine the primary (symptoms, functioning and so on) and secondary (psychosocial) effects of physical exercise in arthritis sufferers.

After 16, 1-h-long sessions over a period of 8 weeks, the intervention group reported significant improvements in pain, fatigue and self efficacy. A total of 6 months after completion of the program, participants still reported a positive impact on their pain and fatigue. However, function and self efficacy worsened. The researchers suggest that this may be related to the fact that participants felt less confident without the class structure and social support, indicating that social engagement can play an important role in helping sufferers. Those participants who continued the program independently reported continued improvements, suggesting that such exercise programs can play a significant role in arthritic care.

Source: Callahan LF, Mielenz T, Freburger J *et al.*: A randomized controlled trial of the people with arthritis can exercise program: symptoms, function, physical activity, and psychosocial outcomes. *Arthritis Rheum.* 59(1), 92–101 (2007).

Growth hormone as a potential fibromyalgia treatment

A pilot study conducted by researchers from the Centro Medico Teknon (Barcelona, Spain) suggests that treatment with growth hormone may reduce symptoms of pain in some fibromyalgia sufferers.

Some fibromyalgia patients are found to have low serum concentrations of IGF-1, hinting that growth-hormone therapy may alleviate symptoms.

A total of 24 sufferers were enrolled in a trial in which the growth hormone was administered to a random 50% of participants for 1 year.

Those receiving the hormone showed a 60% reduction in the number of tender points compared with the control group. It is hoped that larger clinical trials will lead to the establishment of growth hormone therapy in treating some fibromyalgia cases.

Source: Cuatrecasas G, Riudavets C, Guell MA, Nadal A: Growth hormone as concomitant treatment in severe fibromyalgia associated with low IGF-1 serum levels. A pilot study. *BMC Musculoskelet. Disord.* 8(1), 119 (2007).

Controversy over bisphosphonates continues

The use of bisphosphonate treatments for osteoporosis has come under intense scrutiny in recent weeks following a warning issued by the US FDA regarding "severe and sometimes incapacitating" pain associated with their use.

Published on January 7, the FDA's statement explains that the pain experienced is additional to the acute pain occasionally felt by patients receiving bisphosphonates, which usually resolves within a few days with continued drug use.

By contrast, the severe musculoskeletal pain described in the statement is said to occur "within days, months, or years after starting a bisphosphonate". It goes on to say that, while in some the pain subsides quickly following discontinuation of bisphosphonates, other patients "have reported slow or incomplete resolution".

With the ink barely dry on the FDA's statement, a study published online in the *Journal of Rheumatology* demonstrates a link between bisphosphonates and the development of bone necrosis, a condition that can lead to incapacitating pain and, potentially, disfigurement.

Bone necrosis occurs when the bone is starved of blood for prolonged periods of time, leading to the death and eventual collapse of bone tissue, resulting in severe pain and loss of mobility. While relatively rare in the general population, Mahyar Etminan of the University of British Columbia and Vancouver Coastal Health Research Institute (Canada) and colleagues found that, amongst women receiving bisphosphonates, the risk of developing bone necrosis is increased almost threefold.

Although the necrosis side effect is rare, bisphosphonates are widely used (with more than 190 million prescriptions worldwide) and their use is expected to increase. Etminan is worried that the proposed link between estrogen and breast cancer will prompt increasing numbers of women to switch to bisphosphonate therapies for osteoporosis, leading to an increase in the cases of bone necrosis.

By contrast, a study appears in the January issue of the *Journal of the American Dental Association* that indicates that, while intravenous bisphosphonates significantly increase the risk of osteonecrosis, the use of oral bisphosphonates actually reduces the incidence of bone necrosis.

Athanasios Zavras of the Harvard School of Dental Medicine (MA, USA) and colleagues analyzed a database of over 700,000 patients to test for a correlation between jaw bone necrosis and the mode of bisphosphonate ingestion.

Zavras has faith in the group's results: "Our findings on intravenous bisphosphonates are consistent with the literature, which makes me confident that our findings on oral bisphosphonates are correct". However, the authors do concede that clinical studies over the long term are needed to confirm their results.

Sources: www.fda.gov, Etminan M, Aminzadeh K, Matthew IR, Brophy JM: Use of oral bisphosphonates and the risk of aseptic osteonecrosis: a nested case–control study. *J. Rheumatol.* 35, 3 (2008); Cartsos VM, Zhu S, Zavras AI: Bisphosphonate use and the risk of adverse jaw outcomes: a medical claims study of 714,217 people. *J. Am. Dent. Assoc.* 139, 23–30 (2008).