Firazyr launched for the treatment of hereditary angioedema

Firazyr (icatibant), a selective bradykinin-B2-receptor antagonist which can be administered subcutaneously, is now available in the UK for treating patients with hereditary angioedema, including those with life-threatening laryngeal attacks.

Licence approval follows results from the FAST-2 study, a randomized, double-blind, phase III study which compared icatibant with the antifibrinolytic, tranexamic acid. The study showed that icatibant provided a rapid onset of clinically significant symptom relief (2 hours *vs* 12 hours, $P<0.001$), with the first symptom improvement seen after a median time of 48 minutes.

Hereditary angioedema is characterized by unpredictable and recurrent swelling of the skin or mucous membranes. This can occur in the face, hands, feet, genital region, gastrointestinal tract or larynx.

Most hereditary angioedema episodes develop over a period of 12–36 hours and may persist for around 1 week. However, laryngeal oedema develops rapidly and is potentially fatal. If immediate medical attention is not sought, intubation or tracheotomy may need to be performed.

Professor Marco Cicardi, Professor of Medicine, University of Milan, and FAST-2 lead trial investigator said: 'FAST-2 has shown that Firazyr is effective for all types of hereditary angioedema attacks, provides rapid symptom improvement, shortens attack duration, and is effective in subsequent attacks.

'Given these results and how satisfied patients have been with the treatment so far, I am convinced that Firazyr will improve the quality of life of many hereditary angioedema patients.'

Hereditary angioedema is a relatively rare disease, with current epidemiological data suggesting a worldwide prevalence of between 1 in 10 000 and 1 in 50 000. In the UK, around 1200 patients are estimated to have the condition, although patients with gastrointestinal symptoms are often misdiagnosed as having ulcerations or irritable bowel syndrome.

To date, more than 700 hereditary angioedema attacks have been treated with subcutaneous icatibant, without a single case of a drug-related serious adverse event. The most common observable side effects have been mild local reactions at the injection site, burning, itching and pain. All symptoms have resolved spontaneously within a few hours.

Professor Marco Cicardi, Professor of Medicine, University of Milan

Steve Dawber

Protelos reduces hip fracture risk

Protelos (strontium ranelate) is the first osteoporosis treatment to demonstrate long-term reduced risk of hip fracture.

Results of a new study (Reginster et al, 2008) confirm a long-term reduction in the risk of fractures with strontium ranelate in postmenopausal women with osteoporosis. The trial, which studied the efficacy of strontium ranelate (2 g/day) over a 5-year period, showed significant reductions of up to 43% ($P<0.036$) in the risk of hip fractures.

TROPOS (TReatment Of Peripheral OSteoporosis), a randomized, double-blind placebo-controlled trial, was designed to investigate the long-term efficacy of strontium ranelate in reducing the risk of non-vertebral fractures in postmenopausal osteoporosis. Performed in 75 centres across Australia and Europe, 5091 women took part in the study, of whom 2714 (53%) completed the full 5 years.

The study also found a 24% decrease in vertebral fractures and a 15% reduction in non-vertebral fractures, compared to those who received placebo for 5 years.

The safety profile of strontium ranelate remained unchanged compared to previous 3-year data.

Commenting on the results, Professor Tim Spector of St Thomas' Hospital, London, said: 'It is encouraging to see data demonstrating clear fracture prevention over 5 years. These results will help doctors to improve long-term quality of life in our patients.'

Reginster JY, Felsenberg D, Boonen S et al (2008) Effects of long-term strontium ranelate treatment on the risk of non-vertebral and vertebral fractures in postmenopausal osteoporosis: results of 5-year randomized placebo-controlled trial. *Arthr Rheum* **58**(6): 1687–95

Combination treatment helps patients reach HbA_{1c} targets

Nearly nine out of ten patients with type 2 diabetes achieved a glycosylated haemoglobin (HbA_{1c}) target of ≤7.5% with a repaglinide (Prandin) and metformin treatment strategy, says a review published in *Clinical Therapeutics*.

Furthermore, updated National Institute for Health and Clinical Excellence guidance on the management of type 2 diabetes now recommends that rapid-acting insulin secretagogues (such as repaglinide) may be considered as a first option to add to metformin in patients with non-routine daily patterns to help attain their individual target.

Professor Anthony Barnett, Professor of Medicine and Clinical Director Diabetes and Endocrinology, Heart of England NHS Foundation Trust, commented: 'This new analysis presents a win:win scenario for doctors and patients. Prescribing repaglinide and metformin together as an early option, rather than monotherapy, helps nine out of ten patients achieve the HbA_{1c} target of ≤7.5% – only 6 out of ten achieved such targets in 2005/6.

'For patients, both products are easy to take together at mealtimes. While this is most relevant to those with irregular mealtimes, it has implications for all people who regularly or even occasionally skip meals or have to change the timings of their meals to fit in with their lifestyles.'

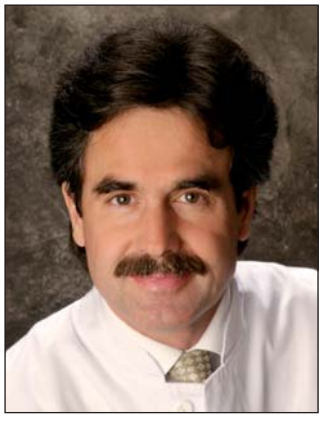
Moses RG (2008) Achieving glycosylated haemoglobin targets using the combination of repaglinide and metformin in type 2 diabetes: a reanalysis of earlier data in terms of current targets. *Clin Ther* **30**: 552–4

Joint approach to treating acute swollen knee

Delegates at the 9th Congress of the European Federation of Orthopaedics and Traumatology (EFORT) heard how orthopaedic surgeons and rheumatologists are working together to improve management of the acute swollen knee throughout Europe. The EFORT congress was held in Nice, France, from 29 May to 1 June 2008.

According to Professor Klaus-Peter Günther from the University of Dresden, Germany, who helped to convene the task force between EFORT and the European League Against Rheumatism (EULAR): 'At present different health-care professionals in different countries seem to approach management of the swollen knee in a different way. We wanted to develop an evidence-based algorithm that allows the best possible diagnostic and therapeutic approach for as many people as possible in European countries.'

Professor Klaus-Peter Günther, University of Dresden, Germany



The EFORT-EULAR guidelines are designed to provide clinicians with an evidence-based approach to the management of the swollen knee that integrates both pharmacological and non-pharmacological therapies. This will include recommendations on recognition, referral and initial treatment, with the aim of limiting long-term disability by promoting a rapid return to normal functioning.

There are no detailed data on the prevalence of acute swollen knee. It is, however, a very common presentation in both hospital and the community, probably affecting 10-15% of the population given the prevalence of its causes, which include degenerative disorders, inflammatory conditions, joint trauma, infections, neoplasms, malformations and haematological disorders.

Professor Günther adds: 'The condition that leads most often to knee swelling is knee osteoarthritis, and the health burden of this condition is enormous in terms of pain, loss of function and quality of life. Other conditions occur less often, but can have a severe impact on general health (i.e. systemic involvement in rheumatoid arthritis) or even be life threatening (i.e. malignant tumours), while septic arthritis can completely destroy knee joints within a very short time.'

The EFORT-EULAR guidelines have been submitted for publication, and it is hoped that they will be available within the next few months and will be disseminated through national societies. In the meantime, Professor Günther believes that the key message from the guidelines lies in their recommendations on appropriate referral.

'After the onset of knee swelling, the urgency of specialist referral depends on the likely cause. Patients with suspected septic arthritis or trauma with an onset of swelling within 12 hours should be referred immediately to a physician experienced in musculoskeletal diseases. Bone tumours are rare, but patients with a suspected bone tumour should be referred to an orthopaedic surgeon within 1 week. Patients with suspected inflammatory arthritis should be referred to a rheumatologist within 6 weeks,' he explains.

Sue Lyon

Extending prophylaxis with oral anticoagulant

The RECORD2 (REgulation of Coagulation in major Orthopaedic surgery reducing the Risk of DVT and PE) study (Kakkar et al, 2008) confirms the benefit of extended thromboprophylaxis beyond the hospital setting and further demonstrates the efficacy and safety profile of rivaroxaban – the first in a new class of oral anticoagulants called factor Xa inhibitors.

Over 2500 patients undergoing total hip replacement surgery were enrolled into the RECORD2 study which sought to compare the effect of extended prophylaxis (31–39 days) with rivaroxaban (10mg tablet once daily) with short-term prophylaxis (10–14 days) with enoxaparin (40 mg injection once daily).

Patients in the rivaroxaban group had a 79% relative risk reduction in total venous thromboembolism compared to those receiving short duration enoxaparin.

Kakkar AK, Brenner B, Dahl OE et al (2008) Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* **372**(9632): 31–9

NICE recommends Humira for chronic plaque psoriasis

Humira (adalimumab) has been recommended by the National Institute for Health and Clinical Excellence as a treatment option for adults with severe chronic plaque psoriasis.

Adalimumab is the only fully human anti-TNF (tumour necrosis factor) monoclonal antibody licensed for the treatment of plaque psoriasis in the UK.

New lipid-modifying therapy on the way

Tredaptive (nicotinic acid/laropiprant) 1000 mg/20 mg modified-release tablets, a new lipid-modifying therapy for patients with dyslipidaemia and primary hypercholesterolaemia, has been authorized for marketing in the European Union.

Oral treatment is equal to intravenous for colon cancer

Data presented at the World Congress on Gastrointestinal Cancer show that patients with colon cancer who receive the oral chemotherapy Xeloda (capecitabine) after surgery live just as long as those who receive intravenous 5-fluorouracil/folinic acid chemotherapy. This allows patients to carry on working during treatment and spend more time with their families.

ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY (EULAR)
PARIS, 11–14 JUNE

Tocilizumab is first biologic therapy 'superior' to methotrexate

Data presented at EULAR showed that tocilizumab is the first biologic therapy to have achieved superiority over methotrexate.

Results from the phase III AMBITION (Actemra versus Methotrexate double-Blind Investigative Trial in mONotherapy) trial also showed that nearly three times as many patients treated with tocilizumab achieved disease remission compared to methotrexate-treated patients. Presenting the data, lead investigator Professor Graeme Jones, Professor at the University of Tasmania in Hobart, Australia, said: 'These compelling results further establish the efficacy of tocilizumab in treating the signs and symptoms of rheumatoid arthritis.'

The AMBITION study evaluated the efficacy and safety of tocilizumab 8 mg/kg compared to methotrexate in 673 patients with active rheumatoid arthritis.

Patients were randomized to one of these two treatment arms (methotrexate *n*=288, tocilizumab *n*=284) or a placebo arm (*n*=101). Improvement in ACR20 scores was 70% and 53% for tocilizumab and methotrexate respectively at week 24 of treatment. Remission rates (DAS28<2.6) were 34% *vs* 12%.

Professor Paul Emery, President-Elect of EULAR and Clinical Director (Rheumatology) at the Leeds Teaching Hospitals Trust, said: 'These data are interesting because this is the first study to show that a biologic gives added value over methotrexate.'

ACR50s and ACR70s for tocilizumab and methotrexate respectively were 44% *vs* 34% and 28% *vs* 15%. Serious adverse events and serious infections were higher with tocilizumab (4%/3% *vs* 1.3%/0.7%).

Total cholesterol increases occurred more in the tocilizumab arm (13% *vs* <1%). Transient decreases in neutrophil counts were also more frequent with tocilizumab treatment but no grade 4 neutropenia was reported.

Rhonda Siddall

Disease remission achieved in patients refractory to anti-TNFs

A third of rheumatoid arthritis patients refractory to anti-tumour necrosis factors (TNFs) achieved disease remission with tocilizumab plus methotrexate, according to trial results.

Findings from the RADIATE (Research on Actemra Determining effIcacy after Anti-TNF FailurEs) trial showed that after 24 weeks of treatment 30.1% (*P*<0.0001) of rheumatoid arthritis patients receiving tocilizumab 8 mg/kg plus methotrexate who had active rheumatoid arthritis despite anti-TNF treatment achieved DAS28 remission compared with only 1.6% of the placebo arm. Almost a fifth of the population in the trial had failed to respond to three or more prior anti-TNF therapies.

Presenting the data at EULAR, Professor Paul Emery, President-Elect of EULAR and Clinical Director (Rheumatology) at the Leeds Teaching Hospitals Trust, said: 'These results are promising for rheumatoid arthritis patients who need a variety of treatment options, particularly when they have failed to achieve adequate pain and symptom relief with anti-TNF therapies'.

The trial randomized 499 patients to three treatment groups: placebo, tocilizumab 8 mg/kg or 4 mg/kg in addition to methotrexate 10–25 mg weekly. The results were based on an intention-to-treat population of 489 patients.

A quarter of patients on tocilizumab 8 mg/kg withdrew or were on rescue therapy before the study treatment period ended. ACR20, ACR50 and ACR70 responses for tocilizumab 8 mg/kg were 28.8% and 12.4% compared to 3.8% and 1.3% in the control group. Serious infections occurred in 5% of those treated with tocilizumab 8 mg/kg compared to 3% of controls.

Professor Emery said: 'The dose response favoured tocilizumab 8 mg/kg. The responses seen in this study are remarkable given that the population was a resistant group.'

Rhonda Siddall

Professor Paul Emery, Clinical Director (Rheumatology), Leeds Teaching Hospitals Trust

Task force proposes cardiovascular risk screening

Patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis should undergo cardiovascular risk management, according to a EULAR task force on cardiovascular risk. An annual screen was recommended for all rheumatoid arthritis patients.

The task force also called for existing cardiovascular risk calculators such as Framingham to be adapted to reflect the increased cardiovascular risk in inflammatory rheumatic disease patients.

Other recommendations included: consideration of statin and antihypertensive treatment according to cardiovascular risk and aggressive inflammation suppression.

The task force said that there is mounting evidence that inflammation is the underlying cause of raised cardiovascular risk in these patients.

Rhonda Siddall

ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY (EULAR)
PARIS, 11–14 JUNE

New anti-TNF therapy shows joint protection at 16 weeks on X-ray

Radiographic assessment of how effectively a treatment for rheumatoid arthritis is preventing structural damage to joints is the ultimate test of treatment efficacy.

This can now provide information as early as 16 weeks, according to a study of a new anti-tumour necrosis factor (TNF) drug, certolizumab pegol. The finding is unprecedented and could lead to earlier imaging to ensure patients are on track to remission – the goal of modern rheumatoid arthritis management.

Professor Desiree van der Heijde of Leiden University Medical Centre, Leiden, The Netherlands, conducted a comparative post-hoc radiographic analysis at 16 weeks of a subset of patients with rheumatoid arthritis in two double-blind phase III trials, RAPID 1 and 2.

Patients had been randomized to receive either certolizumab pegol (Cimzia) a new PEGylated anti-TNF alpha drug, or placebo, added to methotrexate.

Comparing X-rays taken at 16 weeks with those taken at baseline, she found patients randomized to certolizumab pegol and methotrexate showed significantly less progression of joint damage than those of placebo and methotrexate-treated patients.

The certolizumab pegol and methotrexate-treated patients also had lower modified total Sharp scores (a composite of bone erosion and joint space narrowing measurements). Assessment scores were calculated by three 'blinded' independent reviewers.

The finding was remarkable not only because this was the earliest time point that joint-damage response to therapy had been carried out, but because it occurred in patients who had withdrawn from RAPID 1 and 2 because of a perceived lack of clinical response according to the ACR20 measure.

'This demonstrates that radiographic assessment is sufficiently sensitive to pick up effects on structural preservation as early as 16 weeks and supports shorter-term imaging studies in rheumatoid arthritis,' Professor van der Heijde concluded.

Assessment at 16 rather than 24 weeks was part of an 'escape' built into the trial for patients who were failing treatment so that they could then be offered open-label alternative treatment. 'It is unethical to leave patients longer than this on treatments to which they might not be responding,' she explained.

Early effective treatment in a 'window of opportunity', within 5–10 months of patients experiencing their first symptoms, is now recommended if rheumatoid arthritis patients are to preserve joints and physical function before permanent structural changes occur.

Early induction therapy with a combination of an anti-TNF agent and methotrexate has produced the best outcome to date.

Mean total Sharp scores score change from baseline was even lower for certolizumab pegol and methotrexate-treated patients in RAPID 1 and 2 who completed 52 and 24 weeks treatment before final assessment, Professor van der Heijde added. In patients receiving the higher 400 mg dose plus methotrexate not only did damage not progress but some reversal of structural changes and repair was evident.

The 16-week time point reported is the earliest to assess effects on joint protection to date. 'It is a big advance,' she commented. 'It indicates how effectively a drug is working and its speed of onset.'

Olwen Glynn Owen

Frame promotes cartilage repair

Using a surgical frame around a degenerated joint (joint distractio) promotes cartilage repair in severe end-stage osteoarthritis of the knee, according to data presented at EULAR.

Researchers from University Medical Center Utrecht, in The Netherlands, used an external fixed frame with springs to bridge the knee joint in 19 osteoarthritis patients aged less than 60 years. The frame was then distracted by 5 mm over 2 months, with the aim of promoting knee repair by removing mechanical stress on the knee.

Functional ability and pain scores improved significantly following joint distraction: from 40% to 80% and from 30% to 80% respectively.

Cartilage volume and subchondral bone covered with cartilage increased by 50% and 40% respectively, and mean cartilage thickness increased over the year of follow up.

The researchers reported that the results were sustained over 2 years. This suggests that there is the potential for joint distraction to delay the need for use of a joint prosthesis.

Rhonda Siddall

TRAF1/C5 gene linked to autoimmune diseases

The TRAF1/C5 locus on chromosome 9 plays a major role in systemic lupus erythematosus, according to new data presented at EULAR. This gene has been previously established as a risk factor for rheumatoid arthritis.

Dutch researchers studied 746 patients with systemic lupus erythematosus and showed that the TRAF1/C5 gene was associated with an odds ratio of 1.16. The finding was replicated in another population of patients with systemic lupus erythematosus.

The researchers said that the finding gives insight into potential shared genetic pathways across autoimmune diseases and may stimulate innovation into novel therapeutic targets.

The researchers also found that the gene was associated with type 1 diabetes.

Rhonda Siddall