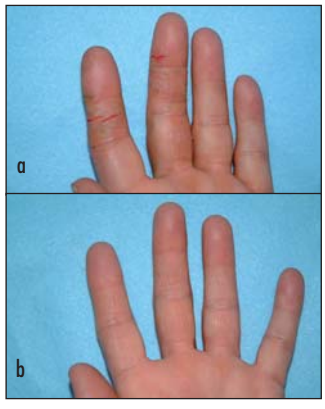
Oral Toctino launched for treatment of severe chronic hand eczema

Toctino (alitretinoin), a naturally occurring, vitamin-A derivative, is now available in the UK to treat adults with severe chronic hand eczema, which is unresponsive to treatment with potent topical corticosteroids.

Licence approval was based on results from a clinical development programme which included the Benefit of Alitretinoin in Chronic Hand Eczema (BACH) trial. This was a 24-week, double-blind, placebo-controlled, phase III study involving 1032 patients with severe, chronic chronic hand eczema. This patient population included subjects who were unresponsive to potent, topical corticosteroids, with an average pre-enrolment disease duration of approximately 9 years. Patients were randomized to receive a once-daily, oral dose of alitretinoin 30 mg, a once-daily, oral dose of alitretinoin 10 mg, or placebo. The study's primary end-point was the proportion of patients whose hands were rated as clear or almost clear by the Physician's Global Assessment.

Patient's hands (a) at baseline and (b) after 24 weeks' treatment with alitretinoin.



When compared to placebo, both doses of alitretinoin evoked statistically superior efficacy. Forty-eight per cent of patients in the alitretinoin 30 mg group and 28% of patients in the alitretinoin 10 mg group achieved clear or almost clear hands, compared with only 17% of the placebo group ($P<0.001$ and $P=0.004$ respectively).

During a 6-month, post-treatment observational period, 35% of the total alitretinoin responders relapsed to a severity which required re-treatment. However, 80% of relapsers achieved clear or almost clear hands following a second course of alitretinoin treatment. The most frequently reported adverse events were headache, flushing, and increased blood lipid levels. These events were dose-dependent and reversible.

Professor Adam Haworth, Consultant Dermatologist, St Mary's Hospital, Portsmouth, and one of the BACH study investigators said: 'Chronic hand eczema is severely disabling for patients and is often difficult to treat. This new, well-tolerated, oral treatment, which has proved effective in clearing hand eczema, is a great addition to our formulary, and will help us to manage this difficult condition.'

Alitretinoin is presented as a once-daily, oral capsule, available in two doses (10 mg and 30 mg). It should be prescribed by only dermatologists or physicians with experience of using systemic retinoids. Since retinoids are known potent teratogens, alitretinoin is contraindicated in females of childbearing potential, unless strict pregnancy testing and prevention measures are followed. These measures should be applied from 1 month before treatment to 1 month after the cessation of treatment.

Steve Dawber

Anticoagulation reduces DVT risk in immobilized leg injury patients

A panel of orthopaedic surgery specialists has urged greater use of low molecular weight heparin to prevent deep vein thrombosis and its complications in adult outpatients who have undergone immobilization of the lower leg (Testroote et al, 2008).

Immobilization of the lower leg with plaster cast or brace is associated with deep vein thrombosis.

The authors say that although treatment with anticoagulants is often used to prevent deep vein thrombosis, different indications for the use of low molecular weight heparin are given in current guidelines.

In an effort to reach an evidence-based conclusion on best clinical practice, Dr Mark Testroote, Viecurie Medical Centre of Northern Limburg, Limburg, The Netherlands, and colleagues reviewed six randomized clinical trials involving a total of 1490 patients, as part of a Cochrane Database Review.

They report an incidence of venous thromboembolism ranging from 4.3% to 40% in patients who had a leg injury that had been immobilized in a plaster cast or a brace for at least 1 week, and who had received no prophylaxis or placebo.

This was significantly lower in patients who had received daily subcutaneous injections of low molecular weight heparin during immobilization (event rates ranging from 0% to 37%, odds ratio 0.49). Complications of major bleeding events were extremely rare (0.3%) and there were no reports of heparin-induced thrombocytopenia.

Dr Testroote and his co-authors concluded: 'The use of low molecular weight heparin in outpatients significantly reduces the number of venous thromboembolic events when a plaster cast or brace is required.

'Because deep vein thrombosis can lead to serious morbidity, we advise administration of low molecular weight heparin during the entire period of immobilization of the lower extremity.

'Even with low molecular weight heparin as a prophylactic measure, incidences of deep vein thrombosis ranging from 0–10% mean a very high absolute rate of morbidity in the population, given the enormous frequency of trauma to the leg.

'Immobilization should be avoided as much as possible, and treatment requiring less immobilization should always be considered.

'In order to further reduce the number of venous thromboembolic events, we encourage all research to develop less immobilizing treatment options, and to develop even more effective and safe thromboprophylactic drugs.'

Stephen Pinn

Testroote M, Stigter W, de Visser DC, Janzing H (2008) Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. *Cochrane Database Syst Rev* (4): CD006681

Alteplase improves stroke outcome up to 4.5 hours

Thrombolysis with alteplase significantly reduces the risk of patients with mild to moderate stroke being left with residual disability when given within 4.5 hours of symptom onset – extending the time for administration beyond the currently licensed 3 hours – according to a study reported at the World Stroke Congress (24–27 September, Vienna, Austria).

The European Cooperative Acute Stroke Study (ECASS 3) study randomized 821 stroke patients to alteplase or placebo, as well as standard therapy, when treatment was started between 3 and 4.5 hours after stroke onset. Patients treated with alteplase had a 34% improvement in the odds of recovering with no residual disability 90 days after their stroke, compared to those given placebo (52.4% *vs* 45.2%; odds ratio 1.34; 95% confidence interval 1.02–1.76; *P*=0.04).

Reporting the findings, Professor Werner Hacke, Professor of Neurology at the University of Heidelberg, Germany, emphasized that early thrombolytic treatment achieves the best outcomes. However, he said: 'The new data show that stroke can be effectively managed also in patients who are unable to reach a stroke centre within 3 hours.' He added: 'A large group of patients currently excluded by the 3-hour limit may benefit from this therapy.'

Professor Werner Hacke, Professor of Neurology, University of Heidelberg, Germany

As expected, the incidence of intracranial haemorrhage was higher with alteplase. Intracranial haemorrhage of any type occurred in 27.0% of alteplase-treatment patients, compared to 17.6% of those given placebo (*P*=0.001). However, symptomatic intracranial haemorrhage affected only 2.4% of patients, and 0.2% of the placebo group (*P*=0.008). Mortality was low in both groups, with no difference between the two (Hacke et al, 2008).

'Adding 1.5 hours to the time window for thrombolytic use will increase the number of patients who can benefit,' concluded Professor Hacke.

Susan Mayor

Hacke W, Kaste M, Bluhmki E et al (2008) Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* **359**: 1317–29

Improving chronic myeloid leukaemia treatment

The European Treatment and Outcomes Study (EUTOS) for chronic myeloid leukaemia 1-year data shows chronic myeloid leukaemia management is becoming standardized across Europe, reported the European LeukemiaNet meeting (17–19 October, Cannes, France).

EUTOS for chronic myeloid leukaemia, a collaboration between European LeukemiaNet and Novartis initiated in October 2007, aims to improve chronic myeloid leukaemia management across Europe. The initiative set out to achieve its goals by developing an expanded patient registry, providing 'real-world' insights into chronic myeloid leukaemia incidence, treatment and outcomes, and also by improving access to state-of-the art disease monitoring techniques.

Professor Richard Clark, Royal Liverpool University Hospital, Liverpool, commented: 'We hope that the unique programme is already improving outcomes for patients by helping to standardize management of chronic myeloid leukaemia and provide access to the latest monitoring techniques.'

EUTOS milestones presented at the meeting included:

Over 2500 patients, across 11 countries, have now been entered into the EUTOS registry, including those taking imatinib front-line and those already registered in existing databases, irrespective of front-line treatment.

Standardization of real-time quantitative polymerase chain reaction has been achieved in 27 out of a target of 50 laboratories across Europe, with the remaining laboratories on schedule for 2009. Standardization will allow comparison of molecular monitoring data from different laboratories.

Imatinib blood levels have been analysed on 1100 samples taken from patients suspected of not adhering to treatment, or of not responding as expected. Preliminary results indicate that around 60% of samples had imatinib levels lower than those associated with best response to imatinib treatment. Blood testing is currently available at 23 laboratories across Europe.

'Quality control of molecular testing and blood testing is vital because it will allow us to interpret outcomes from the registry,' explained Rudiger Hehlmann, Universitat Heidelberg, Germany.

Janet Fricker

Treatment for adults with partial-onset epileptic seizures

Vimpat (lacosamide), a new adjunctive therapy for partial-onset seizures with or without secondary generalization in patients with epilepsy aged 16 years and older, has been launched in the UK.

Improving functional outcomes in patients with multiple sclerosis

A post-hoc analysis has shown that Tysabri (natalizumab) treatment increases the chance of achieving sustained improvement in physical disability over 2 years compared to placebo, the first evidence that natalizumab improves functional outcome in patients with relapsing multiple sclerosis.

Higher cure rates for patients with hepatitis C

In a study presented at American Association for the Study of Liver Diseases, Professor Colombo, Head of the 1st Division of Gastroenterology and A.M. Migliavacca Center for Liver Disease, University of Milan found significantly higher cure rates in hepatitis C patients treated with peginterferon alfa-2a and ribavirin than those treated with peginterferon alfa-2b and ribavirin (66% *vs* 54%, *P*=0.02).

EUROPEAN RESPIRATORY SOCIETY CONGRESS
BERLIN, 4–8 OCTOBER

Tiotropium improves lung function and reduces COPD exacerbations

Treatment with the inhaled anticholinergic tiotropium (Spiriva; Boehringer Ingelheim) significantly improves lung function and quality of life and reduces exacerbations and mortality in patients with chronic obstructive pulmonary disease (COPD), according to results from the UPLIFT study reported at the European Respiratory Society annual congress. Further results confirmed the drug's safety.

The study randomized 5993 patients with COPD and reduced lung function (mean forced expiratory volume in 1 second (FEV_1) of 48% of predicted value) to tiotropium (18 μg once daily) or placebo, in addition to other therapies, including long-acting bronchodilators and inhaled corticosteroids (but not anticholinergics) at the discretion of the treating physician.

Patients treated with tiotropium had significantly greater FEV_1 than control patients throughout the 4 years of the trial (87–103 ml before bronchodilation; $P<0.001$), although both groups showed a similar rate of FEV_1 decline (the primary end-point of the study).

The researchers suggested the low rate of FEV_1 decline, which was lower than in previous trials, may have been associated with widespread use of corticosteroids and long-acting beta-agonists. Nearly two-thirds of patients were on a long-acting beta-agonist and/or an inhaled corticosteroid at baseline, increasing to three-quarters by the end of the study. This may explain the lack of impact on FEV_1 decline in the tiotropium group as a whole compared to the control group, they said.

A sub-group analysis showed the rate of FEV_1 decline was significantly lower ($P=0.046$) in the 1554 tiotropium-treated patients who were not on inhaled corticosteroids or long-acting beta-agonists at baseline, compared with controls.

Patients treated with tiotropium showed a significant delay in time to first exacerbation, by an average of 4.1 months ($P<0.001$), as well as a 14% reduction in the number of exacerbations per patient-year ($P<0.001$). Tiotropium also reduced the risk of exacerbations resulting in hospitalization by 14% ($P<0.002$) compared to the control group.

Tiotropium-treated patients showed an improvement in health-related quality of life, with an average St George's Respiratory Questionnaire score 2.3–3.3 units higher across the 4-year trial, compared to the control group.

Marc Decramer, Professor of Medicine and Chief of the Respiratory Division, Katholieke Universiteit Leuven, Belgium, and a lead investigator in the trial, said: 'The unique trial design of UPLIFT reflects everyday treatment patterns and shows that tiotropium impacts of the clinical course of COPD, with sustained treatment benefits.' He predicted that the findings would lead to COPD being treated earlier in the disease course and more aggressively.

David Halpin, Consultant Physician and Honorary Senior Lecturer, Peninsula Medical School, Exeter, and principal investigator in the UK, added: 'The results show an additive effect of tiotropium in patients already on other treatments, with a step up in lung function, fewer exacerbations, fewer hospitalizations, better health status and reduced mortality.'

The rate of myocardial infarction was 27% lower in patients treated with tiotropium than in the control group. There was no increased risk of stroke (relative risk 0.95) or respiratory failure (relative risk 0.67). The only adverse events more common with tiotropium were consistent with its known safety profile, including dry mouth and constipation.

'This study reaffirms the safety profile for tiotropium. Results showed a reduction in cardiac morbidity and mortality and in respiratory failure,' Dr Halpin concluded.

Susan Mayor

Tashkin DP, Celli B, Senn S et al (2008) A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* **359**: 1543–54

Surgical resection for non-small cell lung cancer doubled in 10 years

The rate of surgical resection for patients with stage I/II non-small cell lung cancer doubled over the 10 years from 1995 to 2005, according to figures from a London teaching hospital.

Researchers at St George's Hospital, London, carried out a retrospective audit of patients diagnosed with non-small cell lung cancer in 1995 and 2005, looking at staging, treatment and survival.

Results showed that all patients (96/96) were fully staged in 2005, compared to just over half in 1995 (46/84 patients). The proportion of patients diagnosed with stage I/II non-small cell lung cancer remained similar over time. Of the patients who were staged, 39% (18/46) were stage I/II in 1995, and 28% (27/96) in 2005.

Half (52%; 14/27) of the stage I/II patients underwent surgical resection in 2005, increasing from just over one-third (39%; 7/18) in 1995. All patients with early stage disease who did not have resection in 2005 had a clearly documented reason, usually poor lung function. The survival rate in these patients had increased from a median of 227 days in 1995 to 947 days in 2005 ($P=0.003$). Overall survival rate for all stages of non-small cell lung cancer had not changed (median 147 days in 1995 *vs* 246 days in 2005; $P=0.09$).

The research group noted: 'The proportion of patients diagnosed with stage I/II non-small cell lung cancer has not increased over time. However, our surgical resection rate has improved, from 9% to 15% of all non-small cell lung cancer patients.'

They added: 'Those diagnosed with stage I/II disease have shown improved survival, perhaps as a result of the higher surgical rates as well as better preoperative selection and staging.'

Susan Mayor

SOCIETY FOR ACUTE MEDICINE
LONDON, 29–30 SEPTEMBER

Acute medicine champions improved patient care

Acute medicine has achieved major improvements in the management of patients with acute illness, Dr Rhid Dowdle, president of the Society for Acute Medicine told the 650 health professionals from ten countries around the world attending the society's recent international conference. 'Over the last decade the acute medicine movement has championed improvements in the care of the acutely ill patient in hospital,' he said.

'Most hospitals now have acute medical units supervised by acute physicians, who form the most rapidly growing group of medical specialists in the UK,' said Dr Dowdle. 'Research presented at the meeting shows the true value of this new way of working, but there is still much more to be done.'

Professor George Alberti, Clinical Director for Service Reconfiguration, Department of Health

Professor George Alberti, Clinical Director for Service Reconfiguration with the Department of Health, told delegates: 'Interest in acute medicine has been rekindled with the realization that the first few hours in hospital for a person with a medical emergency are critical – and that the patient needs a highly skilled, experienced physician to deal with their acute problem.'

There are still far too few physicians trained in acute medicine, Professor Alberti warned, but many are now coming through the training system. 'In future, every acute hospital will have at least six to eight such acute physicians who will be responsible not just for new admissions but also for patients on surgical wards and anyone falling acutely ill while in the hospital', he said. 'This is a critical role and I anticipate a new appreciation of the importance of the specialty of acute medicine, which has risen phoenix-like from the ashes of general medicine'.

Susan Mayor

Acute medical units reduce deaths and length of stay

Being cared for in an acute medical unit reduces the risk of death and length of hospital stay in people with acute medical conditions, according to new research reported at the conference.

The introduction of an acute medical unit at the Chelsea and Westminster Hospital, London, reduced the overall mortality rate for people admitted with medical illnesses from 1.6% in 2005, before the unit was developed, to 1.125% in 2007, once the unit was functioning. It also reduced the average length of hospital stay from 8.84 days to 6.9 days, according to an audit of hospital admissions for patients with acute medical conditions, such as chest pain or respiratory illness, reported at the conference.

Nearly twice as many people were able to go home within 24 hours of going to hospital compared to before the unit was developed (41.8% of people were discharged within 24 hours, compared to 22.6% previously), and this did not result in an increase in the number of readmissions.

Further results showed that the proportion of patients waiting more than 3 hours in the emergency department fell significantly, from more than 70% to fewer than 50%.

Dr Gary Davies, consultant in respiratory and acute medicine at Chelsea and Westminster Hospital Foundation Trust, and a member of the research group, said: 'The development of an acute medical unit significantly improved overall mortality rates, discharge rates, length of stay and waiting times in accident and emergency. Our study shows how an organizational change to the service can positively impact on patient care. It provides evidence for the continued development of acute medical units.'

Susan Mayor

Significant reduction in death rates

An Australian study reported similar results to the study at Chelsea and Westminster Hospital (see left), showing that in-hospital deaths of medical patients fell significantly, from 5.6% in 2003, before setting up an acute medical unit, to 3.8% in 2006, after it was fully functioning (P=0.006). The researchers noted that the reduction in deaths occurred despite a significant 31% increase in acute medical admissions (4422 admissions compared to 3366).

The Australian researchers found the average length of hospital stay fell, and the number of patients discharged within 24 hours increased, from 13% to 17% (P=0.002). They estimated that this saved the hospital 5129 bed-days in 2006 for this 500-bed hospital, equivalent to a cost of £1.38 million (A$ 3 077 712).

Reporting the findings, Dr Jordan Li, consultant physician in the Department of General Medicine, Flinders Medical Centre, Adelaide, Australia, said: 'The establishment of an acute medical unit significantly reduces all-cause hospital mortality and length of stay in acute medical patients. This structural reform in the process of acute medical care has translated not only to the improvement of quality of patient care but also to cost savings.'

Susan Mayor