Longer valganciclovir treatment halves kidney transplant patients' incidence of CMV infection

New data show that doubling the length of valganciclovir (Valcyte) treatment to 200 days prevents the development of cytomegalovirus (CMV) disease in 84% of high-risk kidney transplant patients within the first year post-transplant. This equates to a relative reduction of 56% in incidence compared to the current standard of care (100 days of therapy).

Cytomegalovirus infection could affect more than 1700 new kidney transplant patients in the UK annually and if left untreated is a major complication for solid organ transplant patients (liver, lung, heart and kidney).

The new data, presented at the 2009 European Society for Organ Transplantation (Jardine et al, 2009), provide further support for the prevention of cytomegalovirus disease with valganciclovir. The study showed that 200 days' prophylaxis significantly reduces the proportion of patients with cytomegalovirus disease within the first year post-transplant to 16%, compared to 37% with 100 days' valganciclovir prophylaxis ($P<0.0001$).

Professor Alan Jardine, lead author of the study and Consultant Nephrologist, Western Infirmary, Glasgow, said: 'Cytomegalovirus disease is a major problem for solid organ transplant patients and contributes to reduced quality of life, reduced survival of transplants and can be life threatening.'

He continued: 'The IMPACT study shows that preventative treatment with valganciclovir in transplant recipients at risk of cytomegalovirus for 6 months, rather than the conventional 3 months, is associated with a dramatic reduction in cytomegalovirus disease. By 6 months, most transplant patients have reduced immunosuppression treatment to long-term maintenance levels, and their immune system is strong enough to resist infections. This is likely to have long-term benefits for patients, such as prolonging transplant function and reducing the human costs of cytomegalovirus disease.'

Jardine AG, Lebranchu Y, Vincenti F et al (2009) The IMPACT Study: prophylaxis with valganciclovir for up to 200 days post-transplant in high risk kidney recipients significantly reduces the incidence of CMV disease compared to 100 days use followed by placebo. Presented at the European Society for Organ Transplantation Congress, Paris, France, Wednesday 2 September: abstract #O-337

Treatment of open fractures of the lower limb

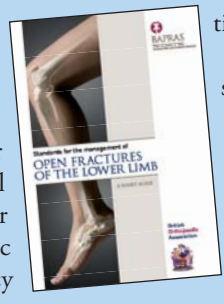
Updated multidisciplinary standards for the treatment of open fractures of the lower limb have been published by the British Association of Plastic, Reconstructive and Aesthetic Surgeons and the British Orthopaedic Association.

The evidence-based standards detail the optimal treatment for people with these challenging injuries to improve patient outcomes. The standards, which will be shared on a national and international level, replace previous UK guidelines and contain new and important recommendations for medical professionals working with patients with lower limb trauma.

The standards are compatible with the proposals for trauma systems and trauma centres in England. They are also relevant to pre-hospital, emergency room and hospital clinicians worldwide.

A working group of experienced clinicians was set up to define the standards. The authors are all practicing specialists in the UK with a particular interest in the evidence-based management of open fractures of the lower limb, from an orthopaedic, plastic surgery and infection control viewpoint.

Keith Willett, National Clinical Director for Trauma Care, said of the published work: 'Standards for the management of open fractures of the lower limb is an essential reference text for orthopaedic, plastic surgery, emergency medicine and rehabilitation specialists who treat these injuries, as well for those who plan and commission trauma care.



'The transfer for definitive care of these patients into specialist orthoplastics surgical facilities will be integral to the planned development of regional trauma networks.'

Professor Willett said that he would ask the National Institute for Health and Clinical Excellence to consider the standards as part of their formal process for setting quality standards.

A short guide to the standards (*left*), containing all the key recommendations, is available to download from www.boa.ac.uk and www.bapras.org.uk

Pemetrexed extends life of patients with lung cancer

Patients with certain types of lung cancer could live over 5 months longer if they are given pemetrexed (Alimta) maintenance therapy after their initial treatment (Ciuleanu et al, 2009).

A randomized double-blind trial in 20 countries included 663 patients with non-squamous non-small cell lung cancer. Patients received either maintenance (ongoing) treatment with pemetrexed and best supportive care or placebo with best supportive care. The average total survival of patients in the pemetrexed group was 15.5 months from initial treatment compared to 10.3 months in the placebo group.

Professor Nick Thatcher, Professor in Medical Oncology, The Christie NHS Foundation Trust, Manchester, commented: 'The standard of care following initial chemotherapy until recently has been to provide as much comfort to the patient as possible without drug therapy. The results tell us we may want to think differently about how and when patients are treated for this type of disease, as this is a significant benefit.'

Ciuleanu T, Brodowicz T, Zielinski C et al (2009) Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *The Lancet* (e-pub before print 20 September doi:10.1016/S0140-6736(09)61497-5)

Thinnest cochlear implant allows faster surgery

Like everyone, people with impaired hearing want to lead an active and connected family and social life, without worrying that their hearing will hold them back.

The Cochlear Nucleus 5 System helps these people to hear clearly in different situations, such as communicating in groups without being distracted by background noise or talking easily on the telephone.

The new cochlear implant system uses the world's thinnest cochlear implant at only 3.9 mm. Precise stimulation of the cochlea is essential for optimal performance. These implants have 22 half banded platinum electrode contacts, providing focused stimulation to the spiral ganglion cell region of the cochlea.

This system offers patients of all ages a hearing solution that is easy to use, faster to fit, thinner, smaller and more robust.

The new wireless remote assistant makes it convenient and easy for the user to monitor and adjust the sound processors during use. The sound processor is ergonomically designed to be more secure and comfortable to wear. The modular design means it can easily be adjusted to fit children and adapted to withstand the bumps and knocks that are a part of every child's life.

Professor Gerard O'Donoghue, Professor of Otology and Neurotology at the University of Nottingham and Nottingham University Hospitals NHS Trust in Nottingham, and cochlear implant surgeon, commented: 'The launch of the Cochlear Nucleus 5 System represents a quantum leap forward in hearing implant technology.

Professor Gerard O'Donoghue, Professor of Otology and Neurotology, University of Nottingham, Nottingham

'The new slim design makes for minimally invasive surgery techniques and reduces operating time, which is highly advantageous when implanting infants and young children. Many young children are now receiving implants simultaneously in each ear, so that reducing operating time has never been more important. The new design also means that the implanted electronics can barely be seen beneath the skin, which is cosmetically very pleasing.'

The Cochlear Nucleus 5 System comprises four components, the implant, the sound processor, the remote assistant and a simplified method of programming, each developed in close collaboration with leading surgeons around the world.

New treatment for both 'poles' of bipolar disorder

Quetiapine prolonged release (Seroquel XL) is now licensed as a monotherapy for major depressive episodes in bipolar disorder. Quetiapine prolonged release is already licensed in bipolar mania, so for the first time there is an effective, once-daily atypical treatment that can treat both 'poles' of bipolar disorder, thereby streamlining and simplifying therapy for patients and physicians.

The new license to treat bipolar depression is a significant advance as people with bipolar disorder spend, on average, three times longer in the depressive phase than the manic phase. This equates to about a third of every year.

Although bipolar depression is often treated with a combination of mood stabilizers and antidepressants, no antidepressant had been licensed for bipolar depression. Use of unlicensed treatments can cause treatment-emergent mania (switching patients from a depressive to a manic phase), which can have a detrimental effect on the course of the illness.

In an 8-week, double-blind, placebo-controlled study in adults with bipolar I or II disorder, quetiapine prolonged release had a relatively low incidence of treatment-emergent mania (4.4% in people taking 300 mg (n=133) *vs* 6.4% with placebo (n=137)).

This study showed fast onset of action, with an improvement in symptoms *vs* placebo as early as week one. A significantly greater proportion of patients achieved remission with quetiapine prolonged release compared to placebo after 8 weeks of treatment (54.1% *vs* 39.4%, P=0.018).

'Clinicians urgently need an effective and licensed alternative to antidepressant treatment for bipolar depression, with a relatively low incidence of mania. Evidence suggests that quetiapine prolonged release will effectively meet this need', said Professor Anthony Hale, Professor of Psychiatry at the University of Kent.

Improving disease control and quality of life in COPD patients

Compared with tiotropium alone budesonide/formoterol added to tiotropium improved overall lung function and daytime and night-time symptoms, and reduced severe exacerbations in patients with chronic obstructive pulmonary disease (COPD) eligible for inhaled steroid and long-acting β2-agonist combination therapy.

Once-daily tablets for the treatment of overactive bladder

Trospium chloride (Regurin XL) is now available as a once-daily, prolonged-release capsule to treat patients with overactive bladder. Regurin XL provides rapid, significant and consistent improvements in the symptoms of overactive bladder and has reduced potential for CNS side effects as it does not cross the blood–brain barrier.

Single-use autoinjector pen for etanercept

Enbrel (etanercept), Wyeth's biological treatment for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and psoriasis, is now available as an easy-to-use pre-filled auto-injector device, known as the Enbrel MYCLIC pen.

INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN
LISBON, PORTUGAL, 9–12 SEPTEMBER

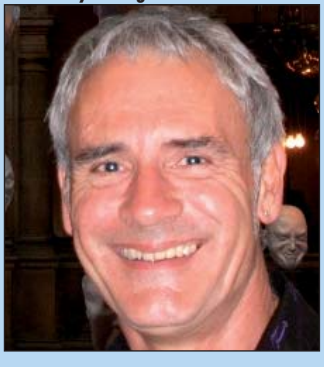
Fewer opioid-related side effects with tapentadol

New phase III clinical trial data were reported for tapentadol in the management of chronic pain, a centrally-acting analgesic with a dual mode of action – μ-opioid-receptor agonism and noradrenaline reuptake inhibition.

Professor Anthony Dickenson from the Department of Pharmacology, University College London, said that both mechanisms of action are likely to contribute to the analgesic effects of tapentadol and explain its broad efficacy in nociceptive as well as neuropathic pain models.

'With tapentadol, the potential for opioid-typical side effects such as nausea and vomiting may be reduced due to an "opioid-sparing" effect because of this new mechanism of action,' he explained.

Professor Anthony Dickenson, Department of Pharmacology, University College London



Tapentadol PR (prolonged release) provided effective relief of chronic low back pain with better gastrointestinal tolerability than oxycodone CR (controlled-release) at equianalgesic doses over a 12-week maintenance period (Shapiro et al, 2009).

The authors found 61.9% of patients treated with oxycodone CR (20–50 mg twice daily) experienced gastrointestinal treatment-emergent adverse events compared to 43.7% in the tapentadol group (100–250 mg twice daily).

Gastrointestinal treatment-emergent adverse events were the most common reason for discontinuing treatment in the oxycodone group (18.3%); in the tapentadol PR group only 5.3% of patients discontinued because of these side effects.

These findings were confirmed in a 12-month long-term phase III trial in patients with chronic low back pain or osteoarthritis pain (Weber et al, 2009). Treatment-emergent adverse events led to discontinuation of therapy in 36.8% of patients in the oxycodone CR group (20–50 mg twice daily) and 22.1% of patients in the tapentadol PR group (100–250 mg twice daily).

The most commonly reported treatment-emergent adverse events leading to treatment discontinuation were gastrointestinal- or CNS-related, reported by a lower percentage of patients in the tapentadol PR group than in the oxycodone CR group (8.6% *vs* 21.5% for gastrointestinal-related treatment-emergent adverse events; 9.1% *vs* 14.3% for CNS-related treatment-emergent adverse events respectively).

Professor Dickenson commented: 'While classical opioids are the standard of care for treating severe chronic pain, their use is often limited by associated side effects. Additionally, they may not provide adequate pain relief to patients when a neuropathic component is present.'

Stephen Pinn

Shapiro DY, Buynak R, Okamoto A et al (2009) Tapentadol prolonged release for chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled trial. Poster presented at the 6th Triennial Congress of the European Federation of Chapters of the International Association for the Study of Pain, September 9–12

Weber H, Lange R, Kuperwasser B et al (2009) Tolerability of tapentadol prolonged release based on discontinuations due to adverse events in a 1-year randomized phase 3 safety study. Poster presented at the 6th Triennial Congress of the European Federation of Chapters of the International Association for the Study of Pain, September 9–12

Etoricoxib has lowest NNT for osteoarthritis pain

Pain research specialists at the Nuffield Department of Anaesthetics in Oxford have carried out a numbers needed to treat (NNT) analysis to determine the most effective agents for pain relief in patients with osteoarthritis of the hip or knee.

Numbers needed to treat were generated on the basis of the proportion of patients who achieved at least a 30% improvement in pain scores over an 8-week period.

In order of highest efficacy to lowest efficacy, they reported the following numbers needed to treat:

- Etoricoxib 60 mg (3.5)
- Naproxen 1000 mg (3.6)
- Etoricoxib 30 mg (3.7)
- Celecoxib 200 mg (4.5)
- Ibuprofen 2400 mg (5.2).

Stephen Pinn

Improving postoperative acute pain relief

Many critical incidents causing actual or potential damage to patients following treatment for acute postoperative pain could be avoided by adhering more closely to guidelines, according to anaesthetists at Castle Hill Hospital, Cottingham, East Yorkshire.

Fifty such incidents were recorded between January 2006 and January 2009, with 35 (70%) related to patient-controlled epidural analgesia and 15 (30%) to patient-controlled analgesia.

Most incidents (59%) in the patient-controlled epidural analgesia group were related to 'inappropriate administration of anticoagulants with respect to the epidural catheter'. The remainder were attributed to prescribing errors and technical problems. Problems included headaches, one infection and one haematoma.

The patient-controlled analgesia group had mainly prescribing errors and technical problems, resulting in inadequate pain relief and one case of respiratory depression.

The researchers concluded: 'Better education of the guidelines to health-care professionals is needed to reduce the incidence of these events in acute pain.'

Stephen Pinn

EUROPEAN SOCIETY OF CARDIOLOGY CONGRESS
BARCELONA, SPAIN, 29 AUGUST–2 SEPTEMBER

Dabigatran is a new option for stroke prevention in atrial fibrillation

The oral thrombin inhibitor dabigatran seems a promising alternative to warfarin for stroke prevention in patients with atrial fibrillation, according to the results of the RE-LY study (Connolly et al, 2009).

RE-LY (randomised evaluation of long-term anticoagulant therapy) was a non-inferiority study including 18 113 atrial fibrillation patients with at least one risk factor for stroke. Patients were randomized to double-blind treatment with dabigatran 110 mg or 150 mg twice daily, or to unblinded treatment with dose-adjusted warfarin.

After a median of 2 years, dabigatran 150 mg significantly reduced the risk of stroke or systemic embolism (the primary outcome) by 34% compared to warfarin (P<0.001). Dabigatran 110 mg was as effective as warfarin (P<0.001).

The rate of major bleeding per year was 2.71% in the dabigatran 110 mg group *vs* 3.11% in patients receiving dabigatran 150 mg and 3.36% in those receiving warfarin. Haemorrhagic stroke rate per year was 0.38% in warfarin-treated patients compared with 0.12% with dabigatran 110 mg (P<0.001) and 0.10% with dabigatran 150 mg (P<0.001).

According to lead investigator Dr Stuart Connolly, McMaster University, Ontario, Canada, who presented the results at the congress: 'Both doses appear to offer advantages over warfarin. The 150 mg dose reduces the risk of stroke and some aspects of bleeding but did not reduce major haemorrhage. The 110 mg dose is non-inferior to warfarin and clearly as effective against stroke, but with a greater safety profile.'

Dyspepsia was the only adverse event that was significantly more common with dabigatran caused, according to Dr Connolly, by the effects on gastric pH of tartaric acid in the tablet formulation. There was a trend towards a higher risk of myocardial infarction among patients receiving dabigatran 150 mg. 'This unexpected observation may be due to warfarin's greater effectiveness in lowering myocardial infarction risk because of its broader anticoagulation effect,' said Dr Connolly.

Dr Stuart Connolly, McMaster University, Ontario, Canada

Unlike warfarin, dabigatran does not require routine coagulation monitoring or dose adjustment. It is licensed in the UK for the prevention of venous thromboembolism in patients undergoing elective total hip or knee replacement. Submission for an indication for stroke prevention in atrial fibrillation is expected shortly.

Sue Lyon

Connolly SJ, Ezekowitz MD, Yusuf S et al (2009) Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* **361**: 1139–51

Ticagrelor reduces risk of death in acute coronary syndromes

Ticagrelor is significantly more efficacious than clopidogrel in reducing the risk of death from vascular causes, myocardial infarction and stroke in patients with acute coronary syndromes, according to the results of the PLATO study (Wallentin et al, 2009). These benefits were achieved without significantly increasing the risk of major bleeding.

PLATO (a study of platelet inhibition and patient outcomes) randomized 18 624 patients hospitalized for acute coronary syndromes, with or without ST elevation, to either ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) or clopidogrel (300–600 mg loading dose, 75 mg thereafter). All patients were given aspirin 75–100 mg if tolerated.

At 12 months follow-up, the primary composite end-point of death from vascular causes, myocardial infarction or stroke had occurred in 9.8% of patients receiving ticagrelor compared with 11.7% receiving clopidogrel (P<0.0001). Ticagrelor also significantly reduced death from any cause (4.5% *vs* 5.9% in the clopidogrel group; P<0.001).

Presenting PLATO results during a hotline plenary session in Barcelona, lead investigator Professor Lars Wallentin, Uppsala Clinical Research Centre, Sweden, commented: 'This is a unique finding. Over the last 10–15 years, we have not seen any other trial with an antithrombotic compound that lowers total mortality.'

There was no significant difference between ticagrelor and clopidogrel in the rate of major bleeding (11.5% *vs* 11.2%), but major bleeding not related to coronary artery bypass grafting was more frequent in the ticagrelor group (4.5% *vs* 3.8%; P=0.03). Dyspnoea was also more common with ticagrelor (13.8% *vs* 7.8% in clopidogrel-treated patients), leading to discontinuation in 0.9% of patients compared to 0.3% taking clopidogrel.

Current guidelines recommend that patients with acute coronary syndromes with or without ST segment elevation should receive dual antiplatelet therapy with aspirin and clopidogrel. Ticagrelor is an investigational oral antiplatelet agent in development for the prevention of thrombotic events in acute coronary syndromes patients. It is a reversible inhibitor of the adenosine diphosphate receptor P2Y12 and has a more rapid onset and more pronounced platelet inhibition than clopidogrel. Ticagrelor is likely to be submitted to the regulatory authorities by the end of 2009.

Sue Lyon

Wallentin L, Becker RC, Budaj A et al (2009) Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* **361**: 1045–57