Good response for entecavir in chronic hepatitis B

The nucleoside analogue entecavir (Baraclude) achieves a high response rate and progressive decline in liver stiffness in patients with chronic hepatitis B, according to results from the first study in 'real-life' clinical practice which were reported at the Annual Meeting of the American Association for the Study of Liver Diseases (31 October–3 November 2009).

Italian researchers followed 376 consecutive patients, recruited from 16 centres across Italy during 2007–8, who were treated with entecavir (0.5 mg once daily). The patients were generally older than those included in previous clinical trials, with a median age of 58 years, and had more severe liver disease (47% had cirrhosis).

Results showed that nearly two-thirds (64%) of the patients achieved undetectable virus levels (hepatitis B virus DNA <12 U/ml) by 24 weeks. This increased to 91% of patients by 48 weeks and to 96% at 72 weeks. Liver stiffness was reduced, indicating a reduction in fibrosis.

Patients with a low level of viraemia at baseline (DNA <5 logU) were more likely to achieve undetectable virus levels (100% by 12 months) than those with higher viral loads. However, 96% of patients with medium levels of viraemia (DNA 5–8 logU) achieved a virological response by 18 months, and more than three-quarters (77%) of patients with high baseline viral load (DNA >8 logU) reached this by 18 months.

Dr Pietro Lampertico, from the University of Milan, Italy, said: 'We found we can stop replication of the virus in most patients, which we found surprising as many of these patients would be considered difficult to treat because of the severity of their liver disease.' He continued: 'An important message for clinicians is not to stop treating patients after 1 year even if they have residual virus, because the drug will continue to reduce viral levels.'

Professor Mark Thursz, Professor of Hepatology, Imperial College, London, added: 'These are welcome data. Once patients are progressing to cirrhosis it is very important to suppress the virus, but these patients can be difficult to treat.' He warned that awareness of hepatitis B is currently low so that cases are often missed until patients have liver damage.

Susan Mayor

Dr Pietro Lampertico, University of Milan, Italy

Biomarkers for ovarian cancer

Concentrations of the biomarkers CA125, human epididymis protein 4 and mesothelin began to rise 3 years before clinical diagnosis of ovarian cancer (Anderson et al, 2009). However, levels became substantially elevated only in the last year before diagnosis. The stage of cancer at the time of marker elevation is not known.

There are a number of potential ovarian cancer biomarkers, but their behavior in the pre-diagnostic period, with the exception of CA125, has not been evaluated previously.

Anderson GL, McIntosh M, Wu L et al (2009) Assessing lead time of selected ovarian cancer biomarkers: a nested case-control study. *J Natl Cancer Inst* Dec 30 [Epub ahead of print]

Pollution linked to hospitalizations for pneumonia in older adults

Older adults with long-term exposure to higher levels of pollution are at higher risk for hospitalization for pneumonia, according to researchers in Canada (Neupane et al, 2010).

'Our study found that among older individuals, long-term exposure to traffic pollution independently increased their risk of hospitalization for pneumonia,' said principal investigator Dr Mark Loeb, of McMaster University, Ontario, Canada.

Pneumonia is a leading cause of sickness and death among older adults, and rates of hospitalizations for pneumonia among patients aged 65 years and older have been increasing in recent years.

The researchers recruited 365 older adults from Hamilton, Ontario, who had been hospitalized with radiologically confirmed pneumonia in one of Hamilton's four emergency departments between 2003 and 2005. Control subjects from the same catchment areas as the patients were enrolled contemporaneously, and then the exposures of the two groups to nitrogen dioxide, sulphur dioxide and fine particulate matter less that 2.5 µm (PM2.5) were compared using data from air-quality monitoring stations and land use regression models.

In addition to traffic pollution associated with roads, Hamilton has a large industrial steel-making complex in the north end of the city, which creates a large exposure zone for residents.

The researchers found that long-term (more than 12 months) exposures to nitrogen dioxide and PM2.5 were each associated with a more than doubled risk of hospitalization from pneumonia. Individuals with long-term exposure to nitrogen dioxide had 2.3 times the risk for hospitalization with pneumonia; while for PM2.5, the odds ratio was 2.26. Sulphur dioxide did not appear to have any association (odds ratio 0.97).

'We postulate that long-term exposure to air pollution may have increased individuals' susceptibility to pneumonia by interfering with innate immune defences designed to protect the lung from pathogens; this may have included epithelial cell damage, reductions in bronchial macrophages, or reductions in natural killer cells,' said Dr Loeb.

Neupane B, Jerrett M, Burnett RT, Marrie T, Arain A, Loeb M (2010) Long-term exposure to ambient air pollution and risk of hospitalization with community-acquired pneumonia in older adults. *Am J Respir Crit Care Med* **181**: 47–53

Improving care for major trauma patients

The introduction of regional centres for major trauma patients will save thousands of lives and reduce long-term disability for many victims of trauma every year, but requires careful planning. This is the outcome of a detailed plan produced to assist strategic health authorities in developing regional trauma systems across the country, published by the Royal College of Surgeons.

The report, put together by a joint group of senior clinicians representing those colleges and Royal colleges involved in trauma care (Royal Colleges of Surgeons, Anaesthetists, Nursing, Radiologists, Paediatrics and Child Health and Physicians and the College of Emergency Medicine) working alongside the regulator, identifies the need for regional service planners and commissioners to urgently oversee the development of a defined trauma system, considering the needs of all injured patients.

The guidance maps out what is required in terms of equipment, staff, space and experience for centres designated as major trauma centres and trauma units (which will look after patients with less severe injuries), tracking the patient from the first pre-hospital clinical contact following injury right through to rehabilitation.

Richard Collins, chair of the intercollegiate trauma standards working group and Vice President of the Royal College of Surgeons, said: 'Patients with severe multiple injuries from, for example, a major road traffic or industrial accident, need specialist care in a dedicated major trauma centre. With the success of regional trauma systems relying on the skills and expertise of a wide range of health professionals working together, it is vital that the standards for these centres are set by these professions involved in delivering the care to the patient rather than being imposed by central government.'

The document can be accessed at www.rcseng.ac.uk/news/docs/Regional_trauma_systems.pdf

Body mass index and waist circumference predict risk of fatal and non-fatal cardiovascular disease

Body mass index and waist circumference are well known risk factors for cardiovascular diseases, but a new study concludes that these risk factors, when accurately measured by trained staff, can predict the risk of fatal and non-fatal disease (Van Dis et al, 2009).

The findings, which emerged from a large prospective study of more than 20 000 Dutch men and women aged 20–65 years which started in 1993, show that the associations of body mass index and waist circumference with heart disease are equally strong, and explain one half of all fatal and one quarter of non-fatal cardiovascular disease in those who are overweight and obese.

When age-adjusted body mass index and waist circumference measurements were correlated with hospital records and cause-of-death statistics, results showed that in those categorized as overweight and obese around one half (53%) of all fatal cardiovascular disease and one quarter (25–30%) of all non-fatal cardiovascular disease were ascribed to the fact that the individual was overweight or obese.

The study also found that the overall risk of a first non-fatal cardiovascular disease was ten times higher than that of fatal cardiovascular disease.

Commenting on the public health implications of the study, principal investigator Ineke van Dis from the Netherlands Heart Foundation said: 'Throughout western Europe – as in the Netherlands – there has been a decline in cardiovascular mortality in recent years, which is reflected in a prevalence shift from mortality to morbidity. What this study shows is the substantial effect which overweight and obesity have on cardiovascular disease, whether fatal or non-fatal. In the near future the impact of obesity on the burden of heart disease will be even greater.

'For consumer groups and our national heart foundations, these findings underline the need for policies and activities to prevent overweight in the general population. ... GPs and cardiologists can do even more to tackle these problems, especially in obese patients under 65 years, as highlighted in this study.'

Van Dis I, Kromhout D, Geleijnse M, Boer JM, Verschuren WM (2009) Body mass index and waist circumference predict both 10-year non-fatal and fatal cardiovascular disease risk in 20,000 Dutch men and women aged 20-65. *Eur J Cardiovasc Prev Rehabil* **16**(6): 729–34

Combination therapy may be better than monotherapy in bipolar disorder

A controlled trial published in ***The Lancet*** found that patients with bipolar disorder treated with valproate plus lithium were less likely to relapse than those treated with valproate alone; lithium alone was of intermediate benefit.

Low energy diet improves sleep apnoea in obese men

A randomized controlled trial carried out in Sweden has shown that treatment with a low energy diet improved obstructive sleep apnoea in obese men, with the greatest effect in patients with severe disease.

Dabigatran as effective as warfarin for acute venous thromboembolism

In a randomized, double-blind, non-inferiority trial involving patients with acute venous thromboembolism, oral dabigatran 150 mg twice daily was as effective warfarin that was dose-adjusted to achieve an international normalized ratio of 2.0 to 3.0, had a safety profile that is similar to that of warfarin, and did not require laboratory monitoring.

51ST AMERICAN SOCIETY OF HEMATOLOGY MEETING
NEW ORLEANS, LOUISIANA, 5–8 DECEMBER

Adding rituximab to chemotherapy improves overall survival

Adding rituximab (MabThera) to chemotherapy in previously untreated patients with chronic lymphocytic leukaemia significantly improved overall survival, found a study from the German Chronic Lymphocytic Leukaemia Group.

'This is the first randomized study ever to demonstrate that the choice of first-line therapy improves the natural course of chronic lymphocytic leukaemia,' said study presenter Michael Hallek, from the University of Cologne, Germany.

Until now therapies such as chlorambucil, fludarabine, and the fludarabine + cyclophosphamide combination have been associated with longer progression-free survival in chronic lymphocytic leukaemia, but have had no effect on overall survival.

In the CLL8 study, 817 patients with untreated active chronic lymphocytic leukaemia and good prognostic factors were randomized 1:1 to receive six courses of rituximab, fludarabine + cyclophosphamide (n=409) or six courses of fludarabine + cyclophosphamide (n=408).

After 37.7 months results show that overall survival rate was 87.2% for patients receiving rituximab, fludarabine + cyclophosphamide compared to 82.5% for patients receiving fludarabine + cyclophosphamide (hazard ratio 0.664, P=0.012). Progression-free survival was 51.8 months for patients receiving rituximab, fludarabine + cyclophosphamide arm *vs* 32.8 months for those receiving fludarabine + cyclophosphamide (hazard ratio 0.563, P<0.001).

The main adverse event was neutropenia occurring in 21% of patients randomized to the fludarabine + cyclophosphamide arm compared to 33.7% randomized to the rituximab, fludarabine + cyclophosphamide arm (P<0.0001), but this did not result in increased rates of infection.

Commenting on the results, Professor John Gribben from Barts and The London NHS Trust, said: 'It's extremely exciting to see an overall survival advantage so early in a study, which we would expect over the next few months to get even better.' After the results of the CLL8 clinical trial, he added, rituximab, fludarabine + cyclophosphamide should be considered the new standard of care in chronic lymphocytic leukaemia.

In a separate open label phase II study (CLL208), also presented at ASH, rituximab was trialled in combination with chlorambucil chemotherapy in previously untreated chronic lymphocytic leukaemia patients with a median age of 70.5 years. A planned interim analysis, based on the first 50 patients, showed the overall response rate was 17.3% higher in patients who received chlorambucil and rituximab when compared to historical data from similar patients receiving chlorambucil alone.

'While rituximab, fludarabine + cyclophosphamide is the treatment of choice, the reality is that only 50% of patients can tolerate it. The CLL208 study demonstrate that the chlorambucil–rituximab combination offers a real treatment alternative for frailer patients,' said Gribben.

While the European Medicines Agency have approved rituximab use with chemotherapy in chronic lymphocytic leukaemia (leaving it to the clinician's discretion which is used), the National Institute for Health and Clinical Excellence (NICE) ruled that rituximab could only be used in combination with fludarabine + cyclophosphamide.

'It's really frustrating that we have an effective new treatment approach which around half our patients are disenfranchised from using. If they were permitted to use the chlorambucil and rituximab combination they would stand a chance of living longer,' said Gribben.

Subsequent to these new data NICE is planning to review the use of rituximab in first-line treatment of chronic lymphocytic leukaemia.

Janet Fricker

Continuous therapy with lenalidomide in multiple myeloma

Data evaluating continuous therapy with Revlimid (lenalidomide) across all stages of multiple myeloma were presented during the American Society of Hematology congress. The studies demonstrated lenalidomide has significant clinical potential in active newly diagnosed myeloma, for induction therapy followed by continuous treatment and in asymptomatic smoldering multiple myeloma.

A phase III study assessed lenalidomide in 459 elderly patients with newly diagnosed, active myeloma. This three-arm study compared two regimens with fixed treatment duration, melphalan and prednisone and melphalan, prednisone plus lenalidomide, to melphalan, prednisone plus lenalidomide followed by continuous lenalidomide. The study showed that continuing treatment with lenalidomide reduced the risk of progression or death by 50% compared to the fixed duration treatment.

Interim analysis of the first 40 patients of 80 included in another randomized phase III study gave promising results. The trial is looking at early treatment with lenalidomide and dexamethasone to see if this prolongs time to disease progression (to symptomatic disease) compared to no treatment for patients with high-risk smoldering multiple myeloma, who show no overt symptoms. Both groups were well balanced for baseline characteristics.

The results showed a 81% response rate (51% partial, 16% very good partial and 14% complete response). The response rate was 91% for the 16 patients who completed all nine treatment cycles.

'These studies demonstrate that at all stages of multiple myeloma, sustained disease control can be achieved by continuous treatment with lenalidomide,' said lead investigator Dr Antonio Palumbo, from the University of Turin.

CONGRESS OF THE EUROPEAN SOCIETY FOR SEXUAL MEDICINE
LYON, FRANCE, 15–18 NOVEMBER

Improving satisfying sexual events and sexual desire in women

Data from pooled phase III trials showed that flibanserin 100 mg taken once daily at bedtime increased the number of satisfying sexual events and sexual desire in women with hypoactive sexual desire disorder.

The data were derived from three North American trials (DAISY, VIOLET and DAHLIA) and a European trial (ORCHID). The pre-specified pooled analysis of 1378 pre-menopausal women with hypoactive sexual desire disorder showed a statistically significant increase in the frequency of satisfying sexual events per month in women taking flibanserin 100 mg *vs* placebo. The pooled analysis also suggested that those taking the drug had statistically significant improvements in sexual desire compared to the placebo group.

Primary investigator of the European trial, Professor Rossella Nappi, director of the Gynaecological Endocrinology and Menopause Unit at the University of Pavi, Italy, said: 'The 100 mg dose was the most consistently effective dose in the individual trials.'

The ORCHID trial randomized 634 pre-menopausal women with hypoactive sexual desire disorder and found a trend towards an increase in the Female Sexual Function Index desire domain. There was also a statistically significant improvement in the level of distress associated with sexual dysfunction as well as distress related to low sexual desire (*Table 1*).

The most common adverse events reported with flibanserin use including dizziness, nausea, fatigue, somnolence and insomnia, emerged during the first 14 days of treatment and tended to resolve with continued treatment. About 16% of women on flibanserin 100 mg discontinued treatment as a result of adverse events in the ORCHID trial compared to 5% on placebo.

Professor Nappi said: 'Flibanserin is a novel, non-hormonal compound that has been investigated as a treatment for pre-menopausal women with hypoactive sexual desire disorder. Based on the results presented at this meeting, the drug has the potential to help many women suffering from their lack of sexual desire.'

Rhonda Siddall

Table 1. Results of the ORCHID trial

	SSE	e-diary measure of desire	FSFI desire domain	FSFI total	FSDS-R total	FSDS-R item 13
Placebo	0.9	5.4	0.5	2.5	-3.7	-0.4
Flibanserin 50 mg qhs	1.2	5.6	0.5	2.7	-4.8	-0.5
Flibanserin 100 mg qhs	1.5	7.7*	0.7	3.4	-6.4†	-0.6*

*$P<0.05$, †$P<0.001$ *vs* placebo. FSDS-R = Female Sexual Distress Scale-Revised; FSFI = Female Sexual Function Index; qhs = at bedtime; SSE = satisfying sexual events

Podium session update: hypoactive sexual desire disorder in women

Most women with hypoactive sexual desire disorder are not offered treatment by their GPs, according to a UK study based on the IMS Disease Analyser Database.

The study identified 5362 women with hypoactive sexual desire disorder or related diagnoses (mean age 36 years). Overall, over 85% of the women received neither medical treatment nor specialist referral. Seven per cent of patients were prescribed medication, most commonly antidepressants (17% of all prescriptions), and 8% were referred on, usually to gynaecologists or counsellors (25% and 20% of referrals respectively).

Following their first consultation, women were unlikely to seek further help from their GPs: 88% of women presented only once, compared with 2% who consulted three times.

The investigators conclude that their results underline the importance of educating GPs in the management of female sexual dysfunction.

Lee S (2009) GPs' approach to treatments of female HSDD: An epidemiological study. PS-02-006

There are clear differences in brain deactivation in response to visual sexual stimuli between women with hypoactive sexual desire disorder and women without sexual dysfunction, according to a positron emission tomography study.

The study included nine premenopausal women with hypoactive sexual desire disorder and six matched healthy volunteers, who all watched four neutral films, four non-explicit erotic films and four sexually explicit films. In response to the erotic films, there was statistically stronger activation in the left insula and rostral areas, and in Brodmann's areas 43, 44, 45, and 47 in women with hypoactive sexual desire disorder compared with healthy volunteers. There were no differences in the groups' responses to the neutral films.

The investigators suggest that decreased blood flow in these areas of the brain in women is a sign of behavioural disinhibition during orgasm, and that deactivation of the temporal lobe is directly related to high sexual arousal. Conversely, brain activation prevents disinhibition and arousal, indicating that hypoactive sexual desire disorder has an underlying neurobiological component in pre-menopausal women.

Sue Lyon

Holstege G, Willemsen A, Beers C, Lont E, Schultz WW, Sand M, Jansen M, Dierckx R (2009) Differences in brain activity in premenopausal women with Hypoactive Sexual Desire Disorder (HSDD) compared to women without sexual dysfunction. PS-02-002