

Improving control of glycaemia and weight in type 2 diabetes

Two new studies indicate that treatment with liraglutide, a once-daily human analogue of glucagon-like peptide-1 (GLP-1), improves both glycaemic and weight control in patients with type 2 diabetes when added to a sulphonylurea.

The two studies, published by Liraglutide Effect and Action in Diabetes (LEAD) investigators, involved a total of more than 2000 patients.

LEAD-1 showed that 1.2 mg and 1.8 mg doses of liraglutide, when added to glimepiride, produced significant improvements in glycaemic control – glycosylated haemoglobin (HbA_{1c}) values of 8.5% at baseline to -1.1% after 26 weeks of follow up, compared to reductions from 8.4% to 0.2% with placebo ($P<0.0001$) and 8.4% to -0.4% with rosiglitazone ($P<0.0001$) (Marre et al, 2009).

The LEAD-1 investigators recruited 1041 adults with type 2 diabetes (mean age 56 years) from 116 centres in 21 countries. Reductions in fasting plasma glucose were also significant – a decrease of

1.6 mmol/litre with liraglutide, compared to 0.9 mmol/litre for placebo ($P<0.0001$) and 1.0 mmol/litre for rosiglitazone ($P<0.006$).

Changes in body weight with liraglutide (-0.2 kg for the 1.8 mg dose and +0.3 kg for the 1.2 mg dose) were less than for rosiglitazone (+2.1 kg, $P<0.0001$ for both of the liraglutide doses).

The authors said that treatment with the combination of liraglutide and glimepiride was superior to glimepiride monotherapy and the combination of rosiglitazone and glimepiride in terms of improving HbA_{1c}.

They added that the similar findings for reductions in fasting plasma glucose highlight improved 24-hour glucose control with once-daily liraglutide, with substantially more individuals reaching glycaemic targets.

Minor hypoglycaemic events occurred more often with the liraglutide/glimepiride combination than with glimepiride alone – but patients randomized to either dose of liraglu-

tide achieved lower HbA_{1c} values than those randomized to glimepiride monotherapy.

‘At lower HbA_{1c} levels,’ reported the investigators, ‘sulphonylureas are known to elicit hypoglycaemia more readily than at higher levels. In clinical practice, it may be possible to reduce the dose of sulphonylurea (when used with liraglutide) to minimize the risk of hypoglycaemia and maintain HbA_{1c} improvements.’

The authors also commented on the use of other GLP-1-based agents such as sitagliptin. Because sitagliptin inhibits the degradation of GLP-1, its efficacy depends on levels of endogenous GLP-1, which are physiologically low compared to the much higher pharmacological levels of liraglutide. ‘Pharmacological levels may be needed to induce satiety, weight loss and possibly larger HbA_{1c} reductions.’

They concluded: ‘Liraglutide is an effective and well-tolerated, once-daily human GLP-1 analogue that improves overall glycaemic control and indices of

pancreatic beta-cell function with minimal weight gain and risk of hypoglycaemia when used in combination with a sulphonylurea for type 2 diabetes.’

The LEAD-2 study, also conducted over 26 weeks, showed that in 1091 individuals with type 2 diabetes, once-daily liraglutide (0.6 mg, 1.2 mg or 1.8 mg) induced similar glycaemic control, reduced body weight, and lowered the incidence of hypoglycaemia compared to glimepiride – against background therapy of metformin in all those investigated (Nauck et al, 2009).

Stephen Pinn

Marre M, Shaw J, Brändle M et al (2009) Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks, produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). *Diabetic Med* (published online 14 January)
Nauck M, Frid A, Hermansen K et al (2009) Efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes. *Diabetes Care* **32**: 84–90

Graft vs stent for severe coronary artery disease

Coronary artery bypass grafting (CABG) should remain the treatment of choice for three-vessel or left main coronary artery disease, according to trial results published early online in the *New England Journal of Medicine* (Serruys et al, 2009).

CABG is the treatment of choice for patients with severe coronary artery disease, including those with left main artery disease and those with triple-vessel disease, but the evidence base for this is not strong.

The SYNTAX (Synergy between PCI with Taxus and Cardiac surgery) trial sought

to define the optimum revascularization strategy in these patients by prospectively comparing CABG and PCI (percutaneous coronary intervention with a paclitaxel-eluting stent).

A total of 3075 patients were entered into the study, of which 1800 were randomized to undergo CABG ($n=897$) or PCI ($n=903$).

The primary endpoint was a composite of major adverse cardiac and cerebrovascular events up to 1 year after intervention. The primary analysis was a non-inferiority comparison (intention-to-treat).

The authors concluded that CABG should remain the standard of care for patients with three-vessel or left main coronary artery disease, but cautioned that the 12-month follow-up period of this study ‘may not be sufficient to reflect the true long-term effect of CABG as compared with PCI with drug-eluting stents on cardiac-related health’.

Serruys PW, Morice M-C, Kappetein AP et al (2009) Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* (Epub 18 February 2009)

Oesophageal Doppler monitoring saves lives

Oesophageal Doppler monitoring saves lives, reduces surgical complications, and shortens length of stay in hospital. So says the National Institute for Health Research, Health Technology Assessment Programme’s review of the clinical and cost-effectiveness of oesophageal Doppler monitoring in high-risk surgical and critically ill patients.

Reduced risk of hospitalization with dronedarone

The risk of death or cardiovascular-related hospitalization in patients with atrial fibrillation has been reduced by 24% by the anti-arrhythmic drug dronedarone, according to newly-published data from ATHENA – an international, randomized, placebo-controlled clinical trial carried out in 37 countries (Hohnloser et al, 2009).

Dronedarone, a derivative of amiodarone, is under development as an ion-channel-blocking drug, and is, as yet, unlicensed in the UK or elsewhere in Europe.

In ATHENA, it was shown that when dronedarone was added to standard therapy in patients with atrial fibrillation and at least one other cardiovascular risk factor, the risk of first cardiovascular hospitalization or death was reduced significantly (31.9% vs 39.4% for placebo, hazard ratio 0.76, $P < 0.001$).

A total of 4628 atrial fibrillation patients were randomized to dronedarone (400 mg, twice a day) or placebo and followed for a mean of 21 months. There were 63 deaths from cardiovascular causes (2.7%) with dronedarone, compared to 90 deaths (3.9%) linked to placebo (hazard ratio 0.71, $P = 0.03$) – largely as a result of a reduction the

rate of death from arrhythmia with dronedarone.

However, dronedarone was associated with a greater number of significant adverse events, including diarrhoea, nausea, bradycardia and an increase in blood creatinine.

The patients studied in ATHENA were either 75 years of age or older (with or without cardiovascular risk factors) or 70 years of age or older (with at least one additional cardiovascular risk factor).

The ATHENA investigators said that their data, while encouraging, should be treated with some caution. 'No significant increase in the rates of thyroid or pulmonary disorders was seen with dronedarone,' they noted. 'This observation may suggest that dronedarone has a more benign side-effect profile than amiodarone.'

'However, the mean follow-up was only 21 months, and in many cases patients treated with amiodarone have such side-effects (particularly pulmonary toxic effects) later than 2 years after initiating therapy.'

They also emphasized that the rate of premature discontinuation of the study drug (30.2%) was very high, and that although this may have resulted in an underestimate of the benefit of dronedarone,

it may also have limited the likelihood of demonstrating an increase in the rate of adverse events.

'No anti-arrhythmic agent other than dronedarone has been evaluated in a large trial involving patients with atrial fibrillation for the prevention of hospitalization due to cardiovascular events or death. Therefore, it is not possible to know the relative efficacy or safety of dronedarone compared to other drugs for this outcome.'

The ATHENA authors pointed out that an earlier study of dronedarone in patients with advanced, symptomatic congestive heart failure, but without atrial fibrillation, had to be terminated prematurely because of an excess of deaths among those taking the study drug – 25/310 patients (8.1%) died at 2 months vs 12/317 patients on placebo (hazard ratio 2.13, $P = 0.03$) (Køber et al, 2008).

Stephen Pinn

Hohnloser SH, Crijns HJ, van Eickels M et al; for the ATHENA Investigators (2009) Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* **360**: 668–78

Køber L, Torp-Pedersen C, McMurray JJV et al (2008) Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* **358**: 2678–87

Lack of awareness about tuberculosis in pregnancy

A national study has highlighted a lack of awareness about tuberculosis in pregnancy (Knight et al, 2009). The study found that ethnic minority women, particularly those who have recently arrived in the UK, are most commonly affected.

In this study, researchers identified cases of tuberculosis during pregnancy using the UK Obstetric Surveillance System (UKOSS) between

August 2005 and August 2006. All 229 of eligible UK hospitals participated, representing 100% coverage of women giving birth in the UK.

A total of 33 women were diagnosed with tuberculosis during pregnancy. All of these women were non-white. Researchers found that tuberculosis in pregnancy in the UK appears to be exclusively limited to ethnic minority women

and almost exclusively to those born outside the UK.

The authors noted that, while recommended, screening for tuberculosis during pregnancy does not seem to be undertaken routinely. This may contribute to a delay in diagnosis.

Knight M, Kurinczuk J, Nelson-Piercy C, Spark P, Brocklehurst P on behalf of UKOSS (2009) Tuberculosis in pregnancy in the UK. *BJOG* **116**: 584–8

Increasing effectiveness of radiation therapy

A team of medical physicists in Canada have successfully taken a magnetic resonance image at the same time as radiation therapy is being delivered. In future, this could allow radiation to be guided specifically to the tumour during treatment.

Predicting treatment success in hepatitis B

Data presented at the Asian Pacific Association for the Study of the Liver meeting showed that, for the first time, doctors can predict which hepatitis B patients treated with Pegasys (peginterferon alfa-2a) have the highest chance of achieving a positive treatment outcome – and even a clinical cure.

Zoledronic acid reduces risk of breast cancer recurrence in premenopausal women

A study in the *New England Journal of Medicine* shows that, in premenopausal women with early breast cancer, administering zoledronic acid along with post-surgery hormone therapy reduced the risk of recurrence 36% more than hormone therapy alone (hazard ratio 0.64; 95% confidence interval = 0.46–0.91; $P = 0.01$).