EMERGENT THERAPIES

NEW ANTIDIABETIC SHOWS PROMISE IN PATIENTS WITH RENAL DISEASE

Data from a new phase 3 study has demonstrated that once-daily liraglutide (Victoza) provided greater glycaemic control versus placebo with no worsening of renal function in adults who have type 2 diabetes coupled with moderate renal impairment (stage 3 chronic kidney disease).

Renal impairment is one of the more common and challenging long-term complications of diabetes and limits the use of available antidiabetic treatment options. In the UK, the risk of developing chronic kidney disease stages 3b-5 among people with diabetes is around eight times higher in women and over 12 times higher in men, compared with those who do not have diabetes.

"About a third of people with diabetes also have chronic kidney disease. It can be a particular problem, especially in the over 65s, limiting diabetes treatment options and increasing the risk of hypoglycaemia," said Steve Bain, Professor of Medicine at Swansea University and Clinical Lead for the Diabetes Research Network, Wales

Liraglutide is a human glucagon-like peptide-1 (GLP-1) analogue which works by stimulating the beta cells to release insulin and suppressing glucagon secretion from the alpha cells only when blood sugar levels are high.

The 26-week, double-blind, randomised, controlled LIRA-RENAL study investigated the efficacy and safety of liraglutide compared with placebo when added to pre-existing oral antidiabetic treatment, insulin or a combination thereof. The study showed that adults with type 2 diabetes and moderate renal impairment treated with liraglutide had significantly greater improvements in mean HbA1c, were more likely to achieve target HbA1c, and experienced significantly greater weight loss from baseline versus placebo.

A lower incidence of hypoglycaemia, with no worsening of renal function, was also observed in patients treated with liraglutide compared with those on placebo.

The most common adverse events seen in this study were nausea, vomiting, diarrhoea and constipation.

Overall, there is limited experience with liraglutide in patients with mild, moderate, and severe renal impairment, including end-stage renal disease. Presenting their data at the Annual Scientific Sessions of the American Diabetes Association in August, the researchers warned that liraglutide should therefore be used with caution in this patient population.

NOVEL ANTI-GOUT AGENT DEMONSTRATES POSITIVE TRIAL RESULTS

Promising data have emerged from three pivotal Phase 3 clinical trials investigating the potential of lesinurad, a selective uric acid re-absorption inhibitor (SURI), as a combination therapy for the treatment of patients with symptomatic gout. Lesinurad is an investigational agent that inhibits the URAT1 transporter, increasing uric acid excretion and thereby lowering serum uric acid (sUA).

Two of the trials, CLEAR1 and CLEAR2, studied lesinurad in combination with the xanthine oxidase (XO) inhibitor allopurinol, in symptomatic gout patients not achieving target sUA levels on their current allopurinol dose. The third trial, CRYSTAL, studied lesinurad in combination with the XO inhibitor febuxostat in gout patients with tophi (visible nodules of uric acid crystals that are deposited in joints and skin).

In the CLEAR1 and CLEAR2 trials, lesinurad, at both trialled doses (200mg and 400mg), in combination with allopurinol, met the primary endpoint, with a statistically significant higher proportion of patients reaching the target sUA goal of <6.0mg/dL at month 6 compared to allopurinol alone ($p<0.0001$).

In the CRYSTAL trial, lesinurad 400mg in combination with febuxostat met the primary endpoint, with a statistically significant higher proportion of patients reaching the target sUA goal of <5.0mg/dL at month 6 compared to febuxostat alone ($p<0.0001$).

The most commonly reported adverse events in the lesinurad-treated patients across the three trials were upper respiratory tract infection, nasopharyngitis, arthralgia and back pain. A full assessment of the safety and tolerability findings of all three studies is ongoing.

The trial findings suggest that lesinurad may help address a significant unmet need, with 40 to 70% of gout patients not reaching target levels of serum uric acid with the current standard of care.

AUTHORISATION AND APPRAISAL

EC APPROVES DRUG FOR TREATMENT OF DVT AND PE

The European Commission has approved apixaban (Eliquis) for the treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE).

The approval broadens the clinical use for apixaban, which is also approved for use in the EU for the prevention of venous thromboembolism (VTE) in adults who have undergone elective total hip or knee replacement surgery, and the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation.

The EC approval is based on the results of two trials. One of these, AMPLIFY (Apixaban for the initial Management of PuLmonary embolIsm and deep vein thrombosis as First-line therapY) found apixaban to be non-inferior for the primary efficacy endpoint of recurrent VTE/VTE-related death, and superior in the primary safety endpoint of major bleeding, compared with enoxaparin/warfarin.

VTE accounts for approximately 60,000 deaths each year, costing the NHS between £340 and £640 million. Dr Alexander T. Cohen, a consultant vascular physician at Guy's and St Thomas' Hospitals, London, said: "In the AMPLIFY trial apixaban was shown to be effective in the treatment of venous thromboembolism, with the additional benefit of having a significantly lower risk of bleeds compared to current standard therapies, which is positive news for patients and healthcare professionals.

"This improved risk benefit profile will provide clinicians with confidence when considering prescribing this treatment and provide greater reassurance for patients. The fact it is an oral treatment that does not require INR monitoring has additional advantages in terms of convenience for patients with the additional potential to reduce hospitalisations."

NICE ISSUES GUIDELINES FOR TREATMENT OF CIC

NICE has published technology appraisal guidance recommending the use of

lubiprostone (Amitza) for the treatment of chronic idiopathic constipation (CIC) and associated symptoms in adults who have failed laxatives.

Lubiprostone is recommended for use if at least two laxatives from different classes, at the highest tolerated recommended doses for at least six months, have failed to provide adequate relief, and if invasive treatment for constipation is an option.

The NICE guidance states: *"If a patient has chronic idiopathic constipation and the doctor responsible for their care thinks that lubiprostone is the right treatment, it should be available for use, in line with NICE's recommendations.*"

Constipation is classified as chronic when specified symptoms (including straining, hard stools, and sensation of incomplete evacuation) persist for a period of three months with symptom onset at least six months prior to diagnosis. If this is not caused by other diseases or by the use of medications, the condition is labelled idiopathic.

CIC is a debilitating condition with an estimated 300,000 patients under the care of a GP in the UK and approximately 84,000 who have failed two previous laxatives. The approval of lubiprostone addresses an unmet clinical need, as there are currently few effective treatments available in the UK.

"Constipation places a significant burden on the UK healthcare system," said leading gastroenterologist Dr. Ramesh Arasaradnam. "For many of the patients who are refractory to standard laxatives, effectively treating with lubiprostone in primary care could negate the need to progress to a secondary or tertiary care referral." *www.nice.org.uk/guidance/TA318*

SCOTLAND EXPANDS TREATMENT OPTIONS FOR RA PATIENTS

People suffering with rheumatoid arthritis (RA) in Scotland will soon have the ability to select how they receive their medication, bringing improved quality of life to thousands of patients, the Scottish Medicines Consortium (SMC) has said.

This follows the announcement of the acceptance of a new subcutaneous formulation of tocilizumab (RoActemra) which has been accepted for use on the NHS in Scotland, meaning patients receiving treatment with tocilizumab can now be in control of where and when they have their treatment.

Tocilizumab is the first anti IL-6 receptor inhibitor to be available as both subcutaneous and intravenous (IV) formulation, for both combination therapy with methotrexate (MTX) and for use without MTX for those patients who cannot or will not continue with MTX.

Professor Ernest Choy, Professor of Rheumatology, Cardiff Institute of Infection & Immunity, said: "[This] positive decision brings a valuable option in the management of this chronic condition for people with RA in Scotland, of which patient choice is extremely significant. The convenience of self-administration in a subcutaneous formulation not only benefits patients, giving them more choice and better control of their disease, but also improves cost-effectiveness by freeing up capacity in Scottish hospitals."

NICE CALLS FOR MORE INFORMATION ON EMPAGLIFLOZIN

NICE has requested further evidence from Boehringer Ingelheim on its new anti-diabetic drug empagliflozin.

Empagliflozin (Jardiance) is the latest agent to emerge in the class of drugs known as sodium glucose co-transporter (SGLT-2: See *BJFM* July/August p.29)

Professor Carole Longson, Director of the NICE Centre for Health Technology Evaluation, said: "There is good evidence which shows that empagliflozin is clinically effective. But we need more information to demonstrate that it is cost effective when compared with other treatments the NHS already provides."

Consultees, including the manufacturer, healthcare professionals and members of the public are now able to comment on the preliminary recommendations via the NICE website (www.nice.org.uk/guidance/indevelopment/GID-TAG441).

BJFM Challenge answers (see pages 4-5)

1.	a, b, c, e, f	(See pages 19-23)
2.	b, c, e	(See pages 19-23)
3.	a, c, d	(See pages 19-23)
4.	f	(See pages 24-28)
5.	d	(See pages 24-28)
6.	c	(See pages 30-33
7.	a, b	(See pages 30-33)
8.	a, d, f	(See pages 30-33)
9.	ALL	(See pages 16-18)
10.	a, c, e	(See pages 16-18)
11.	d	(See pages 13-15)
12.	a	(See pages 13-15)
13.	c, d	(See pages 37-40)

REGULATORY NEWS

LINEZOLID LINKED WITH POSSIBLE RISK OF HYPOGLYCAEMIA

The US Food and Drugs Administration (FDA) has updated its warnings and precautions relating to linezolid after an inquiry into the effects of people with diabetes who received the drug from April 2000 to March 2012.

The study came about after reviews of a report into symptomatic hypoglycemia related to linezolid in a 64-year-old man with diabetes. A search of the FDA Adverse Event Reporting System identified 41 reports of hypoglycemia among people who received linezolid. Twenty-six cases were excluded as they demonstrated no temporal association between the hypoglycemia and linezolid exposure.

Of the remaining 15 studies, the link was "highly probable" in seven cases, "probable" in four cases and "possible" in four cases. Eight patients received oral linezolid and six received IV linezolid. Information was not available for one patient. The median time to hypoglycemia after starting linezolid was seven days. Hypoglycemia resolved in ten patients after discontinuing linezolid. The outcomes for the other five are unknown.

In total, 12 of the patients (80 per cent) had diabetes, nine were taking oral hypoglycemic drugs and two were taking insulin. Treatment information was not available for one patient. In eight of the patients, adjustment to the diabetes drug regimen did not resolve the hypoglycemia, but did resolve after linezolid was discontinued. There was no outcome data for the other four patients.

The researchers said: "Our review suggests that there is a potential relationship between linezolid use and hypoglycaemia. Health care providers should be aware of this possibility when prescribing linezolid, especially in diabetic patients."