Vildagliptin: a new treatment for type 2 diabetes

Choice of treatment for type 2 diabetes increased still further in April with the UK launch of vildagliptin. In studies, when added to metformin monotherapy, vildagliptin 100 mg daily resulted in a significant additional mean reduction in glycosylated haemoglobin of 1.1% compared to placebo ($P<0.001$) (Bosi et al, 2007) and was as effective as pioglitazone (Bolli et al, 2008).

These benefits were associated with improvement in measures of beta-cell function, without weight gain or increased incidence of hypoglycaemia. Vildagliptin is indicated in combination with metformin in patients who cannot achieve sufficient glycaemic control despite the maximum tolerated dose of this first-line oral treatment for type 2 diabetes. The drug is also licensed in combination with a sulphonylurea or thiazolidinedione.

Dr Marc Evans, Consultant Diabetologist, Cardiff, envisages that vildagliptin's initial role will be for patients needing add-on therapy. 'These include the elderly, in whom hypoglycaemia is often a concern, and obese patients on metformin monotherapy, in whom other add-on therapies, in particular the thiazolidinediones and sulphonylureas, are associated with weight gain,' he explains.

Vildagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor, and reduces blood glucose levels by increasing levels of active incretin hormones, so enhancing insulin and reducing glucagon secretions. The second DPP-4 inhibitor to be launched in the UK, vildagliptin is also available in a combination tablet with metformin. Sitagliptin, the first DPP-4 inhibitor to market, is also likely to become available in a metformin combination following a recent positive opinion from the Committee for Medicinal Products for Human Use.

A Cochrane review (Richter et al, 2008) has recommended that, while DPP-4 inhibitors have some theoretical advantages over existing oral therapies, the lack of long-term outcome data means that they should be restricted to individual patients.

Dr Evans accepts the validity of these concerns, but considers it important for specialists to use new therapies in order to gain knowledge of their potential to improve outcomes in diabetes. 'As long as new products such as vildagliptin are used in accordance with their licence – which takes into consideration efficacy as well as safety – there is no real indication for us not to use them,' he concludes.

Sue Lyon

Bolli G, Dotta F, Rochotte E, Cohen SE (2008) Efficacy and tolerability of vildagliptin vs. pioglitazone when added to metformin: a 24-week, randomized, double-blind study. *Diabetes Obes Metab* **10**: 82–90

Bosi E, Camisasca RP, Collober C, Rochotte E, Garber AJ (2007) Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. *Diabetes Care* **30**: 890–5

Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch CL (2008) Dipeptidyl peptidase-4 (DPP-4) inhibitors for type-2 diabetes mellitus. *Cochrane Database Syst Rev* Issue 2: CD006739

PRoFESS study adds to stroke evidence base

Results from the largest-ever recurrent stroke prevention trial, PRoFESS (Prevention Regimen For Effectively avoiding Second Strokes), were presented at the XVII European Stroke Conference in Nice, France.

In this double-blind, placebo-controlled clinical trial, 20 332 patients in 35 countries were randomized to receive extended-release dipyridamole (200 mg) plus aspirin (25 mg) twice daily or clopidogrel (75 mg) once daily, and simultaneously randomized to telmisartan 80 mg or placebo.

'We have gained valuable information on different therapeutic options, enabling doctors to individualize their patient's treatment to prevent post-stroke vascular events,' commented Professor Ralph L Sacco, University of Miami, Florida, USA, one of the principal investigators.

More deaths and strokes with beta-blockers after non-cardiac surgery

Patients given beta-blockers after non-cardiac surgery have a higher risk of death or stroke than if they had been given a placebo, according to new data from the PeriOperative ISchemic Evaluation (POISE) trial (Devereaux et al, 2008).

The study compared metoprolol to placebo in 8351 patients undergoing non-cardiac surgery in 190 hospitals across 23 countries. Treatment was started 2–4 hours before surgery and continued for 30 days.

Patients given metoprolol were 16% less likely to reach the primary end point: a composite of cardiovascular death, non-fatal myocardial infarction or non-fatal cardiac arrest ($P=0.04$). The specific risk reduction for a myocardial infarction was 27% in favour of the beta-blocker ($P=0.002$), but there was a 33% greater mortality risk associated with metoprolol ($P=0.03$), and the risk of a stroke more than doubled ($P=0.005$).

The authors commented: 'These data suggest that for every 1000 patients undergoing non-cardiac surgery, extended-release metoprolol would prevent 15 patients from having a myocardial infarction, three from undergoing cardiac revascularisation, and seven from developing new and significant atrial fibrillation. The results also suggest that the beta-blocker would result in an excess of eight deaths, five patients having a stroke, 53 experiencing clinically significant hypotension, and 42 experiencing clinically significant bradycardia for every 1000 patients treated.'

They concluded: 'Our results highlight the risk in assuming perioperative beta-blockers have benefit without substantial harm.'

Commenting on the data, Dr Lee Fleisher (University of Pennsylvania School of Medicine, Philadelphia, USA) said that the study clearly shows that acute administration of higher dose beta-blocker therapy perioperatively is associated with greater risk than benefit.

However, he pointed out that protocols using low dose beta-blockers have a beneficial effect on postoperative outcome without an increased incidence of stroke. Dr Fleisher recommended careful use of low-dose beta-blockers perioperatively, supervised by clinicians who are experienced in haemodynamic care during surgery.

Stephen Pinn

Devereaux PJ and members of the POISE study group (2008) Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* published online May 13 2008

Meningitis B vaccine could give protective response

UK infants played a key role in testing a vaccine which has the potential to be the first to provide broad coverage against meningitis B, according to new phase II data presented at the European Society for Paediatric Infectious Diseases meeting, held in Graz, Austria. Eighty-five strains of meningitis B were examined in developing the vaccine.

Dr Ray Borrow (Head of Vaccine Evaluation, Manchester Royal Infirmary) commented: 'The prospect of one vaccine that protects infants worldwide against meningococcal serogroup B would be a key achievement in global disease prevention.'

The study involved 150 UK infants, immunized at 2, 4, 6 and 12 months. The results showed that 1 month after the third dose, the percentage of subjects achieving a protective immune response against the three strains was 89%, 96% and 85%. The fourth dose resulted in 100%, 98% and 93% of infants achieving a protective immune response.

Dr Andrew Pollard (Head of the University of Oxford Vaccine Group) said these preliminary results are encouraging. 'The problem with producing a vaccine against meningitis B is that there are so many different strains. These data show that the vaccine induces an immune response against strains containing the vaccine components. The next step is to find how broad these responses are against other strains that cause disease.'

Dr Pollard added: 'There is still a long way to go, but a vaccine that gives broad protection against meningitis B would be hugely significant. Meningitis B causes the most cases and the most deaths from meningitis currently in the UK – and around the world its effects are devastating.'

In England and Wales for the first 50 weeks of 2007 (January to mid-December) the Health Protection Agency reported a total of 1029 cases of Group B invasive meningococcal infections.

The vaccine entered phase III clinical trials in the first quarter of 2008. Scientists pioneered an innovative approach called 'reverse vaccinology' to develop the MenB vaccine. By first decoding the entire genetic make up of a pathogenic meningococcal serogroup B strain, 600 novel proteins were discovered.

Reproduced through genetic engineering for further investigation, the vaccine contains multiple antigens that showed the greatest ability to stimulate the immune system to kill bacteria from a panel of 85 strains of meningitis B representative of global and temporal diversity.

Stephen Pinn

Attention-deficit hyperactivity disorder in adults

Attention-deficit hyperactivity disorder (ADHD) is characterized by inattention, hyperactivity and impulsiveness. In adults, ADHD is a seriously impairing disorder, with an average prevalence of around 3.4%.

ADHD is widely considered to be a disorder of childhood, but full-blown ADHD persists into adulthood in at least 15% of sufferers, with at least 65% of affected children retaining some symptoms of ADHD into adulthood.

The LAMDA (European Long-Acting Methylphenidate in Adult ADHD) trial was designed to evaluate the efficacy and safety of three fixed dosages of prolonged-release methylphenidate.

The primary measure of efficacy in the LAMDA study was change in total score on the Conners' Adult ADHD Rating Scale (CAARS), assessed at the study's end point and compared with baseline scores. A number of secondary and safety outcomes were also assessed.

A total of 402 adults with ADHD were randomized to receive one of three oral doses of prolonged-release OROS methylphenidate – 18 mg, 36 mg or 72 mg/day – or placebo daily for 5 weeks; of these, 365 (91%) completed the 5-week double-blind study.

Treatment with all three doses of OROS methylphenidate was associated with a significantly greater improvement in CAARS total ADHD symptom scores compared to placebo.

The mean change in CAARS total ADHD symptom scores from baseline to end point was –10.6 in the OROS methylphenidate 18 mg/day group (P=0.015), –11.5 in the 36 mg/day group (P=0.013) and –13.7 in the 72 mg/day group (P<0.001). All reductions were statistically significant when compared to the –7.6 change observed in the placebo arm.

Overall, the safety profile of OROS methylphenidate in the LAMDA study was consistent with its established safety profile in paediatrics.

Medori R, Ramos-Quiroga JA, Casas M et al (2008) A randomized, placebo-controlled trial of 3 fixed dosages of prolonged-release OROS methylphenidate in adults with attention-deficit hyperactivity disorder. *Biol Psychiatry* **63**(10): 981–9

Standard of osteoporosis care differs globally

In a first-of-its-kind study in osteoporosis, one in four women surveyed from Europe, North America and Australia reported having one or more bone fractures since the age of 45 years.

Among women considered to be at high risk for a fracture, only 26% reported use of bone-saving drugs, with use reported significantly less frequently in Europe than in North America and Australia.

Call for national sickle cell database

Not enough is known about the severe complications of sickle cell disease that can lead to death, the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) said as it launched the findings of the first national survey of sickle cell disease and thalassaemia deaths.

Launch of biosimilar erythropoietin

Hospira has launched Retacrit (epoetin zeta), its biosimilar erythropoietin, in the UK for the treatment of anaemia associated with chronic renal failure and chemotherapy.

Retacrit has shown comparable efficacy and safety to epoetin alfa.

BRITISH SOCIETY OF RHEUMATOLOGY ANNUAL MEETING
LIVERPOOL, 25–28 APRIL

Rituximab clinically effective in patients ineligible for trials

A study of 104 patients showed that rituximab was effective in patients who would be ineligible for clinical trials and over a long period.

Presenting the data at the British Society of Rheumatology's annual meeting in Liverpool, Dr Shouvik Dass, specialist registrar from the University of Leeds, said: 'Our 5 years of real-life clinical experience also showed that multiple cycles of rituximab appeared to be safe and maintained efficacy.'

Of the 104 patients, 48 received at least two cycles, 26 received at least three cycles, nine received at least four cycles and three patients received five cycles of rituximab. Most (86%) had a moderate or good EULAR (European League Against Rheumatism) response at one timepoint after each cycle.

Median DAS28 (Disease Activity Score) scores improved with repeated therapy from 7.2 at baseline to 3.4 after three cycles. Four patients were switched to alternative therapy because of a lack of response.

Some patients (n=24) had co-morbidities or extra-articular manifestations of rheumatoid arthritis that would have excluded them from drug company-sponsored trials. Dr Dass said: 'No difference in safety or efficacy was noted in these patients.'

Professor Paul Emery, Arthritis Research Campaign Professor of Rheumatology at the University of Leeds, also presented a safety analysis of rituximab patients from clinical trials.

He said: 'This showed a slight upward trend in the rate of infections after four courses of treatment but the rate of serious infections remained stable with repeated treatment.'

Rhonda Siddall

IL-6 inhibitor tocilizumab may have a joint protective effect

Emerging data that the interleukin-6 (IL-6) inhibitor tocilizumab provides radiographic benefit to patients is further evidence that this new agent would be an important addition to treatments for rheumatoid arthritis.

That was the opinion of Professor John Isaacs, Professor of Clinical Rheumatology, Newcastle University, during a session on IL-6 organized by the British Society of Rheumatology at their annual meeting.

He said: 'The recently published OPTION study and other data shows that tocilizumab reduces the signs and symptoms of rheumatoid arthritis and preliminary data from the SAMURAI study suggests a joint protective effect. This is an agent that potentially ticks all the boxes.'

Commenting on safety issues, Professor Isaacs explained that clinical trial data had showed elevations of liver enzymes (mainly alanine transaminase) with tocilizumab treatment. 'But these elevations were mild, transient and reversible suggesting that this issue is not going to be a big problem in practice,' he added.

Regarding raised lipid levels observed in clinical trials with tocilizumab treatment, Professor Isaacs said: 'It looks as if this is something we are going to have to live with. There were no cardiovascular signals and the significance of the lipid effects awaits clarification from ongoing studies.'

Rhonda Siddall

Disappointment at NICE denial of alternatives

The new President of the British Society of Rheumatology has expressed disappointment at the preliminary National Institute for Health and Clinical Excellence (NICE) decision to deny access to an alternative anti-TNF (tumour necrosis factor) therapy if a patients fails on an initial anti-TNF treatment.

Dr Deborah Bax, President, British Society of Rheumatology

Dr Deborah Bax, consultant rheumatologist at Sheffield's Royal Hallamshire Hospital, took up the reins from Dr Andrew Bamji and became the society's new President at the British Society of Rheumatology annual meeting.

Five days later, she was responding to a NICE appraisal consultation document *Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis after failure of a TNF-alpha inhibitor* which has recommended, preliminarily, that patients are not allowed access to an alternative anti-TNF if they have experienced an inadequate response with a first anti-TNF.

Dr Bax told the *British Journal of Hospital Medicine*: 'We are very disappointed that NICE has taken this decision, particularly as there is a large and growing database indicating successful treatment with a second anti-TNF.

'We strongly believe the effect of treatment with anti-TNF for many patients with rheumatoid arthritis is substantial. We will continue to press NICE to allow this treatment to be used more widely in the disease.'

She said the British Society of Rheumatology planned to meet NICE officials to discuss the recommendations and other issues affecting the rheumatology profession. The final publication from NICE is due in September 2008.

Rhonda Siddall

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER
MILAN, 23–27 APRIL

Study identifies when to re-treat hepatitis C and in which patients

Difficult-to-treat patients with hepatitis C (HCV) who fail to achieve undetectable levels of virus after 12 weeks of treatment with pegylated interferon alfa-2b plus ribavirin but who show a major reduction in HCV RNA have the best chance of achieving undetectable viral RNA levels with a second course of this treatment, according to a study that helps to identify which patients to re-treat.

The international REPEAT study randomized 942 patients with detectable levels of HCV RNA after at least 12 weeks of therapy with peginterferon alfa-2b (>1.0 μg/kg week) plus ribavirin (>800 mg/day) to a further course of the same combination drug, given at a range of doses, for a further 48 or 72 weeks.

Results showed that 55% of patients who achieved at least a 2 $\log_{10}$ drop in HCV RNA after 12 weeks of a first course of treatment went on to achieve undetectable viral levels after 12 weeks of re-treatment.

Even patients failing to achieve a 2 $\log_{10}$ drop in HCV RNA during their first course of treatment had a significant chance of clearing virus on re-treatment – with 28% of patients in this category achieving undetectable levels of HCV RNA.

'These data show that a good viral response to previous treatment predicts response to retreatment in difficult-to-treat patients with hepatitis C,' commented Dr Donald Jensen, Professor of Medicine and Director of the Centre for Liver Disease at University of Chicago Hospitals, USA, and one of the study authors. 'Viral response at week 12 is a powerful predictor of final treatment outcomes,' he added.

Further data reported at the meeting showed a greater chance of achieving cure in patients with chronic hepatitis C with treatment with peginterferon alfa-2a plus ribavirin than with peginterferon alfa-2b. An investigator-initiated, head-to-head study showed that more than two-thirds (68.7%) of patients treated with peginterferon alfa-2a achieved a cure (sustained virological response, remaining virus free 6 months after completing treatment) compared to just over half (54.4%) of patients on peginterferon alfa-2b (P=0.008).

There was an even greater difference in the most difficult-to-treat patients, with HCV genotypes 1 and 4, with a cure rate of 54.8% with peginterferon alfa-2a compared to only 39.8% with peginterferon alfa-2b (P=0.04).

Another study, IDEAL, demonstrated similar rates of sustained virological response with peginterferon alfa-2a and peginterferon alfa-2b, both with ribavirin, in more than 3000 previously untreated patients with HCV genotype 1. End of treatment response was higher with peginterferon alfa-2a (64% *vs* 49% peginterferon alfa-2b at a dose of 1.0 μg/kg/week).

Susan Mayor

Chronic hepatitis C: 'interferon-like' therapy increases response rates

Compared to standard-of-care, the interferon-like, intracellular signalling enhancer nitazoxanide increases sustained virological response rates in both treatment-naïve and difficult-to-treat, interferon-experienced patients with chronic hepatitis C, according to new data.

In the 48-week STEALTH-C study, 96 treatment-naïve patients with chronic hepatitis C were randomized to one of three groups. The first group (n=40) received 48 weeks of standard-of-care therapy: peginterferon alfa-2a (180 μg/week) plus ribavirin (1000–1200 mg/day).

The remaining patients received either the dual-therapy regimen of nitazoxanide (500 mg twice daily) plus peginterferon alfa-2a (n=28), or triple therapy combining all three medications (n=28).

Twenty-four patients who had previously not responded to interferon therapy were also recruited to the trial. These patients were randomized to receive triple therapy (n=12), or the dual-therapy regimen of nitazoxanide plus peginterferon alfa-2a (n=12). All nitazoxanide-containing cohorts received nitazoxanide monotherapy for 12 weeks, followed by 36 weeks of their respective combination therapies.

Sustained virological response rates were measured 24 weeks after treatment discontinuation (SVR24s). In the treatment-naïve cohort, triple therapy evoked a statistically significant increase in SVR24 *vs* standard-of-care (79% *vs* 50%; P=0.023). In the difficult-to-treat, interferon-experienced cohort, SVR24 was achieved in 25% of triple-therapy-administered patients *vs* just 8% of patients receiving dual therapy.

Dr Emmet Keefe, Chief Medical Officer, Romark Institute for Medical Research, former Professor of Medicine, Chief of Hepatology, and Co-Director of the Liver Transplant Program, Stanford University Medical Center, and one of the principal study investigators said: 'In patients with chronic hepatitis C, the addition of nitazoxanide to standard-of-care therapy provides an opportunity to increase response rates by as much as 30% without compromising safety.

'One of the major concerns with new anti-hepatitis C virus treatments such as protease or polymerase inhibitors is that they could induce viral mutations that would limit future

Dr Emmet Keefe, Romark Institute for Medical Research

treatment. Nitazoxanide does not appear to have this effect, because it enhances the natural anti-viral mechanisms of the host itself, and has no resistance-inducing, direct effect on the hepatitis C virus.'

Further phase III studies of nitazoxanide are now underway in Europe and the US.

Steve Dawber