J R Coll Physicians Edinb 2009; 39:227–30

New treatments for type 2 diabetes

[1]K Kos, [2]JPH Wilding
[1]Clinical Lecturer; [2]Professor of Medicine and Honorary Consultant Physician, Diabetes and Endocrinology Clinical Research Unit, University Hospital Aintree, Liverpool, UK

ABSTRACT Controlling blood glucose in type 2 diabetes remains challenging. All existing drugs have significant limitations and side effects, with some causing weight gain and thereby exacerbating the condition. This short review looks at new groups of drugs on the market and under development, and discusses their potential in the management of type 2 diabetes.

KEYWORDS DPP-IV inhibitors, hypoglycaemia, incretin mimetics, obesity, thiazolidinediones, type 2 diabetes, weight loss drugs

DECLARATION OF INTERESTS Prof. Wilding has received grants, consultancy and lecture fees from numerous pharmaceutical companies, including AstraZeneca, Lilly and Novo Nordisk. Both authors are investigators in trials of DPP-IV inhibitors and SGLT2 inhibitors, and Prof. Wilding is also involved in trials of GLP-1 analogues and glucokinase activators.

Published online ***September 2008***

Correspondence to ***K Kos, University of Liverpool Diabetes & Endocrinology Clinical Research Unit, Clinical Sciences Centre, Longmoor Lane, Liverpool L9 7AL, UK***

tel. ***+44 (0)151 5295874***
e-mail ***K.Kos@liverpool.ac.uk***

CHALLENGES IN ACHIEVING GOOD GLYCAEMIC CONTROL IN TYPE 2 DIABETES

Epidemiological studies clearly link glycaemic control to diabetes complications. However, while the beneficial effects of glucose-lowering interventions are established for microvascular disease,[1] the data for macrovascular disease are less convincing, with recent trials suggesting that very intensive glucose-lowering may even result in an increase in cardiovascular events if implemented late in the course of the disease.[2,3] However, the long-term follow-up of UK Prospective Diabetes Study Group patients suggests persistent effects of good control if implemented early.[4] The main limitations and unwelcome effects of most commonly used drug therapies are hypoglycaemia, fluid retention and weight gain, all of which may theoretically increase the risk of cardiac events (see Table 1).

Hypoglycaemia

Hypoglycaemia is becoming a greater problem in the treatment of type 2 diabetes mellitus (T2DM) as more patients are treated to lower haemoglobin A_{1c} (HbA_{1c}) targets. It is particularly an issue for patients on insulin treatment, but sulphonylureas can also lead to prolonged hypoglycaemia, particularly in the elderly, and clinicians and patients should be aware of this risk.

Obesity

Obesity is strongly related to the development and pathogenesis of T2DM; diabetes outcomes are poorer in obese patients and weight management should be integral to diabetes treatment. Regardless of whether this is achieved through lifestyle changes, drug treatment or bariatric surgery, weight loss significantly improves diabetes control, and in the case of bariatric surgery leads to diabetes remission in up to 70% of patients. Weight gain is a problem with all older oral agents except metformin (considered first-line therapy), and tends to be exacerbated once patients are started on insulin. This insulin-induced weight increment may result in further hyperglycaemia, and patients may find themselves in a vicious circle with escalating insulin dose adjustments in response to the resulting weight gain.

Continuation of metformin can mitigate the increase in weight[5] but is not tolerated by all patients. Thiazolidinediones, which activate peroxisome proliferator-activated receptor gamma (PPARγ)-nuclear receptors in muscle, liver and adipose tissue and indirectly sensitise tissues to insulin via reductions in free fatty acids and possibly adipokines, can also reduce insulin demand when used in combination with insulin therapy but are likely to further exacerbate weight gain. The thiazolidinedione pioglitazone (also known under the trademark Actos in the United States) is licensed for use alongside insulin to substitute metformin should the latter not be tolerated.

More recently there have been concerns over the thiazolidinedione rosiglitazone as a result of a metanalysis suggesting increased cardiovascular disease risk, although this has been disputed. Nevertheless, thiazolidinediones are associated with fluid retention, particularly when used with insulin, and are contra-indicated in patients with heart failure. There is, however, some evidence from the ProActive study that pioglitazone may decrease the risk of cardiovascular disease.[6]

NEWLY AVAILABLE THERAPIES

New therapies are emerging, some of which are addressing the unwanted side effects and limitations of older therapies.

TABLE 1 Common shortfalls of traditional diabetes therapies

Type	Examples	Hypoglycaemia	Fluid retention	Weight	Typical problems
Biguanide	Metformin Metformin SR (slow release)	No	No	Weight neutral or modest weight loss	Lactic acidosis; thus contraindicated in renal failure. Do not use in chronic kidney disease (CKD) 4, caution in CKD 3, liver and heart failure; 10% of patients intolerant to metformin due to gastrointestinal side effects
Sulphonylureas + other insulin secretagogues	Gliclazide Glipizide Glibenclamide Repaglinide	Particularly in the elderly	No	Weight gain	No β-cell preservation
Thiazolidenediones/ Glitazones	Rosiglitazone Pioglitazone	Uncommon	Frequent, especially in combination with insulin	Weight gain	Contraindicated in heart failure; avoid rosiglitazone in ischaemic heart disease, increased fracture risk in women
Insulin	Soluble, basal and biphasic insulin preparations	Frequent	Occasional	Weight gain	Other drawbacks: injection. First inhaled insulin withdrawn for economic reasons; also concerns re lung function and cancer risk

Incretin-based therapies

Incretins are intestinal hormones that increase insulin release from the pancreas and inhibit glucagon release. They are released after the contact of food with the gastrointestinal tract. The main incretin that has found therapeutic use is glucagon-like peptide-1 (GLP-1). Glucose-dependent insulinotropic peptide (GIP) has not yet been explored pharmacologically. GLP-1 improves beta-cell responsiveness to glucose and, unlike GIP, inhibits gastric emptying and has a central nervous system effect, resulting in reduced food intake and a decrease in body weight. Endogenous incretin peptides are short-lived due to their degradation by the enzyme dipeptidyl-peptidase-IV (DPP-IV). The recruitment of the incretin-DPP-IV pathways into diabetes management has led to the development of DPP-IV inhibitors, which protect the natural incretin hormones from deactivation, and GLP-1 analogues resistant to the actions of DPP-IV.

Incretin mimetics

Exenatide (Byetta®) is the first GLP-1 analogue available in the UK, and is licensed for use in addition to oral antihyperglycaemic agents. It is the synthetic version of exendin-4, a specific agonist of the GLP-1 receptor originally isolated from the salivary secretions of the lizard *Heloderma suspectum*, otherwise known as the Gila monster. Its duration of action is longer compared with GLP-1, largely due to its resistance to degradation by DPP-IV. Exenatide appears to be an effective glucose-lowering agent, with an improvement of about 0.9% in HbA_{1c} when used at its maximum dose of 10 μg twice daily, and results in an average weight loss of 1.4 kg.[7]

The improvement in glycaemic control is due to enhanced glucose-dependent insulin secretion, the suppression of postprandial glucagon secretion and slower gastric emptying. In addition, GLP-1 analogues reduce food intake, with subsequent weight reduction and therefore higher insulin sensitivity. Because their effect on insulin secretion is dependent on the prevailing glucose concentration, incretin analogues have a low risk of hypoglycaemia when used alone or in combination with metformin or thiazolidinediones but can increase the risk of hypoglycaemia when used with sulphonylureas.

Nausea is the most commonly reported side effect, affecting up to 44% of patients in clinical trials. This, however, tends to reduce with time, and only 4% of patients in clinical trials withdrew from treatment as a result. There are case reports of acute pancreatitis in association with exenatide use, but it is currently unclear whether this is a true side effect or a chance association. Meanwhile, it seems wise to avoid the use of this drug in patients with a history of pancreatitis or those at high risk (e.g. with severe hypertriglyceridaemia).

Exenatide has to be given by twice-daily subcutaneous injections.[8] However, in clinical practice it is most commonly used when dual therapy with oral agents is no longer able to provide adequate glycaemic control and the usual alternative is insulin or the addition of a thiazolidinedione. Head-to-head trials comparing the addition of exenatide or insulin to oral agents have been conducted, and suggest that exenatide will give equivalent glycaemic control. In these trials the difference in weight was most apparent: it was as much as 5.4 kg in some studies, with insulin-treated patients gaining and exenatide-treated patients losing weight. Whether this can match more modern 'treat-to-target' insulin titration or will improve long-term outcomes is presently unknown.

J R Coll Physicians Edinb 2009; 39:227–30

A once-daily analogue, liraglutide (manufactured by Novo Nordisk), and a once-weekly preparation of exenatide are currently undergoing phase three studies.

DPP-IV inhibitors

Sitagliptin (Januvia®) and vildagliptin (Galvus®) are oral DPP-IV inhibitors that decrease HBA_{1c} by about 0.7–1% when used as monotherapy or when added to other therapies such as sulphonylureas, metformin or glitazones. Like incretin analogues, they only carry an increased risk of hypoglycaemia when used in combination with other insulin secretagogues. DPP-IV inhibitors are weight-neutral in comparison to most other therapies but more expensive than metformin and sulphonylureas. Skin rashes, which were observed in animal studies with some but not all of the drugs in this class, remain a concern, but so far they have not been observed in humans.

Although their place in the therapeutic algorithm remains uncertain, DPP-IV inhibitors may have a particular place in those patients who need additional therapy to metformin, where hypoglycaemia might be a particular problem. This could include vocational drivers and other occupations where hypoglycaemia could present a significant risk and may also be relevant for some elderly patients. There is also potential for patients where weight gain with alternative drugs might be considered a particular problem. Numerous other DPP-IV inhibitors are in development, including saxagliptin, anagliptin and denagliptin, and some claim higher potency and/or longer duration of action.

Weight loss agents

While genetic factors have a significant role in the development of T2DM, the condition is also strongly related to obesity. However, despite the facts that trials of weight loss agents (which lasted up to one year and included pharmacological agents to aid weight management in T2DM) show effectiveness in glucose control and reducing associated cardiovascular risk factors,[9] and all are considered appropriate for use by the National Institute for Health and Clinical Excellence for the treatment of obesity, weight loss agents are not generally considered mainstream therapy for diabetes. Data from long-term clinical trials in T2DM are needed to determine whether the beneficial effects are sustained beyond one year, and whether these effects reduce the long-term risk of complications.

Orlistat (Xenical®) is an intestinal lipase inhibitor that promotes weight loss due to decreased absorption of fat. In trials of patients with diabetes, placebo-subtracted weight loss was 2.7 kg with a reduction of HbA_{1c} by 0.36% over one year. Side effects range from flatulence to faecal incontinence, and this, combined with modest efficacy, has limited its widespread use in the management of diabetes.[10]

Sibutramine (Reductil®) is a weight management agent with central action. It is contraindicated in patients with uncontrolled blood pressure, in cardiovascular disease and in patients taking antidepressants. Clinical trials in patients with diabetes show 4.5 kg weight loss compared to placebo over one year and a mean fall in HbA_{1c} of 0.4%, but greater improvements are seen with weight-loss responders (HbA_{1c} drop of 0.7%).

Rimonabant (Accomplia®) is a cannabinoid receptor 1 antagonist with central appetite-reducing action. Besides its weight-reducing effect of 4.2 kg in a year, rimonabant leads to glucose lowering, which exceeds the amount expected by the weight change per se (HbA_{1c} of 0.7%).[11] However, reports of an increased incidence of depression with rimonabant led to its withdrawal from the market worldwide in October 2008.

The weight loss achieved by these agents is usually not sustained after discontinuation, so these drugs need to be considered as long-term treatments that help initial weight loss, and are then continued for weight maintenance. Data in non-diabetic patients with orlistat show that weight loss can be largely maintained for up to four years, but there are so far no published long-term data for sibutramine or rimonabant, although a five-year study with sibutramine will report later this year. Eventually, these studies should provide data with regard to long-term safety and efficacy in patients with diabetes.

NEW CLASSES OF DRUGS IN DEVELOPMENT

Glucokinase activators

Glucokinase is the main 'glucose sensor' in the pancreas and liver. Defects in the glucokinase gene cause one form of maturity onset diabetes of the young, MODY 2.

Glucokinase activators increase the sensitivity of glucokinase to high levels of glucose, leading to increased insulin secretion, increased liver glycogen synthesis and a decrease in liver glucose output. Potential concerns include hypoglycaemia due to increased insulin secretion. However, 'liver-selective' glucokinase activators with lower potential for hypoglycaemia have also been developed and tested in preclinical models.

SGLT2 inhibitors

Sergliflozin and dapagliflozin, inhibitors of the sodium-dependent glucose transporter 2 (SGLT 2), are experimental drugs that block renal glucose reabsorption, leading to glucosuria, by which they may also cause a urine energy loss of up to 300 kcal per day. Preliminary data from a phase two trial with dapagliflozin suggest that this drug can lower HbA_{1c} by up to 0.9% over three months, with weight loss of 3.4 kg. Potential side effects include polyuria and an increased risk of urinary and genital fungal infections, but these did not appear to be a major problem in the short-term studies reported so far.

Glucagon-receptor antagonists

The abnormal increase of liver-derived gluconeogenesis in T2DM is targeted by glucagon-receptor antagonists, which are currently being tested in humans.

Sirtuins

Sirtuin-deacetylases have been discovered with the study of calorie restriction and resulting prolonged lifespan. Sirtuin 1-activators do not only increase mitochondrial activity but also improve insulin secretion and glycaemia. Human studies in diabetic patients are in progress.

Other agents are expected to emerge from targeting gut hormones and appetite regulators, e.g. PYY3-36, ghrelin-antagonists, melanocortin-4 (MC4) antagonists and microsomal triglyceride transfer protein (MTP) antagonists (which limit gut absorption of fat), and various combinations of the above.

CONCLUSIONS

Control of blood glucose in T2DM is important to improve outcomes, but achieving long-term control is challenging and all existing agents have limitations – particularly as most of the older agents and insulin cause an increase of already surplus fat mass. Newer agents, especially those that target body weight, have significant potential, but their place in the therapeutic algorithm is not yet determined.

While future advances will increase the number of drugs available, it is important to remember that cardiovascular risk prevention by the effective management of hypertension and hyperlipidaemia in T2DM may be as important as glucose control, which has been shown to aid the prevention and delay the progression of macro- and microvascular complications.[12] Diet and exercise should also be maintained and do not lose their effectiveness in T2DM. The recent experience with rosiglitazone should highlight the need for longer-term continued evaluation in clinical practice and the study of hard endpoints for both current and future treatments.

KEY POINTS

- Traditional therapies for type 2 diabetes have significant limitations, including side effects and lack of hypoglycaemic effect.
- Incretin-based therapies, including those derived from GLP-1 (exenatide) and DPP-IV inhibitors (sitagliptin/vildagliptin), are being evaluated.
- All agents or treatments that reduce patients' weight (orlistat/sibutramine/rimonabant/bariatric surgery) also improve glycaemic control.
- Other classes of drugs, including glucokinase activators, SGLT2 inhibitors, glucagon receptor antagonists and sirtuins, are currently being assessed.
- Additional treatment approaches in type 2 diabetes to be considered include the management of lipids and blood pressure as well as glycaemia.

REFERENCES

1 UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; 352:854–65.
2 ACCORD Study Group. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. *Am J Cardiol* 2007; 99:21i–33i.
3 ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; 358:2560–72.
4 Holman RR, Paul SK, Bethel MA et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; 359:1577–89.
5 Nathan DM, Buse JB, Davidson MB et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2006 29:1963–72.
6 Dormandy JA, Charbonnel B, Eckland DJA et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; 366:1279–89.
7 Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *JAMA* 2007; 298:194–206.
8 DeFronzo RA, Ratner RE, Han J et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005; 28:1092–100.
9 Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the Look AHEAD trial. *Diabetes Care* 2007; 30:1374–83.
10 Rössner S, Sjöström L, Noack R et al. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. *Obes Res* 2000; 8:49–61.
11 Scheen AJ, Finer N, Hollander P et al. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. *Lancet* 2006; 368:1660–72.
12 Gaede P, Lund-Andersen H, Parving HH et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008; 358:580–91.

USEFUL LINKS

- American Diabetes Association (ADA): www.diabetes.org
- Association for the Study of Obesity (ASO): www.aso.org.uk
- Diabetes Research and Wellness Foundation: www.drwf.org.uk
- Diabetes UK: www.diabetes.org.uk
- International Diabetes Federation (IDF): www.idf.org

Originally published on the Behind the Medical Headlines website, an international online resource from the Royal College of Physicians of Edinburgh and the Royal College of Physicians and Surgeons of Glasgow: ***http://www.behindthemedicalheadlines.com***