Netherlands
The Journal of Medicine

EDITORIAL

Do we need new drugs for the treatment of type 2 diabetes mellitus?

G. Vervoort*, C.J. Tack

Department of General Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands, *corresponding author: tel.: +31 (0)24-361 47 61, fax: +31 (0)24-354 00 22, e-mail: G.Vervoort@aig.umcn.nl

At this moment, approximately ten different classes of drugs are or soon will become available for the treatment of type 2 diabetes mellitus (*table 1*). Of the glucose-lowering agents, pramlintide has not been approved by the European Medicines Agency (EMEA) and two, a GLP (glucagon-like peptide)-1 and a DPP (dipeptidyl peptidase)-IV-inhibitor, have recently been approved but have not yet become available on the European market. The recent increase in available blood glucose-lowering drugs is remarkable, because after the introduction of insulin (at the beginning of the 20th century), the sulphonylureas and metformin (mid-1940s and 1950s) no innovative treatment modalities had been introduced until less than a decade ago.

The development of new classes of glucose-lowering medications has expanded the treatment options for type 2 diabetes, but has also introduced more uncertainty regarding which treatment option is the most appropriate. Recently, management guidelines have been published that provide a directive for the most appropriate intervention for treating patients with type 2 diabetes.[1,2] Nevertheless, except for the initial therapy, these reports acknowledge that in fact no definitive guidelines can be provided regarding subsequent treatment choices.

The primary goal is achieving glucose levels as close to normal as possible without imposing a high risk of (severe) hypoglycaemic attacks. An HbA1c ≥7% should serve as a call to act by initiating or changing therapy to ultimately reduce microvascular and most likely macrovascular complications in type 2 diabetes.[3]

Since durability and long-term safety have to be established in almost all new drugs, metformin is universally considered to be the drug of choice as it is cheap, safe and effective. Moreover, metformin is associated with either weight stability or weight loss.[2,4]

As type 2 diabetes is characterised by a progressive decline in β-cell function, treatment needs to be adjusted regularly and commonly results in combination therapy of metformin with sulphonylureas or insulin as second-line treatment; both are cheap and cause effective glucose lowering yet often at the expense of weight gain and a higher risk of hypoglycaemia. Some view the failure of clinicians and their patients to effectively implement available interventions as the main reason for insufficient glycaemic control, more so than the lack of available drugs.[5]

So, why do we need new drugs for the treatment of type 2 diabetes if the old ones are so effective?

Table 1. *Different therapeutic modalities for the treatment of type 2 diabetes mellitus and mode of action*

Agents	Mode of action
Insulin	Stimulation of insulin receptor and glucose uptake
Sulphonylureas	Stimulation of insulin secretion
Metformin	Inhibition of hepatic gluconeogenesis and increase in hepatic insulin sensitivity
Thiazolidinediones	Increase in muscle insulin sensitivity, decrease in lipotoxicity and modulation of adipocytokines
α-glucosidase inhibitors	Delay in glucose absorption
Meglitinides	Stimulation of insulin secretion
GLP-1 analogues	Stimulation of (glucose-dependent) insulin secretion and inhibition of glucagon release
DPP-IV inhibitors	Stimulation of (glucose-dependent) insulin secretion and inhibition of glucagon release via increase of endogenous GLP-1
Rimonabant	Weight reduction through blockade of the cannabinoid receptor-1; probably weight independent effects?
Pramlintide	Inhibition of glucagon release and gastric emptying

First of all, despite currently available treatment options, targets are not met in at least 50% of patients in clinical trials.[6,7] Keeping in mind that patients participating in clinical trials are most probably more motivated and interested, the percentage of patients reaching these targets will be even lower in daily clinical practice. It has been argued that lifestyle changes should always be part of everyday diabetes treatment. We acknowledge that lifestyle interventions flanked by diabetes education and dietary control are the cornerstone of treatment and have proven to be effective both during intervention and onwards.[8] Nevertheless, even then these measures alone are not sufficient to reach glycaemic targets and to sustain metabolic control. Secondly, even more stringent targets have been set recently with respect to HbA1c.[9,10] It is to be expected that these guidelines will be followed by other organisations and societies. Finally, as mentioned before, hypoglycaemia and especially weight gain are of particular concern with sulphonylureas and insulin.

The question arises whether combinations of new drugs, each specific with its pharmacological mechanism of action, can expand our ability to manage patients with diabetes.

Thiazolidinediones (or peroxisome-proliferator-activated receptor-gamma (PPAR-γ) agonists) represent a class of drugs with a new mechanism of action. In response to PPAR-γ activation the expression of different genes within the target cells changes. PPAR-γ is mainly expressed in fat cells and activation will lead to (pre)adipocyte differentiation. As such, fat cells take up triglycerides more easily while lipolysis is inhibited. Subsequently, the level of circulating free fatty acids decreases resulting in an increase in insulin sensitivity. Other mechanisms may also play a role in improving insulin sensitivity.[11]

The efficacy with respect to blood glucose lowering with thiazolidinediones is comparable with (but not better than) sulphonylureas and metformin. Recently two long-term trials were performed that investigated treatment with pioglitazone (PROactive trial) or rosiglitazone (ADOPT).[12,13] In the PROactive trial HbA1c levels were on average 0.5% lower in patients randomised to pioglitazone than to placebo, but no benefit was found with regard to its primary combined cardiovascular endpoint. A 16% decrease in its secondary endpoint (death, myocardial infarction and stroke) after three years was noted. However, this should be balanced against the main adverse effects, such as fluid retention, which are probably related to heart failure and weight gain. The trial outcome is therefore viewed controversial.[14]

In ADOPT, the study's primary endpoint was to compare glycaemic control achieved by rosiglitazone, metformin, and glyburide monotherapy. Rosiglitazone was found to be superior to glyburide (a sulphonylurea derivative) with respect to durability during five years of treatment. However, the differences between rosiglitazone and metformin were quite small and of questionable clinical relevance. Again weight gain and fluid retention were the main side effects in the rosiglitazone-treated group. Although insulin secretion (β-cell function) improved shortly after rosiglitazone treatment, this was unfortunately not sustained.

Recently, new side effects of the available thiazolidinediones (both rosiglitazone and pioglitazone) were reported.[15] The incidence of upper arm, hand, or foot fractures was significantly higher in women receiving rosiglitazone than in those receiving metformin or glyburide treatment. The company's clinical trial database also revealed that pioglitazone-treated women were more likely to have sustained a fracture than those receiving a comparator drug or placebo during a maximum period of 3.5 years. No increased risk for fracture was identified in men with either drug.

Because of weight gain, fluid retention and the increased risk of bone fractures in women, the thiazolidinediones do not appear to be the ideal drugs for intensification of combination therapy.

The α-glucosidase inhibitors and meglitinides are, certainly in the Netherlands, less widely prescribed. The α-glucosidase inhibitors have serious gastrointestinal side effects but are not associated with weight gain. The meglitinides are short acting so that optimal timing with meals is of crucial importance and they confer a risk of hypoglycaemia, although less than sulphonylureas. As such they can be used as an alternative for but should not be added to sulphonylureas.

All other new classes are characterised by a lack of sufficient data from long-term studies with 'hard' outcomes and limited experience, leaving us with questions about durability and especially side effects. In general the expectations with respect to glucose-lowering effects should not be that high in these new drugs. However, it would be of particular interest to find out what the effects will be, for example on weight gain, when these agents are combined with other drugs.

The glucagon-like peptide (GLP)-1 analogues stimulate insulin secretion, suppress glucagon and slow gastric emptying. The first results with these agents show that the effect on glycaemic control is moderate (decrease in HbA1c of 0.5 to 0.9%) but sustainable during 18 months of treatment.[16] They lower body weight, but serious gastrointestinal side effects occur and they need to be injected subcutaneously. Although it needs to be confirmed in humans, improvement of β-cell function was found in animal studies.[17]

As a natural gastrointestinal peptide, GLP-1 is rapidly inactivated by dipeptidyl peptidase IV (DPP-IV). Inhibitors of DPP-IV (gliptins) have been developed to increase levels of endogenous GLP-1. On top of metformin, sitagliptin

decreased HbA1c by 0.6% during a short follow-up of 24 weeks.[18] Distinct from GLP-1 analogues, DPP-IV inhibitors do not appear weight neutral and to lack gastrointestinal side effects.

Rimonabant is also an interesting option with respect to its effects on weight reduction. Nevertheless the glucose-lowering effects are limited.[19]

The amylin analogue pramlintide is currently not registered in the Netherlands. Its beneficial effect on weight is promising, but this drug also needs to be injected.

It can be concluded that at the moment the availability of new drugs should not preclude metformin and sulfonylureas (and insulin) as initial therapy since the 'oldies' are still very useful. For various reasons, a significant number of patients with type 2 diabetes will not reach the glycaemic target with these drugs. Therefore, we do need new drugs for the treatment of type 2 diabetes mellitus. These new drugs are promising but (long-term) comparative trials with different combinations focussing on glucose-lowering and disease-modifying effects, durability, as well as side effects (especially with respect to weight gain), are required. In short, we especially do need to know when and in whom to use the new drugs. We need to sort out which combination therapy should be given to a specific person with type 2 diabetes. Individualised medical therapy with different combinations of drugs has the future.

REFERENCES

1. Heine RJ, Diamant M, Mbanya J-C, Nathan DM. Management of hyperglycaemia in type 2 diabetes: the end of recurrent failure? BMJ 2006;333:1200-4.
2. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycaemia 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. Diabetologia. 2006;49:1711-21.
3. American Diabetes Association. Standards of medical care in diabetes-2007. Diabetes Care 2007;30(Suppl 1):S4-41.
4. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.
5. Nathan DM. Finding new treatments for diabetes: How many, how fast, how good? N Engl J Med 2007;356:437-40.
6. Goudswaard AN, Stolk RP, de Valk HW, Rutten GE. Improving glycaemic control in patients with Type 2 diabetes mellitus without insulin therapy. Diabet Med 2003;20:540-4.
7. Dijkstra RF, Braspenning JC, Huijsmans Z, et al. Introduction of diabetes passports involving both patients and professionals to improve hospital outpatient diabetes care. Diabetes Res Clin Pract 2005;68:126-34.
8. Lindstrom J, Ilanne-Parikka P, Peltonen M, et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet 2006;368:1673-9.
9. Lebovitz HE, Austin MM, Blonde L, et al. ACE/AACE consensus conference on the implementation of outpatient management of diabetes mellitus: consensus conference recommendations. Endocr Pract 2006;12 (Suppl 1):6-12.
10. Ryden L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J 2007;28:88-136.
11. Semple RK, Chatterjee VK, O'Rahilly S. PPAR gamma and human metabolic disease. J Clin Invest 2006;116:581-9.
12. Dormandy JA, Charbonnel B, Eckland DJ, 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.
13. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427-43.
14. Yki-Jarvinen H. The PROactive study: some answers, many questions. Lancet 2005;366:1241-2.
15. Schwartz AV, Sellmeyer DE. Thiazolidinediones: New evidence of bone loss. J Clin Endocrin Metab 2007;92(4):1232-4.
16. Ratner RE, Maggs D, Nielsen LL, et al. Long-term effects of exenatide therapy over 82 weeks on glycaemic control and weight in over-weight metformin-treated patients with type 2 diabetes mellitus. Diabetes Obes Metab 2006;8:419-28.
17. Drucker DJ. Biological actions and therapeutic potential of the proglucagon-derived peptides. Nat Endocrinol Metab 2005;1:22-31.
18. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care 2006;29:2638-43.
19. Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. Lancet 2006;368:1660-72.