Optimizing combination treatment in the management of type 2 diabetes

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Abstract: Obtaining the suggested glycemic control is the most important achievement in order to prevent cardiovascular complications in patients with type 2 diabetes. Monotherapy often fails after a period of treatment, so that multiple drugs are needed to achieve effective glycemic control. A number of oral glucose lowering drugs is now available such as metformin, sulfonylureas, non-sulfonylureas secretagogues (metiglinides derivatives), alpha-glucosidases inhibitors, and the newest agent: thiazolidinediones (TZD). The possible associations of oral glucose lowering drugs for optimal treatment of type 2 diabetes are briefly reviewed. In particular, the effects of different classes of drugs on cardiovascular risk factors (and particular hypertension and dyslipidemia) and well recognized cardiovascular disease markers in type 2 diabetes are analyzed: in this context TZD appear the more innovative drugs and have been shown to play a key role in the management of hypertension, dyslipidemia , inflammation and endothelial disfunction in diabetic patients. The possible adverse effects derived from the association of different drug classes are also considered.

Keywords: type 2 diabetes, combination therapy, cardiovascular risk factors

Introduction

Type 2 diabetes: from lifestyle and diet to pharmacological treatment

Type 2 diabetes mellitus is a complex metabolic disorder characterized by a variable degree of insulin resistance, impaired insulin secretion and excessive hepatic glucose production; all these factors contribute to hyperglycemia. Chronic hyperglycemia determines impairment of beta-cells function thus worsening hyperglycemia (glucose toxicity). Moreover, excessive dietary lipid introduction impairs islet function (lipotoxicity). In the liver, hyperinsulinemia is no longer able to suppress gluconeogenesis, which results in hyperglycemia and decreased glycogen storage by the liver in the post-prandial state (Golay 2005). Lifestyle interventions are suggested for all diabetic patients and in particular for those who present obesity and insulin-resistance. Adequate nutritional advices are essential to achieve recommended levels of fasting plasma glucose (FPG), post-prandial plasma glucose (PPG), glycosilated hemoglobin (HbA1c), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C) triglycerides (TG), blood pressure (BP), and body weight. Regular exercise has been shown to improve blood glucose control, reduce cardiovascular (CV) risk factors, contribute to weight loss and improve well-being. Actually, insulin-resistance may be modulated by physical activity; a regular physical activity reduces blood insulin and triglycerides, increases HDL-C and reduces BP. Generally, patients with type 2 diabetes and/or insulin-resistance are advised to exert aerobic activity (ie, an exercise that lasts for at least 30 minutes at low impact of energy) for 3–4 times a week. Physical exercise improves insulin action, contributes to weight loss, and reduces several risk factors for CV disease. The association between increased levels of physical activity and a reduced

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occurrence of diabetes' long-term complications suggests that regular physical activity has a protective role (Castaneda 2003). Moreover, regular aerobic exercise reduces visceral fat mass and body weight without decreasing lean body mass (De Feo 2006). Since physical activity has been shown to protect against the development of type 2 diabetes, physical training programmes suitable for individuals at risk for type 2 diabetes should be incorporated into the medical care system to a greater extent. People with diabetes should be evaluated in order to reduce the risk of adverse effects that may possible occur in subjects with macro and/or microvascular complications during physical exercise. Advice all patients not to smoke is another important intervention recommended in type 2 diabetes management. In many cases the optimal glycemic control is not achieved only by changes in lifestyle and the most part of type 2 diabetic patients needs a pharmacological treatment (American Diabetes Association 2006). Type 2 diabetes is a progressive condition that requires combination therapy for optimal glycemic control (Turner 1999). When hyperglycemia appears no longer adequately controlled, addition of a second agent with similar or different mechanism of action is recommended (with the exception of SU and non-SU insulin secretagogues). The most common combination regimens are SU plus metformin or TZD, SU plus TZD and metformin plus TZD (Inzucchi 2002). Many evidences suggest that diabetes is strictly related to vascular dysfunction, dyslipidemia, hypertension and at least one of these risk factors is present in the most part of type 2 diabetic patients at the moment of diagnosis. The need to early detect CV dysfunction and risk factors in type 2 diabetic patients in primary care has been recently stressed (Petri 2006).

Vascular damage and cardiovascular risk in type 2 diabetes

A major cause of the reduction in life expectancy in patients with diabetes is CV disease and CV complications. Both impaired glucose tolerance and diabetes predispose to CV alterations (Schnell 2006).

Type 2 diabetes determines a 2-6-fold increased risk of CVD and death. Indeed, the risk of major CV events in type 2 diabetic patients with no history of coronary heart disease (CHD) is equivalent to that observed in non-diabetic subjects with CHD. Evidences suggest that inflammatory processes play an important role in the pathogenesis of atherosclerotic CVD. Thus, markers of inflammation and endothelial dysfunction may provide additional information helpful to stratify patient's risk of developing CVD and may become new targets for treatment. On the other hand, evidence has emerged suggesting that inflammation is also involved in the development of type 2 diabetes. Interventions by lifestyle modification or agents with anti-inflammatory properties may reduce the risk of both type 2 diabetes and atherosclerosis. In this context, drugs exerting anti-inflammatory and vascular effects have future potential to be useful in prevention of CVD in type 2 diabetic patients (Ziegler 2005).

Improving glycemic control with combination treatment and obtaining positive effects on vascular risk in type 2 diabetes mellitus

Improving glycemic control in patients with type 2 diabetes is recognized to be important for the prevention of both microvascular and macrovascular complications, particularly when aggressive treatment is initiated at an early stage of the disease (Vaag 2006). Evidences suggest that combination therapy using oral antidiabetic agents with different mechanisms of action may be more effective in achieving and maintaining target blood glucose levels (Turner 1999) (Table 1). Metformin is currently the first-choice treatment in patients with type 2 diabetes and obesity, characterized by insulin-resistance. Metformin is a biguanide and its mechanism of action has been felt to be due to a decrease in glucose production in the liver. Moreover, metformin improves glucose uptake in adipose tissue and skeletal muscle, peripheral insulin sensitivity and, to some extent, glucose absorption; a reduction of free fatty acid concentra-

Table 1 The major compounds for treatment of type 2 diabetes mellitus

Available glucose lowering drugs
Sulphonylureas: glibenclamide, glipizide, glipizide GITS, glimepiride
Increase insulin secretion
Reduction in HbA1c 1,5–2%
Nonsulphonylureas insulin secretagogues: repaglinide, nateglinide
Increase insulin secretion
Reduction in HbA1c 0,7–1,3%
Biguanides : Metformin
Decrease hepatic glucose production + increase peripheral uptake
Reduction in HbA1c 1,8%
Alpha-glucosidase inhibitors: acarbose , miglitol
Decrease intestinal carbohydrates absorption
Reduction in HbA1c 0,8%
Thiazolidinediones: rosiglitazone, pioglitazone
Adipose (muscle, liver)
Reduction in HbA1c 1,5%

tion in the blood has been observed too and is thought to be related to a reduction in hepatic gluconeogenesis during treatment with biguanides. (Krentz 2005).

Metformin provides reduction of body weight and ameliorates lipid abnormalities in obese and non-obese patients: moreover, metformin is effective in reducing C reactive protein (PCR) and lipoprotein a (Lp(a)) in thus improving, at the same time, endothelial dysfunction (Hundal 2003). If metformin is not tolerated or contraindicated, the second choice is represented by a thiazolidinedione TZD or a sulfonylurea (SU). Sulfonylureas are efficacious and particularly useful in type 2 diabetic patients who present primarily insulin secretion deficiency and, in association with insulin sensitizing drugs (metformin and TZD), in those patients with type 2 diabetes mellitus who do not achieve recommended glycemic control (Derosa 2007).

Acarbose and miglitol, two disaccharidase inhibitors, are effective in combination with SU, even if metformin and insulin in association to SUs seem to be more effective and safe providing a decrease of glycosilated haemoglobin about twice as great as that obtained with acarbose plus SUs (Rendell 2004). Anyway, evidences are available concerning with a potential risk of cardiovascular mortality in subjects treated with metformin in association with SUs (Evans 2006). In the UKPDS a significant increase in mortality was observed in those patients in whom metformin was added to initial SU treatment. Other evidences point out a potential risk in adding metformin to SUs therapy in patients with CHD. A theoretical cardiac risk for first generation SU has been observed. Newest sulfonylureas, glimepiride, gliclazide and glipizide have lower affinity for cardiac SUR-receptors and, in animal models, glimepiride seems ineffective in reducing the protective effect of ischemic preconditioning (Riveline 2003).

Metiglinides derivatives (repaglinide and nateglinide) are a class of insulin secretagogues acting increasing insulin secretion by activating the same or similar receptors activated by SUs. Repaglinide is the available drug in the market and presents some advantages vs other SUs, the most important being a reduced risk of hypoglycemia. Repaglinide is effective in combination treatment with TZD or metformin, and seems to be useful in association with a single daily administration of insulin (Rendell 2004). The peroxisome proliferator-activated receptors (PPARs) are part of a nuclear receptor superfamily which plays a fundamental role in cell metabolism, particularly in relation to adipogenesis, lipid metabolism and peripheral tissue insulin-sensitivity.

Thiazolidinediones are PPARγ agonists that improve insulin-sensitivity by complex mechanisms. The thiazolidinediones currently available for treatment of type 2 diabetes are pioglitazone and rosiglitazone while troglitazone has been withdrawn due to the report of many cases of hepatic toxicity. Efficacy and safety of pioglitazone and rosiglitazone as antidiabetic drugs has been well established in a number of clinical studies. Increasing interest is now focused on the range of pleiotropic effects of TZD (Roberts 2003).

In non-diabetic patients with CV risk factors, pioglitazone treatment enhances insulin sensitivity, decreases PCR, and improves endothelial vasodilator function. These effects do not appear to be closely related to improvement in glycemic control, suggesting that pioglitazone may have beneficial vascular properties independent of its effect on insulin sensitivity and inflammation (Campia 2006).

Association of metformin and rosiglitazone is effective in reducing factors related to an increased CV risk in patients with type 2 diabetes end/or insulin-resistance. In 90 patients treated with the association of metformin and rosiglitazone for 24 weeks, matrix metalloproteinase-9 (MMP-9) levels and plasminogen activator inhibitor type 1 (PAI-1) levels have been decreased by 14% and 33% with the contemporary administration of rosiglitazone (8 mg/day) and metformin (1000 mg/day) vs an increase in MMP-9 levels of 22% and a reduction in PAI-I levels of 0.6% with only metformin at a dosage of 2000 mg/day (Weissman 2004). In an other study, treatment with rosiglitazone (4 mg/day) and metformin (2000 mg/day), contemporary administered to 95 type 2 diabetic patients, has determined, after 12 months, a greater significant reduction of PAI-1 levels (26.6%, $p < 0.01$) vs treatment with glimepiride in association with metformin (Derosa 2005 a).

Fixed dose combination of rosiglitazone and metformin is now available in the market (Avandamet, Glaxo Smith Klein) while a fixed dose combination of metformin and pioglitazone has been undergoing analysis since 2004 (Campbell 2005).

Addition of rosiglitazone to sulfonylurea has been shown to improve glycemic control in patients with type 2 diabetes previously treated with sulfonylurea monotherapy and produced a positive effect on insulin resistance, beta-cell function, CV risk markers, and adiponectin, thus supporting the rationale of combining rosiglitazone with sulfonylurea drugs in patients with type 2 diabetes (Pfuntzer 2006). A combined fixed dose of rosiglitazone plus glimepirirde has been recently approved (Avandaryl, Glaxo Smith Klein).

Hypertension is one of the most frequent conditions associated with type 2 diabetes, and represents one of the

major causes of stroke in diabetic patients. Moreover, antihyperglycemic drugs might have a small, but clinically significant, beneficial effect on BP in patients with diabetes mellitus. In a 12-month study, combination treatment with rosiglitazone and metformin, but not glimepiride and metformin, was associated with a significant improvement in BP control (Derosa 2005b).

Another well established CV risk factor frequently affecting type 2 diabetic patients is dyslipidemia. Combination of glimepiride and pioglitazone in subjects with type 2 diabetes mellitus and metabolic syndrome, who had not previously achieved adequate glycemic control with sulfonylurea or metformin or had undergone adverse effects, has demonstrated to be significantly more effective in improving lipid abnormalities (Derosa 2004).

Insulin-resistance is associated to elevated concentrations of plasmatic fibrinogen, increased blood viscosity and platelet activation and aggregation. Plasminogen activator inhibitor – type 1 (PAI-1) is a potent inhibitor of fibrynolisis and its concentration is directly related to hyperinsulinemia (Jokl 1994).

Beyond glycemic control, association of metformin plus TZDs sems to be effective in reducing different markers of CV risk factors as PAI-I levels, platelet aggregation and expression of a number of molecules which provide adhesion to chronic inflammation markers (Bailey 2005). The addition of a thiazolinedione to glimepiride treatment in type 2 diabetic subjects with the metabolic syndrome determines a slight but significant reduction of PAI-1 values, related to a similar reduction in insulin resistance (Derosa 2005c).

Pioglitazone plus metformin administered for 8 weeks in a group of patients with type 2 diabetes mellitus and hypertension has been shown to reduce significantly both mean systolic and diastolic BP during the night independently of the reduction of glycemia (Negro 2004).

Like almost all secretagogues, glimepiride can determine increase in body weight. Anyway, glimepiride has shown to reduce weight gain when a combination treatment of insulin NPH and glimepiride was compared with an insulin regimen. Rosiglitazone might determine fluid retention and exacerbate heart failure in type 2 diabetic patients and is not recommended for patients in NYHA class 2–4 heart failure. Screening underlying cardiac disease in patients as well as the use of drugs related with the development of fluid retention of pedal edema is recommended before starting therapy with a TZD associated with a SU (Nesto 2004). Thiazolidinediones has demonstrated to induce weight gain in type 2 diabetic patients. The weight gain appears to be related to the dose. Rosiglitazone/glimepiride combination therapy is affected by weight gain more then rosiglitazone or sulfonylurea administered as monotherapy (Hussein 2004).

Weight loss following a low calories diet is associated with a decrease in PPAR-γ expression in subcutaneous adipose tissue, related with the differentiation of adipocytes. Experts suggest a program of nutritional education and exercise at prescription, with restriction in calories intake in particular in those patients at high risk of weight gain (Fonseca 2003). Moreover, the association of thiazolidinediones and diuretics seems to be a possible choice to reduce edema during treatment and must be considered when a combination of a TZD and a SU appears to be the best treatment to obtain the optimal control of type 2 diabetes (Mudaliar 2003).

The use of insulin in association with oral hypoglycemic drugs has been encouraged in the last five years. In particular, the incoming of insulin glargine has reduced the risk of hypoglycemia which limited the association of a long acting insulin (like NPH) with secretagogues, like SUs and repaglinide

Metformin therapy in association with insulin (regular or long acting insulins like glargine and NPH) is a successful strategy in patients who need to contain body weight increase, but have not obtained the recommended goals with metformin alone (Rendell 2004) (Table 2).

Conclusions

Excellent glycemic control does not impact non traditional risk factors for CVD equally, but various diabetes

Table 2 Approved FDA association

Compound	FDA approved association
Metformin	Monotherapy
	Sulfonylureas
	Non-sulfonylureas
	Alpha-glucosidase inhibitors
	Thiazolidinediones
	Insulin
Sulfonylurea	Monotherapy
	Metformin
	Thiazolidinediones
	Alpha-glucosidase inhibitors
	Insulin
Non-sulfonylureas	Monotherapy
	Metformin
Alpha-glucosidase inhibitors	Monotherapy
	Sulfonylureas
	Metformin
	Insulin
Thiazolidinediones	Monotherapy
	Sulfonylureas
	Metformin
	Insulin (pioglitazone only)

medications have different effects on these risk factors. These findings may be useful for appropriate therapeutic choices for patients with type 2 diabetes, although larger studies with more appropriate treatment comparisons may be necessary. Increasing comprehension of the complex pathogeneses of type 2 diabetes, and related CVD, determines the awareness that systematic application of a scheme in treating type 2 diabetic patients is no longer the adequate approach.

Even if not formally approved by the FDA, triple therapy is common in clinical practice and experimental results demonstrate the possibility to obtain better glycemic control and effectiveness on other recognized CV risk factors. Anyway, the fear of adverse events is usually the cause of discontinuation of multiple therapies by patients and physicians too. Increasing evidences suggest that an individualized therapeutic scheme with oral glucose lowering agents in combination and in combination with insulin may be successful and may be affected by loss side effects, such as weight gain, which commonly occur with more accepted monotherapy as sulfonylureas.

Of the currently available agents, metformin and thiazolidinediones seem to be the most effective drugs in CV protection. Metformin has a positive effect on several CV risk factors and has been shown to reduce cardiac events in overweight subjects with type 2 diabetes. Thiazolidinediones favorably modulate a large spectrum of conventional and non-conventional CV risk factors. Rosiglitazone and pioglitazone possess beneficial effects on other cardiovascular risk factors associated with the insulin resistance syndrome. Thus, these agents were shown to decrease blood pressure, enhance myocardial function and fibrinolysis, as well as possess anti-inflammatory and other beneficial vascular effects.

Box 1 Cardiovascular effects of drugs in monotherapy

Monotherapy
Metformin: demonstrated significant decrease in myocardial infarction incidence and in prevention of cardiovascular complications of type 2 diabetes; it reduces PCR and Lp(a) (Hundal and Inzucchi 2003).
Rosiglitazone: demonstrated significant improvement of systolic and diastolic blood pressure:
Controversial impact on lipid abnormalities. In clinical trials has demonstrated to have a neutral-worsening on lipoproteins.
Pioglitazone: improves lipid abnormalities. Demonstrated to reduce intima-media thickness with a good impact on endothelium disfunction. Pioglitazone and rosiglitazone: reduce vascular inflammation, stimulate fibrynolisis; decrease the production of adhesion molecules and metalloproteinases; (Verges 2004): decreases liver fat and increases insulin clearance (Tiikkainen et al 2004).
Sulphonylureas: may reduce heart "preconditioning" so that are not considered completely safe in patients with previous myocardial infarction. New generation sulfonylureas (glimepiride) is considered safer than others because it is more selective.

Sulfonylureas have beneficial effects on some risk factors but outcome studies have failed to show a reduction these agents. At present, clinical management of insulin-resistant type 2diabetes should be based on metformin, with the addition of thiazolidinediones and sulfonylureas to achieve optimal glycemic control.

In conclusion optimizing combination treatment represent the real strategy to successfully obtain longer control of type 2 diabetes, but, to date, stepwise approach is preferred and combination therapy as initial approach not recommended.

The real challenge is now to obtain goal standards not only in glycemic control but also in the magnitude of mechanisms that underlie early onset of macro and microvascualr complications in type 2 diabetes. Newer agents, such as thiazolidinediones in combination with old, well experimented ones, such as sulfonylureas and metformin, are promising in this context (see Boxes 1, 2, 3, and 4). Boxes 1, 2, 3 and 4 illustrate some interesting results obtained in recent clinical studies; even many of these studies were not powered for

Box 2 Metformin + sulfonylureas

Association	**Cardiovascular risk with association**
Metformin + **Sulfonylureas**	Increase in cardiovascular mortality Glibenclamide in association with metformin therapy seems to present special risk Metformin + Glimepiride: reduce non tradional cardiovascular risk factors (Lp(a) levels and homocisteinemia) (Derosa et al 2005)

Box 3 Thiazolidinediones + sulfonylureas

Association	**Cardiovascular risk with association**
Thiazolidinediones + **Sulfonylureas**	Rosiglitazone + Glimepiride: Improvement in long-term blood pres sure control (Derosa et al 2005) Rosiglitazone or Pioglitazone + Glimepiride: significant decrease in PAI-1 levels (Derosa et al 2005) Pioglitazone + Sulfonylureas: reduction of the urinary albumin-to-creatinine ratio, significant rise in LDL cholesterol, and significant Improvements in triglyceride levels and HDL cholesterol levels (Hanefeld et al 2004) Pioglitazone + Glimepiride: improvement in high-sensitivity C-reactive protein levels (Pfuntzer et al 2006)

Box 4 Metformin + thiazolidinediones

Association	Cardiovascular risk with association
Thiazolidinediones + Metformin	Pioglitazone + Metformin: favorable changes in LDL and HDL subfractions beyond the obtained glycemic control (Lawrence et al 2004) Rosiglitazone + Metformin: significant improvement in blood pressure control (Derosa et al 2005) Metformin + Thiazolidinediones: PAI-I levels, platelet aggregation and expression of a number of molecules which provide adhesion to chronic inflammation markers as PCR (Bailey 2005)

the noted endpoints, the boxes are intended to be stimulating starting points for further research.

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