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REVIEW

Thiazolidinedione derivatives in type 2 diabetes mellitus

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ABSTRACT

In Europe, the thiazolidinedione derivatives pioglitazone and rosiglitazone have been approved for the treatment of type 2 diabetes mellitus either as monotherapy for patients with intolerance or contraindications to metformin or in combination therapy. This class of drugs seems particularly suited for obese patients, but is currently not considered as a first choice for monotherapy. The efficacy with respect to blood glucose lowering is comparable with sulphonylurea (SU) derivatives and with metformin. Long-term data with respect to efficacy and side effects are still limited.

KEYWORDS

Combination therapy, monotherapy, pioglitazone, rosiglitazone, thiazolidinedione derivatives, type 2 diabetes mellitus

INTRODUCTION

Pioglitazone and rosiglitazone, two oral blood glucose lowering drugs for the treatment of type 2 diabetes mellitus, have been marketed in the Netherlands since 2000. Both belong to the class of thiazolidinedione derivatives (TZDs), also referred to as glitazones or peroxisome proliferator-activated receptor (PPAR)-γ agonists. It should be realised that compounds other than the TZDs can also stimulate the PPAR-γ receptor. In this review the term TZDs will be used.

The TZDs represent a new class of drugs with a new mechanism of action. In Europe, TZDs have been approved for type 2 diabetes mellitus, particularly for overweight patients who are inadequately controlled by diet and exercise alone, for whom metformin is inappropriate because of contraindications or intolerance. TZDs have also been approved for use in combination therapy. Unlike the situation in the USA, TZDs are not approved, but even contraindicated for use in combination with insulin in Europe. From the day of approval onwards, there has been discussion concerning the exact place of TZDs within the pharmacotherapy of type 2 diabetes mellitus. Different views have resulted in differences in guidelines and treatment standards. The lack of data on long-term clinical studies with 'hard' endpoints (mortality and new macrovascular events) definitively plays an important role in this discussion. Recently, the first outcome study was published (the PROactive study),[1] but this study has also raised several questions.[2-5]

With respect to glucose regulation, TZDs do not seem to be superior to the conventional drugs metformin or sulphonylurea (SU) derivatives. Therefore, potential additional benefits but also side effects of TZDs, such as fluid retention and weight gain, are important in the discussion on the position of this class of drugs in the pharmacotherapy of type 2 diabetes mellitus.

In this review the following topics will be discussed: pathophysiology of type 2 diabetes mellitus, available drugs, pharmacology and mechanism of action of TZDs, efficacy, side effects and contraindications of TZDs, use during pregnancy and lactation and some future perspectives. Finally, a guide to the use in clinical practice is provided.

PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELLITUS

The pathogenesis of type 2 diabetes mellitus is complex and has only been partially clarified. Clearly, the capacity of the pancreas to produce insulin is reduced. On diagnosis, β-cell function is generally reduced to approximately 50% of what is considered normal. In addition to this defect in insulin secretion, there is a reduced sensitivity to the

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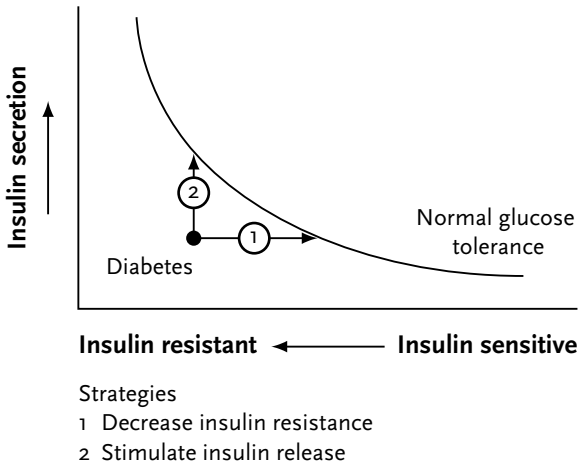
effect of insulin on the target organs (insulin resistance). Insulin resistance is closely related to obesity. Once a state of chronic hyperglycaemia has been reached (diabetes), a number of secondary alterations take place that, although in themselves not the cause, do lead to an additional increase in both insulin resistance and β-cell dysfunction. The term glucose toxicity is used to refer to these secondary defects. *Figure 1* shows the normal relationship between insulin secretion and insulin sensitivity.

Recent data suggest that an increase in fat mass (obesity) results in a reduction in the effect of insulin on skeletal muscles and the liver.[6] With respect to obesity, not only the absolute amount of fat is important, but also body fat distribution. In particular, visceral fat and fatty tissue in skeletal muscle and liver are crucial in the development of insulin resistance. When insulin resistance develops in a subject who already has a (largely genetically determined) β-cell defect, plasma glucose will rise and diabetes will occur.

Figure 1. *Normal relationship between insulin sensitivity and insulin secretion (once insulin secretion can not match insulin resistance, diabetes will develop)*



DRUGS, PHARMACOLOGY AND MECHANISM OF ACTION

Drugs

The prototype of the TZD class of drugs, ciglitazone, was first described in 1982.[7] This agent did not reach the market due to insufficient efficacy and an unfavourable side effect profile. The first marketed TZD was troglitazone. Apart from the thiazolidine-2-4-dione group, troglitazone also contains an α-tocopherol group (analogue to vitamin E). When developing troglitazone the idea was to develop a drug that would inhibit the peroxidation of lipids in addition to having a favourable effect on insulin resistance (thiazolidine group). Troglitazone was taken off the market worldwide in March 2000 due to severe liver toxicity, sometimes with fatal consequences.[8] At present, pioglitazone and rosiglitazone are available on the Dutch market.

Pharmacokinetics

The bioavailability of the TZDs following oral intake is high and once absorbed, TZDs are largely bound to protein in the plasma (>99%). Both pioglitazone and rosiglitazone are mainly metabolised by CYP2C8 and to a small degree by CYP2C9. With normal liver function, the elimination half-life of pioglitazone and rosiglitazone is 5 to 6 and 3 to 4 hours, respectively. The two active metabolites of pioglitazone have an elimination half-life of 26 to 28 hours, which thus facilitates the single daily dose of pioglitazone. A once-daily dosage schedule is also recommended for rosiglitazone.

Pharmacodynamics

The mechanism of action of the TZDs is based on binding to the PPAR-γ receptor.[9] PPAR-γ belongs to the group of nuclear transcription factors. Transcription factors affect the level of expression and thus the activity of various genes. By making some genes more and others less active, transcription factors affect cellular function. In humans, PPAR-γ is mainly expressed in fat cells and this is where the TZDs appear to act primarily. Unlike most other drugs, TZDs do not act by binding to membrane receptors, but by binding to transcription factors in the cell nucleus.

In response to PPAR-γ receptor activation, the expression of hundreds of genes in the target cells changes. The net effect in fat tissue is that (pre)adipocytes differentiate. As a consequence, fat tissue takes up triglycerides more easily while lipolysis is inhibited. Subsequently, the level of circulating free fatty acids decreases, which will indirectly promote glucose uptake in skeletal muscle. After a number of weeks, this results in a decrease in insulin resistance. Other mechanisms may also play a role in improving insulin sensitivity.[9]

Based on this mechanism of action, it is clear that fat mass will increase during treatment with TZDs; in particular the quantity of subcutaneous fat will increase. Treatment with TZDs ultimately leads to an average weight gain of 2 to 4 kg. Interestingly, this weight gain parallels the decrease in insulin resistance. This can be explained by the fact that TZDs reduce the quantity of fat in nonfatty tissues such as the liver and skeletal muscles. So, fat redistribution rather than an increase in fat mass occurs.[6] The net effect of TZDs is a reduction in peripheral insulin resistance; improvement of insulin-stimulated glucose uptake in peripheral tissues, in particular in skeletal muscle. Insulin resistance in the liver is also diminished, resulting in a reduction of endogenous glucose production.[10,11]

EFFICACY

Approved therapeutic indications

According to the official text, pioglitazone and rosiglitazone have been approved as monotherapy for the treatment of patients with type 2 diabetes mellitus, particularly overweight patients who are inadequately controlled by diet and exercise and for whom metformin is inappropriate because of contraindications or intolerance. TZDs are also approved for oral combination treatment in type 2 diabetes mellitus patients with insufficient glycaemic control despite the maximum tolerated dose of oral monotherapy with either metformin or sulphonylurea:

- in combination with metformin particularly in overweight patients;
- in combination with a sulphonylurea derivative only in patients who show intolerance to or a contraindication to metformin.

Finally, rosiglitazone is approved as triple oral therapy in combination with metformin and a sulphonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.

It should be mentioned that in clinical studies with TZDs the following exclusion criteria have generally been used: planned revascularisation procedure, symptomatic heart failure, cruric ulcers, peripheral gangrene or rest pain in the leg, haemodialysis, liver function disorder (alanine transaminase (ALAT) level >2.5 times the upper limit of normal), renal function loss, anaemia and diabetic retinopathy, neuropathy or nephropathy.

Efficacy

The inter-individual differences in the blood glucose lowering response to TZDs are great. Theoretically, patients with a prominent insulin resistance (marked abdominal obesity, fatty liver, high endogenous insulin concentrations) are more suited to TZD therapy than to treatment with sulphonylurea derivatives, but there are no clinical trials to support this notion. TZDs are also effective in other disorders associated with insulin resistance, such as polycystous ovary syndrome[12] and nonalcoholic fatty liver disease,[13] but this has not resulted in specific approved indications.

TZDs (monotherapy or combination therapy) *vs* placebo

Effects on glycemic control

Monotherapy

In two randomised, double-blind and placebo-controlled studies with pioglitazone, the HbA_{1c} level dropped by 1.05% (30 mg) in comparison with placebo[14] and by 0.8% (30 mg) and 0.9% (45 mg).[15] Randomised, double-blind and placebo-controlled studies using rosiglitazone showed a decrease in HbA_{1c} levels of 1.5% (4 mg twice daily) after 26 weeks of treatment in comparison with placebo.[16,17]

Combination therapy

In placebo-controlled studies of the addition of rosiglitazone (4 or 8 mg/day) to metformin, HbA_{1c} level dropped by 1.2% with 8 mg in comparison with placebo.[18,19] In patients who were inadequately controlled by the combination glibenclamide/metformin, the addition of rosiglitazone for 24 weeks reduced the HbA_{1c} level by 1% compared with placebo treatment.[20] Comparable results have been reported for pioglitazone.[21] In summary, TZDs provide an average HbA_{1c} reduction of 0.7 to 1.5% on top of metformin therapy.

Comparative studies with other oral blood glucose lowering drugs

Sulphonylurea derivatives

Compared with gliclazide, 52 weeks of treatment with pioglitazone (45 mg) resulted in a similar reduction in HbA_{1c}, which was 1.4% for both drugs.[22] The average reduction in the fasting blood glucose value was significantly greater with pioglitazone than with gliclazide (2.4 *vs* 2.0 mmol/l). In another study, the effects of pioglitazone and gliclazide were compared for two years in 567 patients.[23] In patients who had received pioglitazone the target value of the HbA_{1c} was reached more often than in the patients who had received gliclazide (47.8 *vs* 37.0%). In a similar study, the efficacy of metformin/pioglitazone (from 15 to 45 mg) was similar to metformin/gliclazide (HbA_{1c} reduction of 1% in both groups).[24]

Metformin

In one study, 45 patients with type 2 diabetes mellitus, who had not previously been treated with drugs, were randomised to treatment with rosiglitazone (4 mg twice daily), metformin or placebo.[25] After 26 weeks, both metformin and rosiglitazone had significantly reduced the HbA_{1c} in comparison with placebo. These observations were confirmed in another study.[26]

Several randomised studies have compared pioglitazone and metformin and showed a comparable fall in HbA_{1c} level.[27-31]

Pioglitazone vs rosiglitazone

A meta-analysis of studies on the effects of TZDs on cardiovascular risk factors concluded that pioglitazone and rosiglitazone have comparable effects on blood glucose control and on body weight.[32] In line with this meta-analysis, a recent study showed a similar effect on glucose regulation in a direct comparison between the two TZDs.[33]

Thus, with respect to the blood glucose lowering effect, pioglitazone and rosiglitazone are comparable and similar in efficacy compared with metformin and SU derivatives.

Effects on cardiovascular risk factors (non-glycemic effects)

Besides their effect on glucose metabolism, TZDs have also been shown to affect cardiovascular risk factors,

including lipids, blood pressure and inflammatory and fibrinolytic parameters.[34-36] These effects are probably linked to changes in gene expression.

Effects on lipids

A literature review on the effects of pioglitazone and rosiglitazone on blood lipids summarises that pioglitazone has a stronger effect on triglycerides, total cholesterol and LDL cholesterol than rosiglitazone.[37] Pioglitazone leads to a reduction in triglyceride concentration, an increase in HDL cholesterol concentration, and a neutral effect on LDL and total cholesterol concentrations. Rosiglitazone raises HDL, LDL and total cholesterol concentrations, and has a neutral effect on the triglycerides.[38] A meta-analysis of randomised placebo-controlled studies of pioglitazone or rosiglitazone shows that pioglitazone has a stronger effect on the serum lipids than rosiglitazone.[32] In general, the LDL composition tended towards a less atherogenic pattern in the studies with pioglitazone than in the studies with rosiglitazone.

Two randomised, double-blind studies have been published in which the effects of pioglitazone and rosiglitazone on blood lipids were compared.[33,39] The effects of these TZDs on lipids differed. The concentration of triglycerides was reduced by pioglitazone, whilst it increased with rosiglitazone. Furthermore, the increase in the concentration of HDL cholesterol was more pronounced whereas the increase in LDL cholesterol concentration was smaller with pioglitazone compared with rosiglitazone. In the second study the effects of pioglitazone and rosiglitazone were compared in patients with type 2 diabetes mellitus and the metabolic syndrome who had already been treated with glimepiride.[39] The results showed that the lipid spectrum was significantly more reduced when taking pioglitazone compared with rosiglitazone.

Although pioglitazone thus appears to have a more beneficial effect on lipids, it should be noted that the patient characteristics in the studies with pioglitazone significantly differed from those of the rosiglitazone studies. Furthermore, the quantitative effects of TZDs on lipid concentrations are limited,[40] and it is important to realise that TZDs are no alternative for lipid-lowering drugs.

Effects on blood pressure

Both pioglitazone and rosiglitazone induce a small reduction in blood pressure, in particular of the diastolic blood pressure.[41-43] In a meta-analysis of four double-blind studies comprising 3700 patients with type 2 diabetes mellitus a comparison between the effects of pioglitazone, metformin and gliclazide on cardiovascular risk factors was made.[44] The blood pressure was reduced to some extent by all treatment modalities, but the reduction with pioglitazone was more pronounced (about 1.5 mmHg). There were no differences in hospital admissions for cardiac or cerebrovascular events, mortality or the occurrence of heart failure.

Effects on inflammatory and fibrinolytic factors

Both pioglitazone and rosiglitazone reduce the concentrations of circulating inflammatory factors such as C-reactive protein and interleukin 6,[42] and affect the fibrinolytic system, thereby causing, among other things, a reduction in tissue plasminogen activator (t-PA).

All these 'nonglycaemic' actions of TZDs hold the promise that TZDs may have positive effects on cardiovascular endpoints, beyond their glucose lowering effect. The final proof for this claim needs to come from cardiovascular outcome studies. One outcome study has recently been published,[1] others are ongoing.[45,46] In addition, a number of studies have yielded positive results on surrogate cardiovascular endpoints. These comprise endothelial function,[47,48] changes after coronary interventions and intima-media thickness.[49,50]

The PROactive study

The 'PROspective pioglitAzone Clinical Trial In macroVascular Events' (PROactive) study has recently become available through internet reports, symposia and has been published in the Lancet.[1] Being the first outcome study, the study has been viewed with considerable interest. PROactive is a randomised double-blind study of 5238 patients with type 2 diabetes mellitus *and* macrovascular disorders in which the efficacy of pioglitazone (45 mg) in reducing the occurrence of new macrovascular events or death was compared with placebo.[51] The average age of the patients when the study was initiated was 61.8 years, most of them were male (66.1%) and 75.4% had hypertension. By definition, all patients had had a cardiovascular event, thus this was, in fact, a secondary intervention setting. The average body mass index (BMI) was 30.9 kg/m^2. The study drug was given on top of the patients usual antidiabetic medication and in one third of the cases in combination with insulin. This design was chosen to assess the effect of pioglitazone on cardiovascular disease *independent* of its effects on lowering blood glucose.

The study results show that pioglitazone treatment was associated with a nonsignificant 10% decrease in the primary, predefined, composite endpoint[51] and a significant 16% reduction in event rate of any of total mortality, nonfatal myocardial infarction or stroke (secondary endpoint). The claim of the paper 'pioglitazone reduces mortality, myocardial infarction and stroke' has, however, met considerable criticisms,[2-4,37] which renders it difficult to translate the results to clinical practice. The major limitations of the study are its population, its design and the side effects. Firstly, the population had a relatively high rate of smoking and a low rate of statin use (43%, given the setting of secondary prevention this should ideally have been 100%), resided in countries with relatively low access

to modern healthcare facilities and, perhaps in line with these characteristics, the population had a higher event rate than expected. This resulted in a more rapid conclusion of the trial than anticipated.

Although the design of the study aimed at similar glycaemic control in both treatment arms, the pioglitazone-treated patients had a better glycaemic control (mean difference in HbA_{1c} 0.5%), which, according to some,[4] may in fact largely explain the beneficial effect. Finally, the positive results were tempered by the increased prevalence of peripheral oedema and congestive heart failure[2] and by the substantial weight gain (average per patient 4 kg).

DIFFERENCES BETWEEN PIOGLITAZONE AND ROSIGLITAZONE

Pioglitazone and rosiglitazone were approved at about the same time and there are more similarities than differences between the two drugs. Rosiglitazone is administered in a dose of 4 mg once daily, which can be increased to 8 mg once daily or (preferably) 4 mg twice daily, whilst pioglitazone is administered once daily in a 30 mg dose. In fact, 30 mg pioglitazone is considered to be equipotent with 6 mg of rosiglitazone. Several studies with pioglitazone have been carried out with the 45 mg dose, mostly in American patients, whilst European studies often used 30 mg doses. Two studies have compared pioglitazone and rosiglitazone with respect to effects on lipids (see above).

SIDE EFFECTS, CONTRAINDICATIONS, INTERACTIONS, USE DURING PREGNANCY AND LACTATION

Hypoglycaemia, one of the main side effects of oral blood glucose lowering drugs, does not occur with TZDs, because they do not affect the secretion of insulin. Hypoglycaemia can occur in combination with other drugs, but in that case it is not due to the TZDs.

Although the hepatotoxicity of troglitazone has clearly been demonstrated,[8] it has been proven that rosiglitazone and pioglitazone are less associated with hepatotoxicity. In fact a slight improvement in liver enzyme values usually occurs, probably as a result of the reduction in the amount of liver fat.[6] Two large retrospective analyses showed that the use of pioglitazone or rosiglitazone over a period of one to two years was not associated with an increase in liver failure or hepatitis, in comparison with other oral blood glucose lowering drugs.[52,53] This does not detract from the fact that severe liver function disorders have been reported and described in the literature during the use of both agents,[54-56] including irreversible, lethal liver damage as a result of pioglitazone.[53] No publications have appeared on rosiglitazone in this respect, but the summary of product characteristics (SPC) text does state that a fatal outcome has been reported in rare cases. The Dutch Lareb Pharmacovigilance Centre has also registered reports of increases in the plasma concentration of liver enzymes. The SPC text still advises against administering TZDs to patients with an ALAT concentration that is increased to >2.5 times the upper limit of normal, and against prescribing it to patients who developed liver function disorders to another TZD.

The most important side effects of the TZDs are fluid retention and an increase in subcutaneous fat, which both contribute to the above-mentioned weight gain. It is not definitively known which part of weight gain is caused by fluid and which by fat. A recent study suggests that fluid accounts for as much as 75% of body weight increase,[57] although others have estimated fat as quantitatively the most important.[6] The quantity of fat in the visceral compartment and ectopic fat (liver and skeletal muscle) remain unaltered following the use of TZDs, or are even reduced.[6] The increase in body weight due to TZDs usually amounts to less than one kilogram after 16 weeks in people without diabetes, but it can be as much as 3 to 4 kg in patients with diabetes mellitus, particularly in combination with sulphonylurea derivatives or insulin. The larger the drop in HbA_{1c}, the larger the weight gain was.[58]

The pathogenesis of fluid retention under the influence of TZDs is largely unknown, and appears multifactorial.[39,43] Fluid retention can lead to oedema, thereby leading to heart failure.[59] The decrease in haematocrit level is also considered to be a result of the increase in plasma volume. In some patients this can result in frank anaemia, although not to a clinically relevant degree. Fluid retention, and the related increased risk of heart failure, occurs in particular when TZDs are combined with insulin. This combination is therefore contraindicated by the European Agency for the Evaluation of Medicinal Products (EMEA). Although fluid retention does occur with the present indications even when the contraindications are taken into consideration, the risk of clinical heart failure is limited, occurring in only a few percent of patients.[59] It should be realised that patients with type 2 diabetes are often elderly, with substantial comorbidity, related or not related to the diabetes. For example, caution will be required in dosing patients with hypertension, coronary heart disease, left ventricular hypertrophy, heart failure, aged >70 years, diabetes mellitus for more than ten years, use of insulin and chronic renal failure.[59]

In view of the fluid retention side effect, all forms of heart failure (New York Heart Association [NYHA] classes I to IV) are a contraindication for using TZDs, as is the combination with insulin. TZDs should be discontinued at the first signs of heart failure. Liver enzyme disorders are also a contraindication for the use of TZDs. For this

reason the plasma concentrations of gamma glutamyl transferase (γGT) and of ALAT should first be determined prior to treatment. In the case of fatty liver disease (hepatic steatosis), serum concentration of the ALAT enzyme is often already raised. In those cases, treatment with TZDs may improve liver steatosis. In practice, therefore, one might consider a TZD in the case of liver function disorders as a result of steatosis, as long as the liver enzymes are strictly monitored. The EMEA recently decided that the obligatory two-monthly liver function check-up could lapse. The advice to check liver function prior to therapy remains unchanged.

Pioglitazone is metabolised via CYP2C8, 3A4 and 1A1, rosiglitazone via CYP2C8 and 2C9. In theory, drug interactions are possible with drugs that have an inhibitory effect on CYP2C8, 2C9, and in the case of pioglitazone, on CYP3A4. Trimethoprim is an inhibitor of CYP2C8 and there is evidence that the chronic use of trimethoprim leads to a reduction in the clearance of rosiglitazone in healthy volunteers.[60,61] A reduction in the clearance of rosiglitazone was also observed in healthy volunteers during an interaction study with ketoconazol.[62] The reductions were 30 to 40% and 47% respectively. These interactions can be expected to lead to a drop in the blood glucose concentration in patients with type 2 diabetes mellitus treated by TZDs.

Rifampicin is a strong inducer of several CYP enzymes and in an interaction study with rosiglitazone, rifampicin doubled the clearance of rosiglitazone in healthy volunteers.[61,63] Therefore, this combination leads to a reduction in the effect of rosiglitazone.

On theoretical grounds, the simultaneous use of an NSAID and pioglitazone or rosiglitazone can increase the risk of oedema. Combining a TZD with insulin can – also on theoretical grounds – increase the risk of heart failure. Finally, gemfibrozil is known to increase[64] the plasma concentration of rosiglitazone.[65]

TZDs are contraindicated during pregnancy (class C evidence) based on the observations of growth retardation in animal studies.

FUTURE PERSPECTIVES

TZDs are not superior to other oral blood glucose lowering drugs with respect to their glycaemic effect. As such, conventional oral therapy will continue to be important in the treatment of type 2 diabetes mellitus as will combination therapy. A recent study from general practitioners in the Utrecht area of the Netherlands showed that standardised, protocol-based conventional care (including lifestyle education, oral medication and insulin), and the deployment of health visitors led to an appropriate glycaemic control for the majority of patients.[66-68]

The results of the first cardiovascular outcome study (PROactive) suggest that one of the TZDs has potential beneficial effects on cardiovascular disea se, but because of several limitations as described in the paragraph above, translation to clinical practice is limited. Even with these new data, metformin remains the first-choice drug because much more experience has been obtained with metformin, because metformin does not lead to weight gain and because the drug is much cheaper. According to this line of reasoning, TZDs will then become an alternative second-choice drug in patients with cardiovascular disease not being heart failure.[5] However, it is unclear whether the PROactive study results[1] can be extrapolated to the current population of type 2 diabetes, which is largely treated with statins or those without cardiovascular disease. In addition, it is unclear whether the results obtained with pioglitazone are drug specific or a class effect of TZDs. The results of other ongoing outcome studies[45-46] will hopefully reveal more information on this topic.

TZDs may also have a protective effect on the β-cell, either due to a reduction in the concentration of free fatty acids (reduced lipotoxicity) or via other mechanisms. In practice, this should result in a longer period on (mono)therapy before secondary failure. In the ADOPT (A Diabetes Outcome Progression Trial), the time to treatment failure will be compared between rosiglitazone, metformin and glibenclamide.[69] The results will become available by the end of 2006.

CURRENT PLACE OF TZDS IN DIABETES TREATMENT

At present, pioglitazone and rosiglitazone are approved[70] for the treatment of type 2 diabetes mellitus, either as monotherapy for patients (particularly in cases of obesity) who do not tolerate metformin or have a contraindication, or as combination therapy for patients who are already taking a sulphonylurea derivative and/or metformin. This implies that TZDs are not first-choice monotherapy.

With respect to the blood glucose lowering effect, TZDs are comparable with sulphonylurea derivatives and with metformin. The arguments for choosing one drug in preference to another will be addressed point-by-point. The drug acarbose will not be taken into consideration because the balance of efficacy *vs* side effects is considerably less favourable than with metformin and sulphonylurea derivatives. Neither will the meteglinides be taken into consideration because repaglinide is not reimbursed in the Netherlands and nateglinide is not marketed in the Netherlands.

Monotherapy

Metformin is the first choice for patients with type 2 diabetes mellitus and obesity who are insufficiently regulated by diet and lifestyle advice. The results of the

UKPDS study show that, in comparison with conservative treatment, intensive treatment with metformin is not only associated with a reduced risk of developing microvascular complications, but also with a significant reduction in cardiovascular morbidity and mortality.[71] This does require the administration of an adequate dose. Up till now metformin was the only blood glucose lowering drug that has convincingly shown a reduction in mortality.

It is estimated that about 15 to 20% of patients have an intolerance or contraindication to metformin and then the choice is between a sulphonylurea derivative and a TZD. There is little difference between the two drugs with respect to efficacy and weight gain. There are no studies that compare the TZDs and sulphonylurea derivatives with respect to cardiovascular mortality. Based on their mechanism of action and the limited evidence from the PROactive trial, TZDs and more particularly pioglitazone may have some advantage (positive effect on cardiovascular risk factors), whilst theoretically sulphonylurea derivatives can be disadvantageous (inhibition of cardioprotective mechanisms). However, tens of years of experience with sulphonylurea derivatives, their rapid onset of action, their favourable side effect profile and the lower costs are arguments in favour of sulphonylurea derivatives. In the future, the oral blood glucose lowering drugs may present themselves on the basis of their protective effect on β-cell function of the pancreas. Such an effect can be translated into a postponement of secondary failure.

Combination therapy

When a patient fails on monotherapy with sulphonylurea derivatives and there is an intolerance or a contraindication to metformin, then a TZD is the most obvious next step. The TZDs were originally approved for this indication. When a patient fails on monotherapy with metformin, a sulphonylurea derivative or a TZD can be prescribed. The arguments to choose a sulphonylurea derivative or a TZD are in fact similar to the situation of metformin intolerance (see previous paragraph). Because type 2 diabetes mellitus is a chronic and progressive disorder, an extra step in pharmacotherapy will be necessary every three to four years, and therefore the majority of patients will ultimately use a combination of drugs.[72]

Combination of three drugs

After some years, many patients will also fail on combination therapy, which in Europe will mainly consist of the combination of metformin with a sulphonylurea derivative. According to most guidelines, patients should then be treated with insulin therapy with continuation of metformin (and even also a sulphonylurea derivative). Theoretically, a TZD could also be added to the combination of metformin and sulphonylurea derivative (triple therapy). A number of studies have shown that triple oral therapy is effective,[20] and approximately as effective as addition of insulin, but not more cost-effective.[73-75]

Combination of TZDs with insulin

Because the combination of TZDs and insulin is associated with an increased risk for development of fluid retention and congestive heart failure, the combination is currently contraindicated in Europe. TZDs do improve glycaemic control in insulin-treated patients[76,77] although often at the expense of substantial weight gain. Use of the combination treatment (TZDs + insulin) thus appears limited and should be restricted to physicians experienced in diabetes treatment.

NOTE

This article is an adjusted version of a manuscript that has recently been published in the Netherlands Drug Bulletin (Geneesmiddelenbulletin) as: Thiazolidinedionderivaten bij diabetes mellitus type 2, Gebu 2005;39:107-15.

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