Troglitazone: Antihyperglycemic Activity and Potential Role in the Treatment of Type 2 Diabetes

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Insulin resistance is a major component of type 2 diabetes; therefore, an insulin sensitizer agent like the thiazolidinedione compound troglitazone is considered a very promising drug. Troglitazone exerts an antihyperglycemic activity in a dose-dependent manner between 200 and 600 mg/day in type 2 diabetic patients treated with diet alone, sulfonylureas, or insulin. Additive antihyperglycemic effect may also be obtained by combining troglitazone and metformin. The antihyperglycemic effect of troglitazone as monotherapy is rather modest (reduction of HbA_{1c} by 0.5–1.0%), but it appears to be somewhat greater when it is combined with other antidiabetic drugs. No double-blind studies have directly compared the activity of troglitazone with that of sulfonylureas or metformin. Troglitazone has been shown to exert additional beneficial effects on serum lipid profile and arterial blood pressure. It may be considered as a valuable alternative in insulin-resistant (obese and hyperinsulinemic) diabetic patients who appear to be the best responders to the drug. However, the efficacy of troglitazone is challenged by its safety profile, and the risk of hepatotoxicity still remains a major concern in clinical practice.

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Type 2 diabetes is a common disease that is associated with an increased risk of microangiopathy, cardiovascular diseases, and premature mortality. Hyperglycemia results from the combination of various defects in insulin secretion and insulin action, but insulin resistance obviously plays a crucial role in the disease (1–3). Despite the use of various antihyperglycemic drugs (4–7), most type 2 diabetic patients cannot achieve normoglycemia. In addition, nonglycemic risk factors associated with insulin resistance, such as dyslipidemia and arterial hypertension, further increase the overall risk of the majority of individuals with type 2 diabetes (8). The recently published U.K. Prospective Diabetes Study (UKPDS) demonstrated that in obese patients with type 2 diabetes, metformin, the compound that has the most favorable effect on insulin sensitivity, was associated with the most impressive reduction in morbidity and mortality rates when compared with other pharmacological strategies such as sulfonylureas and insulin, despite a similar degree of blood glucose control (9).

Considering this situation, the development of troglitazone, the first commercialized compound of a new antihyperglycemic pharmacological class (thiazolidinediones) able to sensitize tissues to insulin action, should be considered as promising and maybe as major progress in the treatment of type 2 diabetes (10–14). The main goals of the present review are *1*) to analyze the results of the clinical trials comparing the antihyperglycemic activity of troglitazone with that of placebo or other oral antihyperglycemic agents in type 2 diabetic patients and 2) to review the other potential positive and negative effects of troglitazone to attempt to more precisely define the potential place of this drug in the overall pharmacological strategy of type 2 diabetes.

TROGLITAZONE AS AN INSULIN SENSITIZER COMPOUND

— Thiazolidinediones are a new class of pharmacological compounds that work by enhancing insulin action, thus promoting glucose utilization in peripheral tissues, possibly by stimulating nonoxidative glucose metabolism in muscle, and suppressing gluconeogenesis in the liver. They are known as "insulin sensitizers" (10–15). Thiazolidinediones act through a novel receptor called peroxisome proliferator-activated receptor-γ (PPAR-γ), a member of the nuclear hormone receptor superfamily. PPAR-γ enhances the expression of a number of genes encoding proteins involved in glucose and lipid metabolism (11,16). Thiazolidinediones stimulate adipogenesis and reduce plasma triglyceride and free fatty acid concentrations. Stimulation of PPAR-γ may decrease the release by the adipocytes of various signaling molecules, such as free fatty acids, leptin, and tumor necrosis factor-α (TNF-α), which all are able to counteract the hypoglycemic action of insulin (16). At present, however, it is unclear whether the beneficial effects of troglitazone on glucose tolerance and insulin sensitivity result secondarily from the alterations in lipid metabolism or represent a direct action on the insulin receptor signal-transduction system or intracellular glucose metabolism in skeletal muscle (16).

Troglitazone, the most studied compound among thiazolidinediones (17–24), has been shown to improve insulin sensitivity and glucose tolerance in nondiabetic individuals characterized by marked insulin resistance (25): obese patients, subjects with impaired glucose tolerance, women with polycystic ovary syndrome, women with previous gestational diabetes, and subjects with Werner syndrome (26,27). Interestingly enough, several components of the insulin resistance syndrome, e.g., lipid abnormalities and arterial hyper-

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Abbreviations: ALT, alanine transferase; FDA, U.S. Food and Drug Administration; FPG, fasting plasma glucose; PPAR-γ, peroxisome proliferator-activated receptor-γ.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

tension, appear to also be improved by troglitazone in insulin-resistant individuals (17–27). In addition, other properties have been described, such as antioxidant effects as shown in vitro, but their role in vivo and clinical significance still remain poorly understood (28).

When glucose turnover and insulin action have been evaluated in patients with type 2 diabetes before and after troglitazone therapy, elevated rates of hepatic glucose production were 15–30% lower, and peripheral insulin action, as assessed during a euglycemic-hyperinsulinemic clamp, improved by ~40–60% (14,20,22,23,29). In addition, recent studies suggested that troglitazone may also improve β-cell function, although it is unclear whether this could be due to a direct effect of the drug or rather to an indirect action attributed to a reduction of glucotoxicity (30,31).

CLINICAL PHARMACOLOGY OF TROGLITAZONE

— The pharmacodynamic and pharmacokinetic properties of troglitazone have been extensively described in a recent review (24). Bioavailability of troglitazone is ~50% and is increased by 35–80% when taken with food (32). Like other thiazolidinediones, troglitazone is strongly lipophilic, is almost completely bound to plasma proteins, is extensively metabolized by the liver, and is eliminated predominantly via bile and feces. The hepatic metabolites of troglitazone are a sulfate conjugate and a glucuronide metabolite (both inactive) and a quinone metabolite (active). The drug has a sufficiently long elimination half-life (9–34 h) to allow for once-daily administration (20,24). Age, body weight, type 2 diabetes, and ethnic group do not have a clinically significant effect on the pharmacokinetics of troglitazone (33,34). In patients with hepatic insufficiency, a reduced capacity to eliminate troglitazone metabolites was observed (35), but troglitazone is not recommended for use in this patient population (see below).

Because troglitazone is almost completely bound to plasma proteins and is metabolized by the liver, the problem of possible drug interactions deserves much attention (24). Displacement interactions between troglitazone and other drugs with high plasma protein binding, such as warfarin and glibenclamide, do not appear to occur. Concomitant administration of cholestyramine and troglitazone should be avoided, since this reduces the absorption of troglitazone by ~70%. Troglitazone is not metabolized by the cytochrome P450 (CYP) 3A isoenzyme pathway. Nevertheless, it appears to decrease plasma concentrations of various CYP3A4 substrate drugs, such as terfenadine, cyclosporine, and both ethinyloestradiol and norethindrone, suggesting that it may act as an inducer of CYP3A4 (24). These findings should be considered when troglitazone is prescribed with other CYP3A4 substrates, such as some statins. No pharmacokinetic interferences were reported between troglitazone and paracetamol or digoxin. Although animal studies failed to demonstrate any teratogenic effects of troglitazone, use of this drug in pregnant women is not recommended.

ANTIHYPERGLYCEMIC ACTIVITY OF TROGLITAZONE IN TYPE 2 DIABETES

Troglitazone versus no treatment or placebo

Troglitazone in diet-treated patients. Numerous open or placebo-controlled studies have shown that troglitazone, at doses from 200 to 800 mg/day, can improve indices of glucose control, especially fasting plasma glucose (FPG) and HbA_{1c} levels, in patients with type 2 diabetes not well controlled by diet alone (31,33–48): reductions of FPG between 0.9 and 3.9 mmol/l and of HbA_{1c} between 0.4 and 1.1% (−2.1% in one trial [29]) have been reported (Table 1). It is noteworthy, however, that some clinical studies have pointed out that only 50–75% of the diabetic patients are good responders to troglitazone: these individuals (more often women and patients of older age) (49) are characterized by higher FPG concentrations, BMI values, and fasting plasma insulin (or C-peptide) levels than nonresponders, suggesting the presence of greater insulin resistance (38,40,49). Furthermore, all these trials are of rather short duration (maximum 26 weeks) when compared with the chronicity of the disease that requires a lifelong treatment, and the rate of secondary failure to the drug is presently unknown.

A few studies compared the antihyperglycemic effects of various doses of troglitazone and generally found a dose-response relationship between 100 and 800 mg/day (31,44,46), except in the European multicenter trial where doses of 200, 400, 600, and 800 mg were found almost equipotential (41). Table 2 summarizes the changes in FPG and HbA_{1c} levels with doses of 100, 200, 400, 600, and 800 mg troglitazone in all trials performed in diet-treated type 2 diabetic patients. When compared with placebo (or no treatment), no significant changes were observed with the lowest dose of 100 mg troglitazone per day; in contrast, all higher doses induced significant reductions in FPG and HbA_{1c} levels. Such a meta-analysis suggests that daily doses of 200 and 400 mg troglitazone have almost the same antihyperglycemic effect but that higher doses (600–800 mg/day) of troglitazone exert a more potent hypoglycemic action.

Troglitazone combined with sulfonylureas. Several studies analyzed the effects of combining troglitazone (200–800 mg/day) with sulfonylureas in type 2 diabetic patients (36,37,50–53) (Table 3). Such a combination makes sense because sulfonylureas will potentiate insulin secretion while the thiazolidinedione compound will enhance cellular insulin action. All trials demonstrated significant diminutions in FPG (between 1.3 and 4.4 mmol/l) and HbA_{1c} (between 0.2 and 2.6%) levels. Two large studies reported a clear-cut dose-response relationship between the daily doses of troglitazone—400, 600, and 800 mg (51) or 200, 400, and 600 mg (52)—and the glucose-lowering activity of the drug.

Interestingly, comparative analysis of the results of Table 1 (troglitazone alone) with those of Table 3 (troglitazone combined with sulfonylureas) suggests that troglitazone exerts a more potent antihyperglycemic activity when it is used together with sulfonylureas, which stimulate insulin secretion, rather than when it is prescribed alone in diet-treated diabetic patients. However, such a conclusion contrasts with the results from an analysis of 10 clinical studies carried out in Japan on 604 type 2 diabetic patients showing that the percentage decrease in FPG after treatment does not differ between groups treated with troglitazone alone (−14.7%) and those treated with troglitazone in combination with sulfonylureas (−15.5%) (49).

Troglitazone combined with metformin. The combination of troglitazone and metformin is very attractive because both agents target insulin resistance and may have additive glucose-lowering effects (54). In a recent open-label study, 29 obese type 2 diabetic patients with secondary failure to sulfonylureas were allocated to either troglitazone (400 mg/day) or metformin (2,000 mg/day) for 3 months (45). Subsequently, the other drug was added for another 3 months. After

Table 1—*Characteristics of the most important clinical trials (open or controlled versus placebo) studying the effects of troglitazone in patients with type 2 diabetes treated with diet alone*

References	*n*	Duration (weeks)	Controlled study (yes/no)	Dose (mg/day)	Fasting plasma glucose (mmol/l)	Fasting plasma insulin (pmol/l)	HbA_{1c} (%)
Iwamoto et al. (36)	8	12	No	400	−2.5	−4	−0.7
Kuzuya et al. (37)	36	12	No	200–400	−2.2	?	−0.4
Suter et al. (38)	11	6–12	No	400	−1.8	−84	?
Mimura et al. (39)	8	12	Yes	400	−1.4	−20	−2.1
Iwamoto et al. (40)	136	12	Yes	400	−1.1	?	−0.5
Kumar et al. (41)	282	12	Yes	200–800	−2.5 to −3.5	−6 to 18	−0.5 to 1.1
Sironi et al. (42)	25	8	Yes	200	−1.9	NS	?
Leutenegger et al. (43)	59	16	Yes	200	−1.4	NS	−0.6
Maggs et al. (44)	77	26	Yes	100–600	−2.3 to −3.9	−50	?
Inzucchi et al. (45)	13	12	No	400	−3.0	NS	NS
Prigeon et al. (31)	14	12	Yes	200–800	−0.9	−10	?
Fonseca et al. (46)	322*	26	Yes	200–600	−2.3 to −3.3	−16 to 44	−0.4 to 1.1
Cominacini et al. (47)	18	8	Yes	200	−2.1	?	−0.5
Kumar et al. (48)	179	12	Yes	400–800	−2.6 to −3.2	−20 to −22	−0.4 to −1.1

*Among whom 81 patients received 100 mg/day troglitazone without any significant improvement. Whenever possible, changes are expressed as delta versus placebo in placebo-controlled studies and in delta versus baseline values in noncontrolled studies.

an initial 20–25% reduction in fasting and postprandial plasma glucose levels with each monotherapy, the combination therapy caused a further reduction in FPG of 2.3 mmol/l and of HbA_{1c} by 1.2% (Table 3). If confirmed by double-blind studies involving a larger sample size, these results offer promise of a new therapeutic strategy in the treatment of type 2 diabetic patients. Furthermore, this trial suggests that the two pharmacological agents have additional antihyperglycemic action through complementary mechanisms: troglitazone mainly acts by stimulating glucose utilization by the peripheral tissues whereas metformin essentially acts by inhibiting glucose production by the liver (45).

Troglitazone combined with acarbose. No single study has investigated yet the potential interest of combining troglitazone with an intestinal α-glucosidase inhibitor such as acarbose or miglitol.

Troglitazone combined with insulin. Some studies have investigated the potential interest of combining troglitazone (200–600 mg/day) with insulin in insulin-requiring type 2 diabetic patients (55–57). The addition of troglitazone significantly improved blood glucose control (55) and/or allowed a marked reduction (~30%) of daily insulin needs (56), depending on the priority objectives of each trial (Table 4). In one study (55), the main objective was to improve blood glucose control by adding troglitazone to insulin: a significant reduction in FPG and HbA_{1c} levels was observed, in spite of a modest reduction in insulin doses. In another study (56), the main objective was to test the insulin-sparing effect of troglitazone without deterioration of blood glucose control: insulin doses could be reduced by 41% with 200 mg troglitazone and by 57% with 400 mg troglitazone when compared with a modest diminution of 18% with placebo. One single open study has shown that the insulin-sparing effect of troglitazone was dose-dependent between 200 and 600 mg/day and persisted in the long-term, up to 16–22 months (57).

Troglitazone versus other oral antidiabetic agents

Interestingly, the insulin-sparing effect of troglitazone in insulin-requiring type 2 diabetic patients has also been reported with sulfonylureas, metformin or acarbose (6) and appears to be of the same order of magnitude with the thiazolidinedione compound as with other oral antidiabetic agents. It is noteworthy, however, that very few (and all open-label) studies have directly compared the efficacy of troglitazone with that of classical oral antidiabetic agents. Obviously, definite conclusions could only be drawn after performing well-designed comparative controlled studies.

Troglitazone versus sulfonylureas. Direct comparison between troglitazone and sulfonylureas has been performed in only two open clinical trials using glyburide (glibenclamide) as reference (52,58) (Table 5). Both enrolled a large number of patients who were followed up

Table 2—*Relationship between the daily dose of troglitazone and its antihyperglycemic effect in type 2 diabetic patients treated with diet alone*

Daily dose of troglitazone (mg)	References	Mean changes in fasting plasma glucose (mmol/l)	Mean changes in HbA_{1c} (%)
100	44,46	−0.82 (97)	+0.10 (81)
200	31,41–44,47	−2.11 (256)	−0.64 (208)
400	31,38–40,45,48	−2.19 (462)	−0.60 (434)
600	31,41,44,46	−3.37 (152)	−0.99 (127)
800	31,41,48	−3.18 (183)	−0.83 (179)

Data are means (number of subjects included in the analysis). Mean changes are expressed as delta versus placebo in placebo-controlled studies and in delta versus baseline values in noncontrolled studies. NS for the dose of 100 mg/day; $P < 0.001$ for doses of 200, 400, 600, and 800 mg/day.

Table 3—*Characteristics of the main clinical trials studying the antihyperglycemic effects of troglitazone in patients with type 2 diabetes already treated with another antihyperglycemic oral agent*

References	*n*	Duration (weeks)	Controlled study (yes/no)	Dose (mg/day)	Fasting plasma glucose (mmol/l)	HbA_{1c} (%)
Sulfonylurea plus troglitazone						
Iwamoto et al. (36)	11	12	No	400	−2.7	−0.6
Kuzuya et al. (37)	110	12	No	200–400	−2.0	−0.9
Iwamoto et al. (50)	122	12	Yes	400	−1.8	−0.9
Corréa et al.* (51)	59	12	Yes	400	−1.9	−0.4
	55	12	Yes	600	−2.7	−0.6
	52	12	Yes	800	−3.0	−0.8
Horton et al. (52)	78	52	No	200	−3.0	−1.6
	76	52	No	400	−3.4	−1.8
	80	52	No	600	−4.4	−2.6
Buysschaert et al. (53)	84	16	Yes	100	−1.3	−0.3
	90	16	Yes	200	−2.5	−0.2
Metformin plus troglitazone						
Inzucchi et al. (45)	29	12	No	400	−2.3	−1.2

Whenever possible, changes are expressed as delta versus placebo in placebo-controlled studies and in delta versus baseline values in noncontrolled studies. *About 30% of the patients included in this study were treated with diet alone.

to 48–52 months. In one study, the antihyperglycemic activity of 800 mg/day troglitazone was similar to that of a titrated dose of glyburide (up to 20 mg/day) (58). In the other trial, 400–600 mg troglitazone appeared to be equipotent to a fixed dose of 12 mg glyburide, whereas a smaller dose of 200 mg troglitazone was clearly less effective (52). The results are, however, difficult to interpret because diabetic patients were treated with sulfonylureas before randomization and not adequately controlled with such treatment, which may represent a selection bias. Furthermore, before inclusion, they had a 2-week washout period in one study (58) but not in the other (52), which probably explains opposite changes after randomization: improvement of blood glucose control in the former study (58) but deterioration in the latter (52) (Table 5). Finally, in a large multicountry double-blind controlled clinical trial published only as an abstract (59), 786 type 2 diabetic patients were randomized to receive 100, 200, or 600 mg troglitazone or glibenclamide titrated to optimal effect (final dose not mentioned) for 1 year. After 6 months, FPG levels were significantly higher with 100 mg/day troglitazone (+11%, $P < 0.001$) and 200 mg/day troglitazone (+8%, $P < 0.01$) when compared with the corresponding values with glibenclamide, while those measured with 600 mg/day troglitazone were similar (+3%, NS).

Troglitazone versus metformin. Only two short-term open-label studies compared the antihyperglycemic activity of troglitazone with that of metformin, and both included a small number of type 2 diabetic patients (45,60) (Table 5). In one trial, a single daily dose of 400 mg troglitazone improved blood glucose control in a similar fashion as metformin at a dose of 2 × 1,000 mg/day: after 12 weeks, both drugs lowered the fasting and postprandial plasma glucose levels by ~20–25% (45). In another 12-week parallel study, 400 mg troglitazone was as effective as 500 mg metformin, although the decrements in HbA_{1c} levels were significantly greater in the metformin group at 4 and 8 weeks after the initiation of treatment, despite the low dose of metformin used in that study (60). Further evaluation can be obtained from indirect comparisons of placebo-controlled studies using either metformin or troglitazone: metformin 1,500–3,000 mg/day decreased FPG by 0.5–4.8 mmol/l and HbA_{1c} by 0.8–2.0% in diet-treated type 2 diabetic patients (61,62), and these decrements are of the same order of magnitude as those reported with 200–800 mg/day troglitazone (Table 1). The positive effects on glucose control of adding troglitazone to either sulfonylurea (Table 3) or insulin (Table 4) in patients with type 2 diabetes not adequately controlled with monotherapy also appear similar to those of adding metformin (61,62).

Troglitazone versus acarbose. No controlled study compared the clinical efficacy of troglitazone with that of an intestinal α-glucosidase inhibitor such as acarbose or miglitol in type 2 diabetic patients. Indirect

Table 4—*Characteristics of the main clinical trials studying the antihyperglycemic effects of troglitazone in patients with type 2 diabetes treated with insulin after failure of oral treatment*

References	*n*	Duration (weeks)	Controlled study (yes/no)	Dose (mg/day)	Fasting plasma glucose (mmol/l)	HbA_{1c} (%)	Daily insulin dose (%)
Insulin plus troglitazone							
Schwartz et al. (55)	116	26	Yes	200	−1.9	−0.8	−12
	116	26	Yes	600	−2.7	−1.4	−30
Buse et al. (56)	75	26	Yes	200	NS	NS	−23
	76	26	Yes	400	−1.2	−0.3	−39
Fonseca et al. (57)	99	82	No	200	−1.4	−0.7	−18
	94	57	No	400	−2.2	−1.0	−21
	93	86	No	600	−1.7	−1.0	−38

Whenever possible, changes are expressed as delta versus placebo in placebo-controlled studies and in delta versus baseline values in noncontrolled studies.

Table 5—*Characteristics of four open-label randomized parallel clinical trials comparing the antihyperglycemic effects of troglitazone with those of either glyburide (glibenclamide) or metformin in patients with type 2 diabetes previously treated with sulfonylureas*

References	*n*	Duration (weeks)	Drug	Dose (mg/day)	Fasting plasma glucose (mmol/l)	HbA_{1c} (%)
Troglitazone versus sulfonylurea						
Ghazzi et al. (58)	77	48	Troglitazone	800	−2.2	−0.5
	77	48	Glyburide	Titrated (→20 mg/day)	−2.7	−0.2
Horton et al. (52)	78	52	Troglitazone	200	+2.3	+1.92
	76	52	Troglitazone	400	+1.1	+0.85
	80	52	Troglitazone	600	+0.6	+0.93
	79	52	Glyburide	12	+1.2	+0.90
Troglitazone versus metformin						
Inzucchi et al. (45)	13	12	Troglitazone	400	−3.0	NS
	15	12	Metformin	2,000	−3.2	NS
Imano et al. (60)	17	12	Troglitazone	400	−2.1	−0.6
	13	12	Metformin	500	−0.9	−0.9

No significant differences were noticed between 400–800 mg/day troglitazone and 12–20 mg/day glyburide on the one hand and between 400 mg/day troglitazone and 500–2,000 mg/day metformin on the other. Changes are expressed versus baseline values obtained in patients on sulfonylurea therapy in various conditions: 2 weeks of wash-out (45,58), stopping of 12 mg/day glyburide just before randomization (52), and maintenance of baseline sulfonylureas throughout the study (60).

comparison in diet-treated individuals suggests, however, that the reductions in FPG levels might be greater with 200–800 mg/day troglitazone (−0.9 to 3.9 mmol/l) (Table 1) than with 150–600 mg/day acarbose (−0.6 to 2.1 mmol/l) (63,64), whereas reductions in HbA_{1c} levels appear to be similar (−0.4 to 1.1% vs. −0.5 to 1.3%, respectively), suggesting a more prominent action of acarbose on postprandial glucose control. Comparable efficacy on HbA_{1c} levels was also obtained with troglitazone (Table 3 and Table 4) and with acarbose (63,64) in sulfonylurea-treated or insulin-treated type 2 diabetic patients.

OTHER EFFECTS OF TROGLITAZONE IN TYPE 2 DIABETES

Favorable effects

Besides its antihyperglycemic activity, troglitazone may modify other macrovascular risk factors in patients with type 2 diabetes (59,65).

Lipid profile. Reductions of plasma free fatty acid and triglyceride levels, sometimes accompanied by a significant increase in HDL cholesterol concentration, have been reported in diet-treated or sulfonylurea-treated diabetic patients receiving 400–800 mg/day of troglitazone (38–41,43,46,48,52,58), but not in those treated by a smaller dose of 100–200 mg/day (41,42,44,46). Recent observations reported significant increases in HDL cholesterol levels even when plasma glucose levels did not improve, suggesting the possibility that troglitazone might have a direct effect on HDL metabolism (66). Troglitazone was unable to affect triglyceride concentrations in insulin-treated type 2 diabetic patients (55,56). As far as total and LDL cholesterol levels are concerned, modest, although significant, increases were described in most studies (41,46,52–58). However, because troglitazone also has been shown to reduce oxidation of LDL lipoproteins (47,67,68), at least in vitro (28), and to decrease small dense LDL concentrations (69), the final influence of such a small rise in LDL remains unclear. Finally, a study in a Japanese diabetic population has shown a 140% increase in lipoprotein(a) levels after 4 weeks of troglitazone therapy (70). However, a much smaller (11%), albeit significant increase, was observed in a recent noncontrolled study (71). Such possible interference of troglitazone with lipoprotein (a) metabolism deserves further consideration.

Arterial hypertension. About half of the patients with type 2 diabetes have arterial hypertension and the latter appears to be partially associated with insulin resistance (8). Troglitazone at a dose of 400 mg/day did not significantly change systolic and diastolic arterial blood pressure in normotensive type 2 diabetic patients (40), but has been shown to improve blood pressure control of hypertensive diabetic patients, in parallel with the diminution of fasting plasma glucose and insulin levels (72). In a large cohort of normotensive patients with type 2 diabetes, a modest, although significant, reduction in diastolic blood pressure was observed with a higher dose of 800 mg/day troglitazone, together with an improvement of left ventricular function attributed to a decrease in systemic vascular resistance (58).

One recent study reported that 400 mg/day troglitazone for 12 weeks ameliorated microalbuminuria in type 2 diabetic patients with incipient nephropathy (60). Such a reduction in microalbuminuria was not observed with 500 mg/day metformin, despite a similar blood glucose improvement, which may suggest that troglitazone has some effects on vascular cells other than lowering plasma glucose levels (60). Similar observations were made in a large study comparing the changes in blood glucose control and microalbuminuria in type 2 diabetic patients randomized to either troglitazone (600 mg) or glibenclamide for 6 months (59).

Fibrinolysis, coagulation, and endothelial cell activation. A recent pilot study performed in 18 patients with type 2 diabetes treated by diet or insulin demonstrated that the addition of troglitazone for 26 weeks was associated with a significant 40% fall in plasma plasminogen activator inhibitor (PAI-1) antigen concentrations (73). In contrast, there was no significant change in plasma prothrombin fragment F1+2, von Willebrand factor, and fibrinogen levels.

These observations, which should be verified in larger trials, suggest that troglitazone may have a beneficial effect on fibrinolysis without any detectable effect on activated coagulation. A recent in vitro study showed that troglitazone, as vitamin E but not pioglitazone, has a potent inhibitory effect on platelet aggregation via suppression of the thrombin-induced activation of phosphoinositide signaling in human platelets (74). Finally, troglitazone (200 mg once daily) has been shown to decrease circulating E-selectin levels, a marker of endothelial cell activation, in type 2 diabetic patients (47). This ability and its correlation with the reduction of LDL oxidation suggest that troglitazone has the potential to delay certain atherogenic activities in patients with type 2 diabetes (47). Preliminary observations from a Japanese group showed that troglitazone treatment (400 mg for 3 months) may decrease the intimal and medial complex thickness of common carotid artery in type 2 diabetic patients, independently of the decline in HbA_{1c} levels, suggesting an inhibitory action of troglitazone on atherosclerosis (75).

Unfavorable effects

Weight gain. Because of its stimulatory effect on PPAR-γ, troglitazone may stimulate adipogenesis and promote weight gain (16). A recent open-label study performed in 20 type 2 diabetic patients demonstrated that troglitazone reduced circulating leptin levels, increased hunger, and promoted weight gain (76). Weight increase during clinical trials performed in diet-treated or sulfonylurea-treated type 2 diabetic patients was not significant (41,43,44,46,48) or only modest (40,53). Nevertheless, a Japanese group reported a significant weight gain when troglitazone (400 mg/day) was added to sulfonylureas for 12 weeks (50). In contrast, in a recent double-blind randomized 12-week trial, treatment with troglitazone at a dose of 600 mg/day decreased intra-abdominal fat mass but did not affect total body fat or weight of type 2 diabetic patients (77). However, it should be pointed out that no controlled study lasted more than 6 months so that long-term progressive weight increase could not be ruled out. In the study with the longest duration (52 weeks), performed in a large cohort of type 2 diabetic patients, a significant dose-dependent weight gain (+2.9, +3.9, and +6.5 kg, respectively) was noticed when 200, 400, or 600 mg/day troglitazone was added to 12 mg/day glyburide (52). If confirmed, progressive weight increase may partially counteract the short-term favorable effects of troglitazone on insulin sensitivity.

Liver toxicity. Hepatotoxicity has proved to be the main clinical concern with troglitazone (78–80). After several reports of severe liver damage in patients taking the drug, strict rules of use were recommended in Japan and the U.S. (see below) (81), and troglitazone's launch was postponed in Europe (after being voluntarily withdrawn from the U.K. market in late 1997). A recent analysis of all phase III placebo-controlled studies indicated that an increase of serum liver enzyme alanine transferase (ALT) levels more than threefold above the upper normal range values was observed in 1.9% of the patients receiving troglitazone (n = 2,510) versus 0.6% of the patients receiving placebo (n = 475) (78). While such liver disturbance is usually mild, asymptomatic, and reversible after stopping exposure to the drug, troglitazone can, in exceptional cases, induce severe damage resulting in fulminant hepatitis and death (82–84) or liver transplantation (85). In most cases, fatal outcomes have been attributed to "idiosyncratic hepatotoxicity," occurring within the first 6 months of therapy. In several patients, the transition from normal to irreversible liver damage occurred within 4–34 days.

Through 5 June 1998, the U.S. Food and Drug Administration (FDA) received 560 reports of troglitazone-associated hepatotoxicity, among which there were 24 cases of liver failure (21 deaths and 3 liver transplants) in which troglitazone appeared to be the likely cause (80). At the end of November 1998, the U.S. manufacturer stated that there had been 26 reports of liver-related deaths and 4 separate reports of liver transplantation in the U.S., thus 0.0022% of >1.4 million troglitazone-treated patients (24). This translates into an incidence of troglitazone-related death or liver transplant of ~1 case in 50,000 patients. No obvious predisposing features, other than initial abnormal liver function, have been recognized. Thus, hepatic impairment must be ruled out before starting troglitazone therapy. Patients with a serum ALT level >1.5 times the upper limit of normal values should be excluded as well as patients with previous history of liver disease or those using multiple drug therapies or who have concurrent conditions that could potentially compromise hepatic function. The U.S. labeling now also requires that liver function (e.g., ALT) is checked monthly for the first 8 months of troglitazone treatment, every 2 months for the remainder of the first year, and at intervals thereafter. If patients on troglitazone have moderately elevated ALT levels (1.5–2 times the upper limit of normal), they should be monitored weekly until ALT levels return to normal, and the drug should be discontinued if ALT concentrations rise to >3 times the upper limit of normal (80,81). Provisional evidence suggests indeed that the abnormal liver function is reversible within a few weeks, provided the condition is detected early and the drug is stopped (78,86). A recently published evaluation of 35 cases of liver dysfunction in Japan indicated that elevation of liver enzymes typically occurred within 2–5 months of starting troglitazone treatment and that, upon discontinuation of the drug, liver enzyme levels generally declined rapidly, usually to less than half of the peak level within 4 weeks (24,87). Focusing specifically on liver-related deaths, the risk associated with troglitazone therapy appears to have steadily declined from 1 in 36,000–44,000 before the inclusion in liver enzyme monitoring to ~1 in 57,000–100,000 among patients beginning therapy after the incorporation of a boxed warning and increased monitoring requirements in the product labeling in 1998 (24,88). However, there is disagreement as to the exact number of "validated" deaths associated with troglitazone in the U.S. (88). It should be noted that most, but not all (83–86), of these serious events occurred in patients with complex medical histories, including potentially confounding medical conditions or medications that have been associated with liver dysfunction (24). The FDA in the U.S. maintains that the benefits of troglitazone outweigh its risk in patients with type 2 diabetes, but will continue to closely monitor the rate of liver dysfunction in patients treated with troglitazone.

Because of such potential severe liver toxicity, the future of troglitazone as an antidiabetic oral agent remains hypothetical (79,88,89). Whether thiazolidinediones will adversely affect liver function as a class effect in humans is yet uncertain, since preclinical studies have not been predictive. Thus, future experience with other compounds such as rosiglitazone or pioglitazone is needed to answer this crucial question.

PLACE OF TROGLITAZONE IN THE TREATMENT OF TYPE 2 DIABETES

— Various pharmacological approaches can be used to improve glucose

homeostasis (4–7). They act via different modes of action: *1*) sulfonylureas essentially stimulate insulin secretion; *2*) biguanides (metformin) act by promoting glucose utilization, reducing hepatic glucose production and diminishing intestinal glucose output; *3*) α-glucosidase inhibitors (acarbose, miglitol) slow down carbohydrate digestion and consequently absorption from the gut and reduce postprandial hyperglycemia; and *4*) insulin stimulates tissue glucose utilization and inhibits hepatic glucose output. These pharmacological treatments may be used individually for certain types of patients or may be combined in a stepwise fashion to provide more ideal glycemic control for most patients. Selection of oral antihyperglycemic agents as first-line drug or combined therapy should be based on both the pharmacological properties of the compounds (efficacy and safety profile) and the clinical characteristics of the patients (stage of the disease, body weight) (90). Furthermore, because cardiovascular disease is the major clinical outcome in type 2 diabetes, antidiabetic agents that also improve the cardiovascular risk profile by decreasing insulin resistance may be considered as an interesting alternative to agents that stimulate endogenous insulin production (9,65,91).

Troglitazone may be theoretically used for treating patients with type 2 diabetes, after diet failure, in combination with sulfonylureas or even metformin, or, at a later stage, in combination with insulin (90) (Fig. 1). Troglitazone should still find its best place in the pharmacological strategy of type 2 diabetes. Whereas it has proven its efficacy as monotherapy in insulin-resistant patients with impaired glucose tolerance or only mild hyperglycemia, the FDA recently recommended that troglitazone should not be used as first-line treatment because of safety reason (liver toxicity). In contrast, the FDA still considers the benefits outweigh the risks in most instances as second-line treatment in combination with sulfonylureas or insulin in patients with refractory hyperglycemia (88). The efficacy of troglitazone has been reported in both nonobese and obese individuals, even if patients with higher BMI appear to have higher response rates to the drug (38,40,49). Its efficacy has not been specifically evaluated in different ethnic groups, and it is not known whether patients of black-African origin, many of whom have more β-cell failure than insulin resistance, respond as well as other individuals to the thiazolidinedione compound. Because of its pharmacodynamic and pharmacokinetic properties (24), troglitazone may be especially suited for treating elderly patients with type 2 diabetes (92). In an analysis of 10 clinical studies on troglitazone carried out in Japan, the percentage decrease in FPG was positively correlated with older age (49). Both the efficacy and safety of troglitazone were confirmed in a large European study of 229 elderly (mean age 75 years; range 69–85) patients receiving 400 or 800 mg/day troglitazone for 12 weeks (48).

As would be expected from its mechanism of action, patients receiving troglitazone as monotherapy (in contrast to those receiving sulfonylureas) are not at risk of developing hypoglycemia; however, hypoglycemic episodes have been reported in some studies in which troglitazone was used in combination with a sulfonylurea agent (50) or with insulin (55–57), necessitating a reduction in the doses of the other hypoglycemic compound. Troglitazone also has the advantage of being well tolerated from a gastrointestinal point of view (in contrast to α-glucosidase inhibitors and, in some individuals, to metformin), and of being safe in diabetic patients with renal insufficiency (in contrast to sulfonylureas and metformin) (20,24,92). As already pointed out, the main concern of troglita-

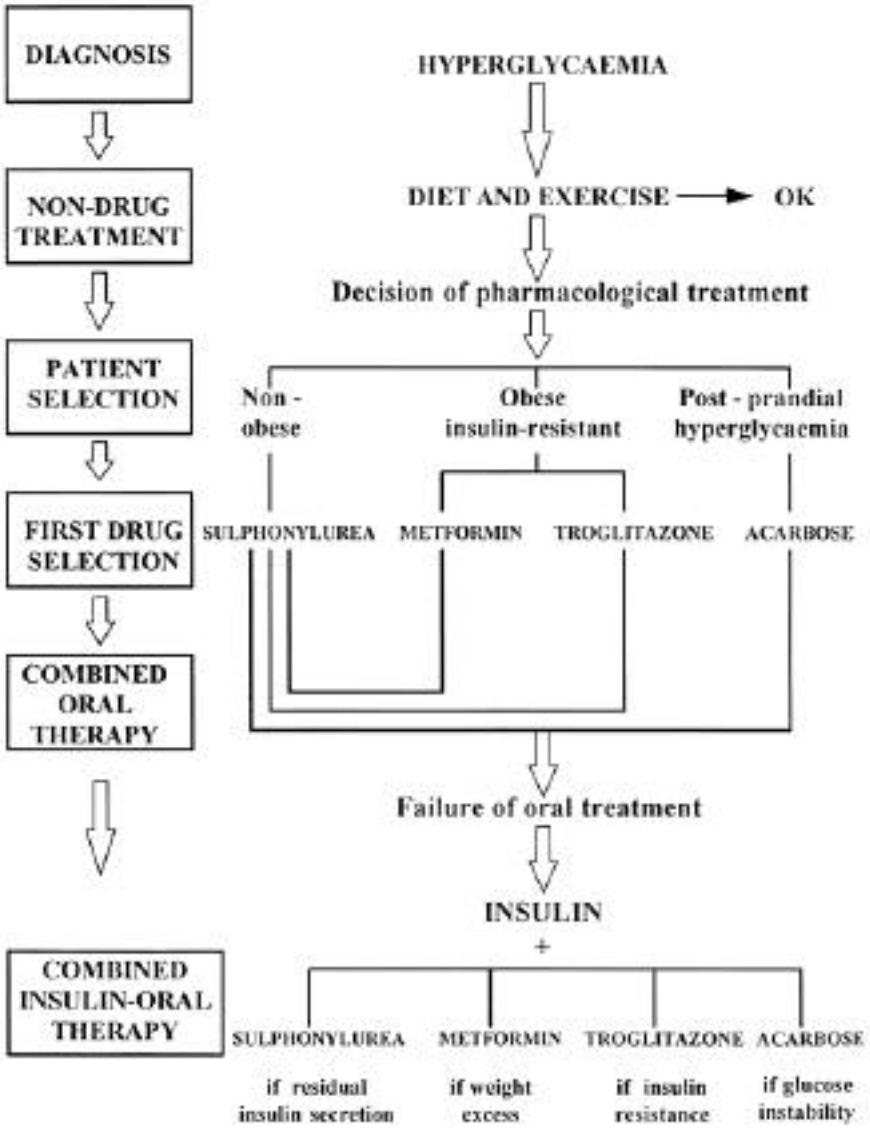

Figure 1—*Stepwise treatment of type 2 diabetes: a guide to selection of oral antihyperglycemic agents and potential place of troglitazone (reprinted with permission from Scheen and Lefèbvre [90]).*

zone use is the risk of liver toxicity. Safety rules of prescription (check of liver enzymes before and careful monitoring during treatment) may raise some difficulties in daily clinical practice. Indeed, mild abnormal liver function is not uncommon in type 2 diabetic patients (93) because of frequent mild steatosis due to obesity, hypertriglyceridemia, alcohol consumption, and/or inadequate blood glucose control.

The time course of onset of action of troglitazone can be variable but seems slower than that of other antihyperglycemic agents: it generally requires 1–4 weeks of therapy for initial plasma glucose– and insulin-lowering effects, with maximal responses after 6–8 weeks. Most studies indicated that the lowest efficacious daily dose of troglitazone is 200 mg; most of them suggested a greater effect with a daily dose of 400 mg and an even greater antihyperglycemic effect with a daily dose of 600–800 mg (17–24,94). Mild weight gain has been reported in some short-term studies, a finding which requires further evaluation in the long-term. An intriguing aspect of troglitazone therapy is the fact that some (~30%) patients with type 2 diabetes fail to respond to the drug when troglitazone is provided either as monotherapy or added to sulfonylurea treatment failures. Nonresponders, who are generally less overweight and have lower plasma insulin (or C-peptide) levels, may be characterized by more profound defects in insulin secretion rather than increased insulin resistance (38,40,44,49).

Thus, crucial objectives when prescribing troglitazone in type 2 diabetic patients would be as follows: *1*) to select the right patients who may be expected to be good responders to the drug; *2*) to carefully monitor liver enzymes during the first year of treatment to early detect liver abnormalities and stop troglitazone administration before severe liver toxicity occurs; and *3*) to avoid progressive weight gain by appropriate dietary counseling.

CONCLUSIONS — Troglitazone exerts an antihyperglycemic activity in a dose-dependent manner between 200 and 600 mg/day. Such an effect is observed in type 2 diabetic patients treated with diet alone, with sulfonylureas, and with insulin. An interesting insulin-sparing effect of about one-third of a daily insulin dose has been described. Additive effect was also observed by combining troglitazone and metformin in one open-label study. In most clinical trials, the antihyperglycemic effect is rather modest (reduction of HbA_{1c} by 0.5–1.0%) as monotherapy, but appears to be somewhat greater when combined to other antidiabetic drugs, especially sulfonylureas. Only few studies have directly compared the antihyperglycemic activity of troglitazone with that of other oral antidiabetic agents and none of them were double-blind. Because troglitazone has additional beneficial effects on cardiovascular risk profile, provided that weight gain is limited, it may be considered as a valuable alternative in insulin-resistant (obese and hyperinsulinemic) diabetic patients who appear to be the best responders to the drug. However, the efficacy of this thiazolidinedione compound is challenged by its safety profile, and the troglitazone-associated potential hepatotoxicity still remains a major concern in clinical practice so that careful monitoring of serum liver enzymes (ALT) before and during troglitazone therapy is mandatory.

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