Thiazolidinediones

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This is the fifth in a series of articles on presentations at the American Diabetes Association Annual Meeting, Orlando, Florida, 4–8 June 2004.

At a debate at the American Diabetes Association (ADA) meeting on the use of thiazolidinediones (TZDs) in type 2 diabetes, David M. Kendall (Minneapolis, MN) discussed their advantages. He presented evidence that the agents improve glycemic control, target the metabolic defects of insulin resistance and insulin deficiency, and potentially preserve β-cell function and, therefore, prevent diabetes. Furthermore, he discussed the role of insulin resistance in increasing cardiovascular disease (CVD) risk, the safety and tolerability of the drugs, and aspects of their cost.

All oral hypoglycemic agents lower plasma glucose by 30–80 mg/dl and HbA_{1c} by up to 2–2.5%. However, Kendall stated, only 25–30% of patients achieve adequate glycemic control with metformin or secretagogue monotherapy and only 15–20% with TZDs. "It is how we get there that is important," he stated, and because hyperglycemia is caused by paired defects of both insulin resistance and deficiency, its treatment requires addressing both pathogenic defects. The U.K. Prospective Diabetes Study (UKPDS) showed that type 2 diabetes is a progressive disease with declining β-cell function but may have been flawed due to a lack of sufficiently high doses of insulin and not having TZDs or insulin analogs available. Kendall noted that the HbA_{1c} goal for individuals with type 2 diabetes should be <7%, and perhaps should be <6%, although he noted that, on a population basis, glycemic treatment has not improved particularly over the past decade.

Although insulin secretion is apparently increased in the setting of compensation to insulin resistance, subsequent progressive β-cell dysfunction occurs that is associated with adverse effects of hyperglycemia, insulin resistance, fatty acids, and adipocytokines. TZDs decrease insulin resistance and prevent the decline in β-cell mass, with Kendall noting the effect of troglitazone (TGZ) on the insulin secretory response to glucose, further suggesting an improvement in β-cell function (1). Although the TZDs "are still new agents," he referred to open-label studies suggesting that these agents sustain glycemic improvement for >2 years.

Addressing their role in the prevention of type 2 diabetes, Kendall discussed the DPP (Diabetes Prevention Project), in which there was a 30% reduction in diabetes development among individuals with impaired glucose tolerance during metformin treatment, although this appeared in part to be a "masking," as withdrawal of the treatment led to the development of diabetes (2). In contrast, Kendall stated that of the 500 patients treated for a median of 10 months with TGZ in the DPP, there was a 75% reduction in risk of progression, and a 25% decrease in risk was seen 3 years later, suggesting sustained benefit. In the TRIPOD (Troglitazone in Prevention of Diabetes) study, TGZ decreased the risk of developing diabetes by 56%, again with the suggestion of sustained prevention after withdrawal of the treatment (3). A number of additional studies are being performed regarding the effects of TZDs on diabetes development.

The metabolic syndrome causes abnormal vascular function with inflammation and increased thrombotic risk, as well as dyslipidemia, hyperglycemia, and hypertension. There may be benefits of TZD treatment extending beyond diabetes prevention to the prevention of cardiovascular complications of the metabolic syndrome. TZDs have many effects on all atherogenic aspects of the metabolic syndrome: lowering blood pressure, decreasing lipid abnormalities, reducing inflammatory mediators (including C-reactive protein, matrix matalloproteinase-9, and leukocyte count), and improving procoagulant abnormalities. In the TRIPOD study, serial carotid intima-media thickness measurement showed benefit of TGZ. Although it is crucial to target each abnormality, the multiple favorable effects of TZDs are attractive and are not seen to the same extent with other glycemic treatments. However, Kendall acknowledged that metformin does improve insulin resistance and lower plasminogen activator inhibitor type 1, that metformin was associated with lower CVD risk in the UKPDS (4), and that insulin was associated with decreased mortality in the DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) (5) and other acute studies.

The adverse side effects of TZDs have been a question, but Kendall stated that there is no evidence of hepatotoxicity and that there is evidence of improvement in nonalcoholic fatty liver disease (NAFLD). Addressing the risk of weight gain, he characterized this as "simply a concern that patients express," stating that weight gain occurs with any intensive therapy of diabetes and is in general associated with improved outcome. Although peripheral edema occurs in up to 15% of treated individuals, he noted that it is less common at low doses, that edema must be distinguished from congestive heart failure (CHF), and, most importantly, that type 2 diabetes is associated with high CHF rates and that TZDs may simply unmask unrecognized heart failure. Kendall suggested that the ADA–American Heart Association CHF consensus statement (6) exaggerates in ascribing adverse consequences to these agents and that CHF "is exceedingly uncommon" in TZD-treated patients.

Finally, Kendall stated that "the cost of diabetes is not about drug acquisition cost." He argued that the cost of TZDs is similar to that of insulin and that, although more expensive than metformin and sulfonylureas, their cost is dwarfed by all the truly expensive health care costs experienced by individuals with diabetes.

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Abbreviations: CHF, congestive heart failure; CVD, cardiovascular disease; FFA, free fatty acid; IAPP, islet amyloid polypeptide; PGZ, pioglitazone; PPAR, peroxisome proliferator–activated receptor; RGZ, rosiglitazone; TGZ, troglitazone; TZD, thiazolidinedione; UKPDS, U.K. Prospective Diabetes Study.

Diabetes care accounts for 10% of health care spending, totaling some $132 billion in the U.S., of which 30% is related to outpatient treatment and 44% to hospital inpatient costs, few of which would be related to drug charges.

Philip Home (Newcastle, U.K.) discussed a number of disadvantages, which lead to his belief that caution is necessary before the widespread therapeutic use of TZDs. He noted that although the drugs lower blood glucose in some individuals with diabetes to approximately the same extent as other classes of oral glucose-lowering drugs, it is important that physicians practice evidence-based medicine. Thus, although they do improve putative procoagulant and proinflammatory risk factors, substantiation of this being beneficial is "thin, with no outcome evidence" that such therapeutic intervention improves health outcomes, as has been well documented for the lowering of glucose, blood pressure, and LDL cholesterol. He suggested that TZDs may lead to "too many genes" being activated for safety, with agents in this class withdrawn because of tumors, that there is fluid retention causing major CHF risk, and that they do cause weight gain, which may have adverse consequences. He noted that the insulin resistance caused by glucose toxicity is highly consequential and is addressed by all glucose-lowering agents. He further suggested that insulin deficiency is the critical difference between insulin-resistant individuals who do and do not develop diabetes, suggesting that insulin secretagogues should not be considered inappropriate agents for the treatment of type 2 diabetes. He stated that in the UKPDS, metformin appeared to be associated with optimal improvement in risk, that sulfonylureas are somewhat more potent than either TZDs or metformin, at least in initial glucose-lowering efficacy, and that sulfonylurea-treated individuals in the UKPDS showed a sustained glucose-lowering benefit over >6 years; therefore, these should be considered "useful drugs, cheap drugs, effective drugs with outcomes proven by that study." If, he said, the use of TZDs delays the introduction of metformin "with its proven advantage," then they may actually result in worse outcome. He suggested that insulin treatment typically lowers HbA_{1c} by 1–1.5%, maintains glucose control in the long term, and has both proven efficacy and long-term safety.

Home referred to cost, and stated he "was horrified by [Kendall's] economic analysis," stating that if a month's supply of insulin costs $83, sulfonylureas $119, metformin $113, and a TZD $227, then the excess cost is "fixed money." Furthermore, he suggested that it would be approximately five times more expensive to use TZDs than metformin given the UKPDS evidence of benefit and assuming that TZDs are as effective in decreasing risk as sulfonylureas and insulin. He also suggested that TZDs reduce fasting blood glucose by >30 mg/dl in only 38–48% of patients, although noting that "it is disguised in many of the studies" by presenting mean falls in glucose in an overall treated population. Based on the reported SDs of the decrease in blood glucose, Home suggested that ~25% of patients do not experience any glucose-lowering benefit from these agents. Weight gain is greater than that seen with sulfonylureas and probably exceeds that with insulin. Home characterized this as "a significant issue for persons with diabetes."

Home then focused on cardiovascular concerns. He noted that CHF is often difficult to detect until symptomatic and that the product labels state that one must "observe for cardiac failure" and that TZDs "may also increase risk of cardiac events." CHF is, he said, "a life-threatening condition that can't be taken lightly." He discussed a study comparing 104 insulin-treated patients receiving placebo, 106 receiving a half-maximal TZD dose, and 103 receiving a maximal TZD dose for 26 weeks. Weight increased 0.9, 4.0, and 5.3 kg; HbA_{1c} decreased 0, 0.5, and 1.0%; and edema was observed in 5, 13, and 16%, respectively. Also CHF was seen in twice as many patients treated with TZD than with placebo (7). Thus, edema, although occurring in 3–4% of patients receiving sulfonylureas and metformin, is a more important issue with TZD administration. CHF, Home stated, is extremely important in individuals with diabetes (8), who demonstrate increased post–myocardial infarction mortality due to pump failure (9), impaired left ventricular relaxation on Doppler, early reduction in diastolic function, and a variety of related abnormalities.

Finally, Home addressed what he termed "the gene transcription concerns." Fully 10% of genes transcribed in adipose tissue are differentially expressed with the use of a peroxisome proliferator–activated receptor (PPAR)-γ agonist, as well as 2% of all genes expressed in liver and 1% of those expressed in skeletal muscle (10). The effects of TZDs on target genes involved in insulin signaling may lead to unexpected adverse effects, with Home recalling that the insulin analog B10Asp increased mammary tumors in rats. Several TZDs led to concern about malignancy: NN 622 was withdrawn because of bladder malignancy in rats and mice, MK 627 was stopped due to the occurrence of a normally rare malignancy in rats, and a model of polyposis coli showed exacerbation of malignant transformation by TZDs. Although PPAR-γ agonists generally promote differentiation and have been proposed as possible therapies for malignancy, Home stated that more investigation is needed. Home noted that malignancy and CHF are very common, so that it is difficult to notice true adverse effects unless their rate of occurrence is specifically studied in an appropriately designed study. (Consider the recent recognition that rofecoxib caused adverse cardiac effect, which was disputed until proven by large long-term clinical trials [11]—Z.B. comment). He concluded by asking, "Why does nature make us insulin resistant?. . . Could it be a metabolically protective response?. . . Might attempts to overcome primary insulin resistance prove toxic to organ systems in the longer term?"

Given these diametrically opposed presentations, it is fascinating to review the many research studies at the ADA meetings addressing the use of PPAR-γ agonists.

New PPAR agonists

Satoh et al. (abstract 1722) described studies comparing a non-TZD halobenzyltyrosine derivative, TY-12780, which has PPAR-γ–activating effects, with pioglitazone (PGZ) in leptin receptor–deficient *db/db* mice. After 2 weeks, glucose decreased 60 vs. 49%, triglycerides decreased 72 vs. 55%, and free fatty acid (FFA) levels decreased 52 vs. 21%. There was a greater improvement in insulin sensitivity and a 330 vs. 74% increase in plasma adiponectin level, a biomarker for PPAR-γ activation, compared with PGZ. Christ et al. (abstract 648) described studies with R483, a PPAR-γ activator that has a 16- and 143-fold greater bind-

ing affinity than rosiglitazone (RGZ) and PGZ, respectively, showing insulin-sensitizing and glucose-lowering effects in rodent models. Kersey et al. (abstract 656) reported human studies with T0903131, a non–TZD-selective PPAR-γ modulator. Adiponectin levels increased 0.71- and 2.22-fold after 8 and 14 days of administration, respectively, in a group of healthy male volunteers.

There has been considerable interest in the development of mixed PPAR agonists. Park et al. (abstract 1719) noted that the PPAR-α activator fenofibrate has been thought to inhibit weight gain by increasing fatty acid catabolism in rats. In a study suggesting a mechanism of benefit of agents having PPAR-α activity, obese rats from age 13 through 61 weeks had 29% lower body weight. There was a decrease in both subcutaneous and visceral fat, increased hepatic uncoupling protein-3 mRNA, and 0.4°C higher esophageal and 1.1°C higher rectal temperature in rats treated with fenofibrate. Less promising benefits of combined PPAR-α/γ treatment were suggested in a human study by Bajaj et al. (abstract 136) in which PGZ or fenofibrate was administered for 3 months to 14 individuals with type 2 diabetes. In subjects given PGZ, fasting glucose decreased from 207 to 138 mg/dl, HbA_{1c} fell from 9.0 to 7.8%, FFA levels decreased from 763 to 580 μmol/l, and adiponectin increased from 5.5 to 13.8 μg/ml, whereas none of these parameters changed with fenofibrate. Hepatic fat measured by magnetic resonance spectroscopy decreased from 20.4 to 10.2 with PGZ and did not change with fenofibrate. Triglycerides decreased similarly with the two agents (from 188 to 143 mg/dl with PGZ and from 190 to 136 mg/dl with fenofibrate). During a subsequent 3 months of combined treatment with both agents, there was no further change in fasting glucose, HbA_{1c}, hepatic fat, or adiponectin, although triglyceride levels continued to decrease to 89 mg/dl. In humans, therefore, combined PPAR-α/γ therapy decreases triglycerides compared with PPAR-γ alone but may not have any further effect on FFA or glucose metabolism.

Nevertheless, new agents are being developed that act at both PPAR-γ and -α. Preller et al. (abstract 1086) compared phytanic acid, a diet-derived PPAR-γ and -α agonist, with BRL49653, a specific PPAR-γ agonist, in a high-fat diet mouse model. Both treatments similarly lowered glucose and lipid levels, with hepatic gene expression analysis showing that stearoyl-CoA desaturase 1 and sterol regulatory element binding protein-1 (a transcription factor for lipogenic genes) and its target were decreased only by phytanic acid, whereas adipsin, an enzyme necessary for the synthesis of acylation-stimulating protein, was upregulated by the TZD but decreased by phytanic acid, suggesting the potential for differential regulation of hepatic lipid metabolism by PPAR-γ agonists versus mixed PPAR-γ and -α agonists. Inoue et al. (abstract 544) studied another PPAR-α/γ agonist, E3030, in *db/db* mice, showing a dose-dependent decrease in blood glucose, FFAs, triglycerides, and insulin and an increase in adiponectin levels. In dog studies from the same group, Kasai et al. (abstract 553) compared this agent with PGZ and fenofibrate, finding little lipid-lowering effect with PGZ but triglyceride- and non-HDL cholesterol–lowering effects with E3030 that were similar to those of fenofibrate. Harrity et al. (abstract 134) compared muraglitazar (BMS-298585), a non-TZD, oxybenzylglycine dual PPAR-α/γ agonist, with RGZ in *db/db* mice and observed greater decreases in fasting and post-oral glucose blood glucose levels. In an in vitro macrophage study, Zhou et al. (abstract 640) showed that muraglitazar increased expression of genes involved in reverse cholesterol transport and stimulated cholesterol efflux to a greater degree than RGZ. In human studies, Swaminathan et al. (abstract 618) demonstrated predictable absorption of muraglitazar after oral administration to normal individuals, and Mosqueda-Garcia et al. (abstract 138) reported a greater glucose-lowering effect with the agent than with PGZ in 38 individuals with type 2 diabetes treated for 28 days. A dose-related fall in triglyceride was also reported in this study by Frost et al. (abstract 1988). Prince et al. (abstract 139) compared the effects of a non-TZD PPAR-γ agonist, LY519818, which has a lesser PPAR-α effect, with those of RGZ in 151 patients with type 2 diabetes treated for 12 weeks. They observed a greater fall in HbA_{1c}, a greater increase in HDL cholesterol, and a trend to less weight gain with the experimental compound.

Ortmeyer et al. (abstract 666) studied the effects of PPARpan, a combination PPAR-α/γ/δ agonist that they had previously shown to increase levels of genes involved in mitochondrial fatty acid oxidation, improve insulin sensitivity, and lower fasting plasma triglyceride and insulin concentrations in five middle-aged pre-diabetic obese rhesus monkeys. Total extractable lipoprotein lipase activity tripled in skeletal muscle, along with a decrease in muscle triglyceride content, while adipose tissue lipoprotein lipase activity decreased 75%, suggesting an increase in fatty acid oxidation in muscle as a mechanism of benefit. Lewis et al. (abstract 565) compared the effects of PPARpan with those of PPAR-α and -δ agonists in high-fat–fed mouse obesity models. They showed a 10% lower body weight and 31% lower fat mass in animals treated with either the PPAR-α or -δ agonist but 18 and 47% reductions, respectively, with combination PPAR-α/γ/δ agonists. HDL increased and FFA and insulin levels decreased with all treatments, while triglycerides decreased only with the PPAR-α and combination agonists. Thus, combination agents may allow TZD-like benefits to be seen in humans without the weight gain effects seen with PPAR-γ agonists.

Nonglycemic TZD effects

Konrad et al. (abstract 658) reported that of 3,140 type 2 diabetic individuals with stage I and stage II hypertension, blood pressure decreased from 145/85 to 138/82 mmHg and from 166/94 to 147/85 mmHg, respectively, in an open-label study of the effects of administration of 30 mg PGZ daily for 16 weeks. Koro et al. (abstract 1009) analyzed a managed care registry of 229 individuals with type 2 diabetes hospitalized for myocardial infarction and compared them with 1,374 control subjects. They showed that TZD, sulfonylurea, metformin, and metformin combined with sulfonylurea were associated with 49, 38, 39, and 44% lower CVD event risk, respectively, than insulin monotherapy, adjusting for age, sex, hyperlipidemia, and hypertension, as well as use of nitrates, ACE inhibitors, β-blockers, and diuretics. Blonde et al. (abstract 506) analyzed 7,922 patients with newly diagnosed diabetes from an electronic medical record database. At 6 months, comparing 3,837, 540, and 3,555 subjects started on sulfonylureas, TZDs, and metformin, respectively, HbA_{1c} decreased 1.6, 1.4, and 1.6%; weight increased 1.8 and 1.9 and decreased 3.9 lb; and systolic blood pressure decreased 3,

5, and 3 mmHg. Masoudi et al. (abstract 124) studied 16,156 diabetic Medicare beneficiaries ≥65 years of age after heart failure hospitalization. One-year mortality among 2,226 patients treated with a TZD was 30.1%, that among 1,861 treated with metformin was 24.7%, and that for the remaining 12,069 individuals was 36%. There was a similar outcome among those receiving sulfonylurea and those receiving insulin. Readmission for heart failure was 6% more likely among individuals treated with a TZD, but all-cause hospitalization rates were not affected by this treatment. The authors suggest "that despite existing recommendations against use in this context, [TZD and metformin] may have important benefits in this patient population."

Regensteiner et al. (abstract 35) treated 17 type 2 diabetic individuals with 4 mg RGZ daily versus placebo for 4 months, showing a 6% improvement versus an 8% worsening in maximal oxygen consumption that correlated with an improvement in endothelial function. Lee et al. (abstract 562) administered 4 mg RGZ daily to 11 individuals with type 2 diabetes, showing a tripling of the rate of hairy skin sweating using a hygrometry system, in association with increased cutaneous blood flow. The degree of body temperature increase after a 30-min heat exposure lessened with treatment, suggesting an improvement in thermoregulation. Pfützner et al. (abstract 669) and Forst et al. (abstract 1270) treated 87 type 2 diabetic individuals with 45 mg PGZ daily versus 1–6 mg glimiperide daily fox 6 months and showed expected improvements with the former agent in insulin sensitivity, insulin levels, adiponectin, resistin, and FFAs. Microvascular skin blood flow measured by laser Doppler fluxmetry in response to local heat improved in both groups, whereas the endothelial response to acetylcholine improved only with PGZ. Viljanen et al. (abstract 1316) treated 38 type 2 diabetic individuals with RGZ, metformin, or placebo for 26 weeks. Femoral subcutaneous adipose tissue glucose uptake and blood flow increased 56 and 57%, respectively, with RGZ and 24% with metformin, suggesting an enhanced perfusion that partially explained the increase in adipose tissue insulin sensitivity with RGZ. Bweir et al. (abstract 369) evaluated the effect of RGZ on the fall in blood pressure with 45° tilt in 14 type 2 diabetic individuals. Systolic blood pressure decreased 11, 5, and 1 mmHg at 0, 2, and 4 weeks, with a 27% decrease in mean toe blood flow from 0 to 4 weeks, suggesting improvement in autonomic function.

Chen et al. (abstract 1431) studied the effect of GI2570X, a PPAR-γ agonist. They showed a 14% increase in plasma volume, a decrease in potassium (from 5.3 to 4.6 mEq/l), an increase in sodium (from 136 to 139 mEq/l), and an increase in chloride (from 102 to 104 mEq/l). Plasma aldosterone decreased 42% and the diuretic response to atrial natriuretic peptide decreased 41%, suggesting effects of the PPAR-γ agonist on water and sodium reabsorption. Sotiropoulos et al. (abstract 135) reported that capillary permeability increased in fat (to a degree correlated with increase in fat mass) and in the retina, but not in the heart or skeletal muscle, after RGZ administration in insulin-resistant rodents. Vascular endothelial growth factor mRNA expression increased 1.5-, 1.3-, and 2.5-fold in the retina, heart, and fat, respectively. Administration of ruboxistaurin, a protein kinase C-β inhibitor, with RGZ normalized fat and retinal vascular permeability and attenuated the increase in fat mass, and protein kinase C-β knockout mice failed to gain weight or show increased vascular permeability with RGZ treatment, suggesting this as a potential therapeutic approach to prevent the edema and weight gain associated with TZD treatment.

Lin et al. (abstract 137), noting the association of type 2 diabetes with increased β-cell apoptosis and the presence of islet amyloid derived from islet amyloid polypeptide (IAPP), showed that IAPP induces apoptosis in cultured human pancreatic islets and that the addition of RGZ to the incubation prevented the IAPP-induced apoptosis. Zhou et al. (abstract 140) treated 17 apparent type 2 diabetic individuals with latent autoimmune diabetes, based on the presence of GAD antibody, with insulin alone versus insulin plus RGZ for 12 months. They showed a >50% decline in fasting and postload C-peptide in the insulin alone group, while endogenous insulin secretion was preserved with RGZ, suggesting a new potential benefit of the β-cell–sparing effect. This particular benefit may not be relevant to treatment of individuals with established type 1 diabetes, as Strowig and Raskin (abstract 617) administered 4 mg RGZ twice daily versus placebo to 50 overweight individuals with type 1 diabetes for 8 months, showing a similar ~3-kg weight gain and improvement in HbA_{1c}, with greater insulin requirement in those receiving placebo but more edema and anemia in those receiving RGZ.

Metabolic TZD effects

Monotherapy

Gastaldelli et al. (abstract 11-LB) treated 30 individuals with PGZ, RGZ, or placebo for 4 months. Insulin secretion, evaluated by deconvolution of C-peptide data, increased with both agents to a degree correlating with the improvement in total body glucose disposal. Andreas et al. (abstract 642) administered 45 mg PGZ versus 1–6 mg glimepiride daily to 83 individuals with type 2 diabetes for 6 months. HbA_{1c} decreased from 7.4 to 6.9 vs. 6.8%, respectively. Homeostasis model assessment of insulin resistance improved 44 vs. 6% and intact proinsulin decreased 33 vs. 17%. Tan et al. (abstract 619) compared glycemic response to 45 mg PGZ versus up to 160 mg gliclazide daily in 130 vs. 110 previously untreated patients with type 2 diabetes. The subjects were treated for 2 years and showed a significant difference in the maintenance of HbA_{1c} <8% beginning at 65 weeks; mean HbA_{1c} decreased from 8.6 to 7.3% with PGZ vs. from 8.7 to 7.8% with gliclazide. Armstrong and King (abstract 497) identified 23 individuals with type 2 diabetes continuously treated with 30–45 mg PGZ daily, reporting a mean weight gain of 2.3 kg at 12 months, 3.9 kg at 24 months, and 5.5 kg at 30 months, but subsequently with stable weight through 48 months, suggesting that this effect might be self-limited. Khan et al. (abstract 555) compared the 12-month lipid effects of PGZ, metformin, and sulfonylureas in 2,444 type 2 diabetic individuals, observing increases of 20, 11, and 7% in HDL cholesterol and decreases of 10, 1, and 5% in triglycerides, respectively.

Combination therapy

Sulfonylurea plus TZD

Vinik et al. (abstract 680) presented 2-year data on the effect of RGZ versus placebo in 215 individuals with type 2 diabetes receiving glipizide, showing that insulin sensitivity improved 14% versus

worsening 18%. The 30-min increase in insulin following oral glucose administration, divided by the increase in blood glucose and corrected for insulin sensitivity, improved in 11% but worsened in 14%. Herman et al. (abstracts 540 and 541) reported health care resource use in a similar study of 110 vs. 115 type 2 diabetic individuals >60 years of age (mean 68 years) who initially received a submaximal dosage of glipizide and were randomized to increased glipizide dosing versus the addition of RGZ. Improved glycemia was previously reported with the latter approach, as well as 5.4 vs. 2.2 emergency room visits and 2.8 vs. 1.4 hospitalizations per 10 patient-years and monthly treatment costs of $567 vs. 428, suggesting cost benefit of TZD use.

Moules et al. (abstract 584) added maximal tolerated daily doses of PGZ (15–45 mg) and metformin (850–2550 mg) to 319 vs. 320 type 2 diabetic individuals with HbA_{1c} 7.5–11% on sulfonylurea treatment. They showed a similar 2-year reduction in HbA_{1c} of 1 and 1.2%, a weight gain of 3.7 kg versus a weight loss of 1.7 kg, and more edema versus more gastrointestinal adverse effects. The authors suggested that the two approaches offer comparable overall benefit and maintenance of glycemic control over the study period. Mariz et al. (abstract 578) reported lipid changes in the study, with triglycerides decreasing 17 vs. 9% and HDL cholesterol increasing 21 vs. 15%, favoring the use of PGZ, while LDL cholesterol decreased 5 vs. 11%, favoring the addition of metformin.

Metformin combinations

Rosenstock et al. (abstract 608) studied 358 vs. 351 type 2 diabetic individuals treated with 1 g metformin daily, comparing strategies of increasing metformin to 2 g daily versus adding 8 mg RGZ daily. Over 24 weeks, there was no significant difference in the fall in HbA_{1c} of 0.6 vs. 0.8%, although greater decreases were found in fasting blood glucose and insulin with the combination, and 55 vs. 45% achieved HbA_{1c} <7%. Weissman et al. (abstract 121) studied the effects on cardiovascular risk markers of increasing metformin versus adding RGZ in 41 vs. 49 patients, reporting an increase in matrix metalloproteinase of 22% vs. a decrease of 14%, a decrease in plasminogen activator inhibitor-1 of 0 vs. 33%, and a decrease in C-reactive protein of 10 vs. 27%. Umpierrez et al. (abstract 627) treated 96 vs. 107 type 2 diabetic individuals with HbA_{1c} 7.5–10% on metformin, adding 2–8 mg glimepiride vs. 30–45 mg PGZ daily for 26 weeks. HbA_{1c} fell from 8.4 to 7.1% vs. 8.3 to 7.1%, with similar changes in triglycerides and no change in HDL or LDL cholesterol with the addition of glimepiride versus an increase in HDL cholesterol from 43 to 48 mg/dl and an increase in LDL cholesterol from 108 to 117 mg/dl with the addition of PGZ. Seven of the latter patients reported edema. Thompson et al. (abstract 623) compared metformin-treated patients 20 months after the addition of RGZ or sulfonylurea. They showed a baseline BMI of 34 kg/m^2 and weight gain of 2.4 vs. 2.2 kg; 22 vs. 20% gained >5% of body weight. Koro et al. (abstract 1010) identified 143 individuals treated with RGZ plus metformin and 1999 treated with metformin plus sulfonylureas in the Mediplus U.K. database. Despite greater age and longer diabetes duration, the former had a 78% lower rate of progression to insulin treatment.

Triple oral combinations and insulin-oral combinations

Roberts et al. (abstract 605) randomized patients receiving metformin plus either RGZ or PGZ with HbA_{1c} >7% to 2–8 mg glimepiride daily versus placebo for 26 weeks, showing a fall in HbA_{1c} from 8.1 to 6.8% vs. from 8.2 to 7.7.8% and a decrease in fasting glucose from 170 to 133 mg/dl vs. from 171 to 167 mg/dl. There was an increase in fasting insulin and C-peptide with the former agent. The authors suggested that this is a useful triple oral agent approach, although they noted that one severe hypoglycemic episode occurred with glimepiride. In another analysis of approaches to triple combination treatment, Rosenstock et al. (abstract 609) randomized 217 type 2 diabetic individuals with HbA_{1c} 7.5–11% on metformin plus sulfonylurea treatment to the addition of 4–8 mg RGZ versus insulin glargine at bedtime, showing a similar 1.5 vs. 1.7% decrease in HbA_{1c} over 24 weeks. There were reductions in fasting glucose of 46 vs. 65 mg/dl, weight gain of 3 vs. 1.6 kg, and peripheral edma developed in 12.5 vs. 0% of patients. Insulin led to a $397/patient saving in projected drug cost, although less symptomatic nocturnal hypoglycemia occurred with RGZ. In a mechanistic study of changes in hepatic glucose production and peripheral glucose output among 13 patients randomized in this protocol, Triplitt et al. (abstract 625) found a similar decrease in basal glucose production and insulin-stimulated glucose disposal with the addition of either RGZ or insulin glargine. Perez et al. (abstracts 522 and 593) studied 112 vs. 110 type 2 diabetic patients with fasting blood glucose <140 mg/dl on either insulin alone or insulin plus metformin and randomized to the addition of placebo or 30 mg PGZ daily. They showed a similar fall in HbA_{1c} of 1.4 vs. 1.6% over 20 weeks, although with a 1-unit/day increase vs. a 12-unit/day decrease in insulin dosage, and with a 3% increase vs. a 11% decrease in small LDL particles. Luetke et al. (abstract 660) reported an observational analysis from 51 outpatient diabetic centers of 299 individuals started on 30 mg PGZ daily as a second oral agent and 102 and 116 subjects switched to insulin alone, either twice or multiple times daily, respectively. HbA_{1c} decreases were similar, and the cost of diabetes management (including that of home glucose monitoring) was similar for PGZ and the twice-daily insulin regimens and ~50% greater with the multiple insulin injections regimen.

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