23 *Role of Dual PPAR γ and α Agonists in Diabetes Mellitus—Have They Met a Road Block or They Are Dead?*

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Abstract: There are three peroxisome proliferator-activated receptors (PPARs) subtypes which are commonly designated PPAR alpha, PPAR gamma and PPAR beta/delta. PPAR alpha activation increases high density lipoprotein (HDL) cholesterol synthesis, stimulates "reverse" cholesterol transport and reduces triglycerides. PPAR gamma activation results in insulin sensitization and antidiabetic action. Combined treatments with PPAR gamma and alpha agonists may potentially improve insulin resistance and alleviate atherogenic dyslipidemia, whereas PPAR delta properties may prevent the development of overweight which typically accompanies "pure" PPAR gamma ligands. The new generation of dual-action PPARs—the glitazars, which target PPAR-gamma and PPAR-alpha (like muraglitazar and tesaglitazar) were on deck in late-stage clinical trials for sometime and were considered effective in reducing cardiovascular risk, but their long-term clinical effects were unknown. Thus glitazars offered a hope of a new approach to diabetes care addressing not just glycemia, but dyslipidemia and other components of the metabolic syndrome, though the side effect profile remains unknown. No human data is available, and so it remains highly speculative. The glitazars and on the newly published results for muraglitazar and tesaglitazar. "The PPAR-alpha is a good target and is being developed to yield more potent drugs that work through PPAR-alpha, and at the same time, improve on the PPAR-gamma. Efforts is on to get the glucose lowering with few of the adverse effects. This thinking has met with problems as many clinical trials have been terminated due to dominant side effects.

Beyond these and other novel agents being developed to meet the challenge of the worldwide epidemic of diabetes, the central place of insulin in diabetes care cannot be forgotten. In view of this the continued efforts of improvement in insulin delivery, kinetics and action have spurred such innovations as the various inhaled insulins and new insulin analogues. There is cause for guarded optimism and excitement about the years ahead as we expect a plethora of new avenues of management.

INTRODUCTION

After many decades of relative therapeutic stagnation since the initial discovery of insulin, followed by some modifications on its structure and only having sulphonylureas and biguanides for many years, the last decade has seen a surge in new therapeutic options for the management of diabetes. The results of the United Kingdom Prospective Diabetes Study and Kumamoto study indicate the need for aggressive glycemic control and the slow inexorable clinical deterioration associated with type 2 diabetes overtime.[1] The propensity for weight gain and hypoglycemia are

the two major limitations that subcutaneous insulin and sulphonylureas have been particularly prone to. The newer anti-diabetic medications and those on the horizon attempt to address these limitations. GLP-1 agonists and the DPP-IV inhibitors exploit the innate incretin system to improve glycemia while promoting satiety and weight management. Like GLP-1 related compounds, pramlintide offers the potential to address postprandial hyperglucagonemia associated with type 2 diabetes only limited by the multiple injections and gastrointestinal side effects. The INGAP peptide represents the holy grail of diabetes care as it offers the potential of a new paradigm: that of islet regeneration and potential for a cure. Modulation of the endogenous endocannabinoid system by rimonabant, which is under regulatory review, has been shown to improve body weight, atherogenic lipid profiles and glycemic control. In addition, enhanced understanding of the pathophysiology underlying the microvascular complications of type 2 diabetes has led to the development of targeted therapies for conditions such as diabetic retinopathy, including the protein kinase C (PKC)-antagonist ruboxistaurin, now in phase III trials.[2]

Peroxisome proliferator-activated receptors (PPARs) are nuclear transcription factors that modulate gene expression. Therapeutic agents targeting 2 distinct families of PPARs (alpha and gamma) have been introduced in the United States.[3] There are three peroxisome proliferator-activated receptors (PPARs) subtypes which are commonly designated PPAR alpha, PPAR gamma and PPAR beta/delta. PPAR alpha activation increases high density lipoprotein (HDL) cholesterol synthesis, stimulates "reverse" cholesterol transport and reduces triglycerides. PPAR gamma activation results in insulin sensitization and antidiabetic action. Until recently, the biological role of PPAR beta/delta remained unclear.[4] However, treatment of obese animals by specific PPAR delta agonists results in normalization of metabolic parameters and reduction of adiposity. Combined treatments with PPAR gamma and alpha agonists may potentially improve insulin resistance and alleviate atherogenic dyslipidemia, whereas PPAR delta properties may prevent the development of overweight which typically accompanies "pure" PPAR gamma ligands.[5,6]

The new generation of dual-action PPARs, the glitazars, which target PPAR-gamma and PPAR-alpha (like muraglitazar and tesaglitazar), are on deck in late-stage clinical trials and may be effective in reducing cardiovascular risk, but their long-term clinical effects are still unknown. A number of glitazars have presented problems at a late stage of clinical trials because of serious side-effects (including ragaglitazar and farglitazar).[7,8] The old and well known lipid-lowering fibric acid derivative, bezafibrate, is the first clinically tested pan—(alpha, beta/delta, and gamma) PPAR activator. It is the only pan-PPAR activator with more than a quarter of a century of therapeutic experience with a good safety profile. Therefore, bezafibrate could be considered (indeed, as a "post hoc" understanding) as an "archetype" of a clinically tested pan-PPAR ligand. Bezafibrate leads to considerable raising of HDL cholesterol and reduces triglycerides, improves insulin sensitivity and reduces blood glucose level, significantly lowering the incidence of cardiovascular events and new diabetes in patients with features of metabolic syndrome. Clinical evidences obtained from bezafibrate-based studies strongly support the concept of pan-PPAR therapeutic approach to conditions which comprise the metabolic syndrome. However, from a biochemical point of view, bezafibrate is a PPAR ligand with a relatively low potency.[9,10] More powerful new compounds with pan-PPAR activity and proven long-term safety should be highly effective in a clinical setting of patients with coexisting relevant lipid and glucose metabolism disorders. Table 23.1 depicts various glitazars used in clinical trials.

PHARMACOLOGY

A. Combined alpha—and γ-peroxisome proliferator-activated receptor agonists (Table 23.1).
   1. Thiazolidinediones ("glitazones") are PPAR-gamma agonists
   2. Fibric Acid Analogs are PPAR-alpha agonists
B. Reduce HbA1c (PPAR-gamma-mediated)

C. Increase HDL (PPAR-alpha-mediated)
D. Reduce triglycerides (PPAR-alpha-mediated)

Specific Drugs

A. Muraglitazar (Pargluva)
B. Tesaglitizar (Galida)

Note: Development of both these agents was discontinued in 2006 by their respective manufacturers before either was approved by the FDA, due to safety concerns.

Adverse Effects

In a review of five randomized placebo-controlled trials involving 3,725 adults with type 2 DM, muraglitazar 5 mg/d vs. placebo was associated with significantly increased incidence of death, MI, or CVA (1.47% vs. 0.67%) (JAMA 2005; 294: 2633).

Muraglitazar is a non-thiazolidinedione, oxybenzylglycine dual PPAR alpha/gamma agonist that is in advanced clinical development for the treatment of type 2 diabetes and its associated dyslipidemia. Muraglitazar, is the next step in the management of multiple risk factors for diabetes because the properties these compounds possess, in a sense, is all of the benefits of insulin sensitizers with, the established benefits of the fibrates. Many studies indicate that postprandial metabolic abnormalities, such as hyperglycemia and dyslipidemia, which are exaggerated and prolonged in type 2 diabetes, are important risk factors for cardiovascular disease. Different pharmacotherapies have been developed to specifically target these risk factors associated with type 2 diabetes. The PPAR agonists, which are potent insulin sensitizers, have been the focus of much research during the past decade. Since their development, PPAR agonists have emerged as an important target for the treatment of insulin resistance and dyslipidemia.[11-13]

Muraglitazar was investigated for its antidiabetic properties and its effects on metabolic abnormalities in genetically obese diabetic db/db mice. In db/db mice and normal mice, muraglitazar treatment modulates the expression of PPAR target genes in white adipose tissue and liver. In young hyperglycemic db/db mice, muraglitazar treatment (0.03-50 mg/kg(-1)/day(-1) for 2 weeks) results in dose-dependent reductions of glucose, insulin, triglycerides, free fatty acids, and cholesterol. In older hyperglycemic db/db mice, longer-term muraglitazar treatment (30 mg/kg(–1)/day(–1) for 4 weeks) prevents time-dependent deterioration of glycemic control and development of insulin deficiency. In severely hyperglycemic db/db mice, muraglitazar treatment (10 mg/kg(-1)/day(-1) for 2 weeks) improves oral glucose tolerance and reduces plasma glucose and insulin levels. In addition, treatment increases insulin content in the pancreas. Finally, muraglitazar treatment increases abnormally low plasma adiponectin levels, increases high-molecular weight adiponectin complex levels, reduces elevated plasma corticosterone levels, and lowers elevated liver lipid content in db/db mice. The overall conclusion was that in db/db mice, the novel dual (alpha/gamma) PPAR activator muraglitazar 1) exerts potent and efficacious antidiabetic effects; 2) preserves pancreatic insulin content; and 3) improves metabolic abnormalities such as hyperlipidemia, fatty liver, low adiponectin levels, and elevated corticosterone levels.[14]

The metabolism and disposition of 14C-labeled muraglitazar (Pargluva), was investigated in eight healthy male subjects with and without bile collection (groups 1 and 2) after a single 20-mg oral dose. Bile samples were collected for 3 to 8 hours after dosing from group 2 subjects in addition to the urine and feces collection. In plasma, the parent compound was the major component, and circulating metabolites, including several glucuronide conjugates, were minor components at all time points. The exposure to parent drug (Cmax and area under the plasma concentration versus time curve) in subjects with bile collection was generally lower than that in subjects without bile collection. The major portion of the radioactive dose was recovered in feces (91% for group 1 and 51% for group 2). In addition, 40% of the dose was recovered in the bile

from group 2 subjects. In this 3 to 8 hours bile, the glucuronide of muraglitazar (M13, 15% of dose) and the glucuronides of its oxidative metabolites (M17a, b, c, M18a, b, c, and M20, together, 16% of dose) accounted for approximately 80% of the biliary radioactivity; muraglitazar and its O-demethylated metabolite (M15) each accounted for approximately 4% of the dose. In contrast, fecal samples only contained muraglitazar and its oxidative metabolites, suggesting hydrolysis of biliary glucuronides in the intestine before fecal excretion. Thus, the subjects with and without bile collection showed different metabolic profiles of muraglitazar after oral administration, and glucuronidation was not observed as a major pathway of metabolic clearance from subjects with the conventional urine and fecal collection, but was found as a major elimination pathway from subjects with bile collection.[15]

In a two-year clinical efficacy study results on 157 participants who continued taking muraglitazar for two years following an initial 985-patient randomized dosing trial that compared five different doses of muraglitazar (0.5-20 mg) with 15 mg of pioglitazone. The 88 patients who completed the extension study (who were in their mid-50s and had type 2 diabetes for at least five years) and continued taking 5.0 mg daily of muraglitazar achieved an average hemoglobin A/C level of 6.5% four months after initiation of muraglitazar. Patients retained that tight control throughout the two-year period. Triglyceride levels decreased 28.4% in patients taking muraglitazar and HDL cholesterol levels increased 19.2%. Thirty-three patients withdrew from the durability study because they were unable to achieve adequate glucose control while taking 5 mg of muraglitazar. The most common adverse effects seen in the study were edema, which affected 8% of participants, and weight gain ranging from 2 to 10 lb among participants in the durability study. These adverse effects have been seen in all studies of PPAR alpha/gamma and occur with use of glitazones, but in most cases have been moderate and have not led to congestive heart failure in patients who do not have underlying heart disease.

In another study evaluating the efficacy and safety of muraglitazar, in adult patients with type 2 diabetes whose disease was inadequately controlled by diet and exercise. This randomized, double-blind, placebo-controlled, parallel-group, multicenter, 24-week mono-therapy study in drug-naive, type 2 diabetes patients with inadequate glycemic control had both men and women aged 18 to 70 years with a body mass index < or = 41 kg/m^2 and serum triglyceride levels < or = 600 mg/dL. These patients received treatment with muraglitazar 2.5 mg, muraglitazar 5 mg, or placebo. The primary end point was the mean change from baseline in HbA_{1C} levels after 24 weeks of treatment. A total of 340 patients (179 men, 161 women) participated in the double-blind treatment phase of the study. Patients had mean baseline HbA_{1C} levels of 7.9% to 8.0%. Monotherapy with muraglitazar 2.5 and 5 mg significantly reduced HbA_{1C} levels (-1.05% and -1.23%, respectively) compared with placebo (-0.32%; $P < 0.001$). At week 24, 58%, 72%, and 30% of the patients receiving muraglitazar 2.5 mg, muraglitazar 5 mg, and placebo, respectively, achieved the American Diabetes Association-recommended HbA_{1C} goal of < 7.0%. Fasting plasma glucose, free fatty acids, and fasting plasma insulin levels significantly decreased during muraglitazar treatment ($P < 0.001$), suggesting an increase in insulin sensitivity. Muraglitazar 2.5 and 5 mg provided improvements from baseline in triglyceride (-18% and -27%), high-density lipoprotein (HDL) cholesterol (10% and 16%), apolipoprotein B (-7% and -12%), and non-HDL cholesterol levels (-3% and -5%) ($P < 0.05$ vs. placebo for each). In a parallel, open-label cohort of 109 drug-naive patients (56 men, 53 women; mean baseline HbA_{1C} level, 10.6%), muraglitazar 5 mg decreased the overall mean HbA_{1C} level from baseline by 2.62% (last observation carried forward) and by 3.49% in the 62 patients completing 24 weeks of study. Changes in lipid parameters during open-label treatment were similar to those observed during double-blind treatment. Muraglitazar was generally well tolerated. Edema-related adverse events of mild to moderate severity occurred in 8% to 11% of patients in all groups. Mean changes from baseline weight in the double-blind treatment groups were 1.1 kg for muraglitazar 2.5 mg, 2.1 kg for muraglitazar 5 mg, and -0.8 kg for placebo ($P < 0.001$); there was a mean 2.9-kg increase in the open-label muraglitazar 5-mg group. They concluded that 24 weeks of treatment with

muraglitazar 2.5 or 5 mg was an effective treatment option for these patients with type 2 diabetes whose disease was inadequately controlled with diet and exercise.[16]

A double-blind, randomized, controlled trial was performed in 1,159 patients with type 2 diabetes inadequately controlled with metformin. Patients received once-daily doses of either 5 mg muraglitazar or 30 mg pioglitazone for a total of 24 weeks in addition to open-label metformin. Patients were continued in a double-blind fashion for an additional 26 weeks. Analyses were conducted at week 24 for HbA_{1C} A/C and at week 12 for lipid parameters. Mean A/C at baseline was 8.12 and 8.13% in muraglitazar and pioglitazone groups, respectively. At week 24, muraglitazar reduced mean A1C to 6.98% (-1.14% from baseline), and pioglitazone reduced mean A/C to 7.28% (-0.85% from baseline; $P < 0.0001$, muraglitazar vs. pioglitazone). At week 12, muraglitazar and pioglitazone reduced mean plasma triglyceride (-28 vs. -14%), apolipoprotein B (-12 vs. -6%), and non-HDL cholesterol (-6 vs. -1%) and increased HDL cholesterol (19 vs. 14%), respectively ($P < 0.0001$ vs. pioglitazone for all comparisons). At week 24, weight gain (1.4 and 0.6 kg, respectively) and edema (9.2 and 7.2%, respectively) were observed in the muraglitazar and pioglitazone groups; at week 50, weight gain and edema was 2.5 and 1.5 kg, respectively, and 11.8 and 8.9%, respectively. At week 50, heart failure was reported in seven patients (five with muraglitazar and two with pioglitazone), and seven deaths occurred: three from sudden death, two from cerebrovascular accident, and one from pancreatic cancer in the muraglitazar group and one from perforated duodenal ulcer in the pioglitazone group. We found that 5 mg muraglitazar resulted in greater improvements in A1C and lipid parameters than a sub maximal dose of 30 mg pioglitazone when added to metformin. Weight gain and edema were more common when muraglitazar was compared with a sub maximal dose of pioglitazone.[17]

For checking safety of these agents a meta- analysis evaluated the incidence of death, myocardial infarction (MI), stroke, congestive heart failure (CHF), and transient ischemic attack (TIA) in diabetic patients treated with muraglitazar compared with controls in phase 2 and 3 clinical trials released under public disclosure laws for the FDA advisory committee meeting. All reviewed trials were prospective, randomized, double-blind, multicenter studies enrolling patients with type 2 diabetes and hemoglobin A(1c) levels between 7% and 10%. Patients (N = 3725) were randomized to receive differing doses of muraglitazar, pioglitazone, or placebo as monotherapy or in combination with metformin or glyburide in trials ranging from 24 to 104 weeks. The primary outcome was the incidence of death, nonfatal MI, or nonfatal stroke. In the muraglitazar-treated patients, death, MI, or stroke occurred in 35 of 2374 (1.47%) patients compared with 9 of 1351 (0.67%) patients in the combined placebo and pioglitazone treatment groups (controls) (relative risk [RR], 2.23; 95% confidence interval [CI], 1.07-4.66; P = .03). For the more comprehensive outcome measure that included TIA and CHF, the incidence was 50 of 2374 (2.11%) for muraglitazar compared with 11 of 1351 (0.81%) for controls (RR, 2.62; 95% CI, 1.36-5.05; P = .004). Relative risks for each of the individual components of the composite end point exceeded 2.1 but were not statistically significant. Incidence of adjudicated CHF was 13 of 2374 (0.55%) muraglitazar-treated patients and 1 of 1351 controls (0.07%) (RR, 7.43; 95% CI, 0.97-56.8; P = .053).

CONCLUSION

The study concluded that when compared with placebo or pioglitazone, muraglitazar was associated with an excess incidence of the composite end point of death, major adverse cardiovascular events (MI, stroke, TIA), and CHF and this agent should not be approved to treat diabetes based on laboratory end points until safety is documented in a dedicated cardiovascular events trial. The fibrate drugs, which activate PPAR alpha, produce robust improvements in dyslipidemia, decrease atherosclerotic lesions and may have an effect on cardiovascular events, but do not affect glycemia. Tesaglitazar is a dual-acting PPAR alpha/gamma agonist currently

being investigated in phase III clinical trials as an alternative treatment for insulin resistance and the characteristic dyslipidemia of type 2 diabetes.[18]

The first dual-PPAR agonist, muraglitazar, was reviewed by a US Food and Drug Administration (FDA) advisory committee on September 9, 2005, resulted in a vote of 8:1 recommending approval for its use in controlling blood glucose levels in patients with type 2 diabetes. The glitazars offered the hope of a new approach to diabetes care addressing not just glycemia, but dyslipidemia and other components of the metabolic syndrome, though the side effect profile remains a major unknown. But at this stage, with no human data available, it remains highly speculative.[18-20] Beyond these and other novel agents being developed to meet the challenge of the worldwide epidemic of diabetes, the central place of insulin in diabetes care cannot be forgotten. In view of this the continued efforts of improvement in insulin delivery, kinetics and action have spurred such innovations as the various inhaled insulins and new insulin analogues. There is cause for guarded optimism and excitement about the years ahead. There is reason to expect that despite the growing burden of diabetes worldwide, we will be better equipped to manage it and its co-morbidities and prevent its onset and possibly even cure it. The glitazars and on newly published results on both muraglitazar and tesaglitazar, the next challenge will be balancing adverse effects without compromising benefits. "The PPAR-alpha is a good target and companies are trying to develop more potent drugs that work through PPAR-alpha and at the same time… improve on the PPAR-gamma. Companies are trying to get the glucose lowering and perhaps lose some of the adverse effects, but that has been a problem".[21]

REFERENCES

1. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352(9131):854-65.
2. Lebovitz H. Diabetes. Assessing the pipeline. Atheroscler Suppl 2006;7(1):43-9.
3. Vamecq J, Latruffe N. Medical significance of peroxisome proliferator-activated receptors. Lancet 1999;354:141-8.
4. Fredenrich A, Grimaldi PA. PPAR delta. An uncompletely known nuclear receptor. Diabetes Metab 2005;31:23-27.
5. Auwerx J. PPAR gamma, the ultimate thrifty gene. Diabetologia 1999;42:1033-49.
6. Kota BP, Huang TH, Roufogalis BD. An overview on biological mechanisms of PPARs. Pharmacol Res 2005;51:85-94.
7. Tenenbaum A, Fisman EZ, Motro M. Metabolic syndrome and type 2 diabetes mellitus: Focus on peroxisome proliferator activated receptors (PPAR). Cardiovasc Diabetol 2003;2:4.
8. Berger JP, Akiyama TE, Meinke PT. PPARs: Therapeutic targets for metabolic disease. Trends Pharmacol Sci 2005;26:244-51.
9. Fruchart JC, Staels B, Duriez P. The role of fibric acids in atherosclerosis. Curr Atheroscler Rep 2001;3:83-92.
10. Forcheron F, Cachefo A, Thevenon S, Pinteur C, Beylot M. Mechanisms of the triglyceride and cholesterol-lowering effect of fenofibrate in hyperlipidemic type 2 diabetic patients. Diabetes 2002;51:3486-91.
11. Staels B, Fruchart JC. Therapeutic roles of peroxisome proliferator-activated receptor agonists. Diabetes 2005;54:2460-70.
12. Israelian-Konaraki Z, Reaven PD. Peroxisome proliferator-activated receptor-alpha and atherosclerosis: From basic mechanisms to clinical implications. Cardiology 2005;103:1-9.
13. Chinetti G, Lestavel S, Fruchart JC, Clavey V, Staels B. Peroxisome proliferator-activated receptor alpha reduces cholesterol esterification in macrophages. Circ Res 2003;92:212-7.
14. Harrity T, Farrelly D, Tieman A, et al. Muraglitazar, a novel dual (alpha/gamma) peroxisome proliferator-activated receptor activator, improves diabetes and other metabolic abnormalities and preserves beta-cell function in db/db mice. Diabetes 2006;55(1):240-8.
15. Wang L, Zhang D, Swaminathan A, et al. Glucuronidation as a major metabolic clearance pathway of 14c-labeled muraglitazar in humans: Metabolic profiles in subjects with or without bile collection. Drug Metab Dispos 2006;34(3):427-39.
16. Buse JB, Rubin CJ, Frederich R, Viraswami-Appanna K, Lin KC, et al. Muraglitazar, a dual (alpha/gamma) PPAR activator: A randomized, double-blind, placebo-controlled, 24-week monotherapy trial in adult patients with type 2 diabetes. Clin Ther 2005;27(8):1181-95.
17. Kendall DM, Rubin CJ, Mohideen P, et al. Improvement of glycemic control, triglycerides, and HDL cholesterol levels with muraglitazar, a dual (alpha/gamma) peroxisome proliferator-activated receptor activator, in patients with type 2 diabetes inadequately controlled with metformin monotherapy: A double-blind, randomized, pioglitazone-comparative study. Diabetes Care 2006;29(5):1016-23.
18. Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. JAMA 2005;23:294(20):2581-6.

19. Desvergne B, Michalik L, Wahli W. Be fit or be sick: Peroxisome proliferator-activated receptors are down the road. Mol Endocrinol 2004;18:1321-32.
20. Argmann CA, Cock TA, Auwerx J. Peroxisome proliferator-activated receptor gamma: The more the merrier? Eur J Clin Invest 2005;35:82-92.
21. Lazar MA. PPAR gamma, 10 years later. Biochimie 2005;87:9-13.