Review Article and Clinical Experience:
A NOVEL "TWO-IN-ONE" DRUG FIXED COMBINATION OF ROS AND MET
Its Roles on IR, Prediabetes, MetS, T2DM and CVD

Askandar Tjokroprawiro
Airlangga University School of Medicine
Diabetes and Nutrition Center,
Dr. Soetomo Teaching Hospital, Surabaya

ABSTRACT

Joint Statement of ADA and EASD in 2005 revealed: the term "metabolic syndrome" (the MetS) refers to a clustering of specific CVD risk factors whose underlying pathophysiology is thought to be related to insulin resistance. Until much needed research is completed, clinician should evaluate and treat all CVD risk factors without regard to whether a patient meets the criteria for diagnosis of the MetS. Rationale Strategies for the treatment of the MetS or insulin resistance syndrome in patients with T2DM are focused on 2 main targets. First, improving insulin sensitivity: Therapeutic Lifestyle Changes (TLCs) and Pharmacological Treatments, f.e Glitazone Compounds, Metformin, Sibutramine, and Orlistat Etc. Second, treating the manifestations of IRS or the MetS: TLC and Pharmacological Interventions. This regimen is targeted (mmHg, ml/dl) for H, D, and L as follows: hypertension (H): < 130/85, and < 130/80 for diabetic patients, diabetes mellitus (D) – FPG < 100 or 2 hour post-75 glucose challenge < 140, and lipids (L) – TG < 150, and HDL-Cholesterol > 40 for men, and > 50 for women. It has been well established that TZDs enhance insulin sensitivity by acting as ligands for the transcription of PPAR-γ. There is a strong relationship between tissue lipid or TG content and insulin resistance in both skeletal muscle and liver. Recent studies demonstrated that rosiglitazone, a TZD, enhances insulin sensitivity in patients with T2DM by promoting increased insulin sensitivity in peripheral adipocytes, which results in lower plasma fatty acid levels and a redistribution of intracellular lipid from insulin responsive organs into peripheral adipocytes. Rosiglitazone (ROS) improves blood sugar levels in patients with T2DM by increasing glucose uptake at the peripheral tissues (acts through the PPAR-γ receptor system) and, to a lesser extent, by inhibiting hepatic glucose production (HGP), hence ROS acts also at the liver level. Complementary, metformin (MET) exerts an antihyperglycemic action by improving insulin action at the liver level and, to a lesser extent, at peripheral tissues

Keywords: *metabolic syndrome (MetS), Rosiglitazone (ROS), Therapeutic Lifestyle Changes (TLCs), insulin resistance syndrome (IRS), T2DM*

Correspondence: Askandar Tjokroprawiro, Airlangga University School of Medicine, Diabetes and Nutrition Center, Dr. Soetomo Teaching Hospital, Jl Mayjen Mustopo 6-8, Surabaya, phone: 62-31-5501625

INTRODUCTION

The improvement in insulin sensitivity is accompanied by enhanced glucose-stimulated insulin secretion by pancreatic β-cells and by falls in fasting plasma insulin, proinsulin, and split proinsulin concentrations. Rosiglitazone has been shown to protect human pancreatic islets from the cystostatic effect of free fatty acids. However, ROS administration to patients with T2DM is associated to a decrease in circulating levels of CRP, vWF, MMP-9, CD40L, E-selectin, fibrinogen, and an increase in adiponectin (an anti-inflammatory adipokine). In muscle tissue, MET increases insulin-mediated glucose uptake, glycogen storage and glucose oxidation, where as at the adipose tissue level MET restrains lypolysis. A reduction of PAI-1 and fibrinogen has been also reported in patients with T2DM and in obese individuals. Based on such complementary pleiotropic effects of ROS and MET, the prefixed combination of these two drugs provide an interesting opportunity and also may improve patients' compliance. Visceral fat and accumulation fat at the ectopic sites, such as the liver and skeletal muscle, is strongly associated with insulin resistance (IR), the key risk factor for prediabetes (Pre-DM), the metabolic syndrome (the MetS), T2DM, and cardiovascular disease (CVD). Thus, the fixed dose combination of ROS and MET may provide a rational therapeutic regimen for these preclinical and clinical diseases. On the basis of the complementary pleiotropic actions of ROS and MET, the combination of these two agents may have potential beneficial impact either in insulin resistance (IR) or in its related preclinical (Pre-DM and the MetS) and clinical diseases (T2DM, CVDs, and

Stroke). Hence, Avandamet TM, a novel "two-in-one" drug fixed dose combination of ROS and MET, can be implemented in patients with IR, prediabetes, the MetS, T2DM with or without CVDs. In addition to such beneficial effects, this prefixed combination may improve patients' compliance.

PLEIOTROPIC EFFECTS OF ROSIGLITAZONE

It has been well established that TZDs enhance insulin sensitivity by acting as ligands for transcription peroxisome proliferator-activated receptor-γ (PPAR-γ). However, PPAR-? is predominantly expressed in adipose tissue, whereas the improvement in insulin sensitivity occurs predominantly in skeletal muscle where PPAR-γ expression is relatively low. This paradox suggests that the TZDs may indeed modulate key communication signals between fat and muscle, such as leptin, adiponectin, TNFa, resistin, and fatty acids. It has been demonstrated that there is a strong relationship between tissue lipid content and insulin resistance in both skeletal muscle and liver.

Recent study, 3 month treatment in patients with T2DM with rosiglitazone (4mg b.i.d) resulted in enhanced insulin sensitivity. This improvement in insulin responsiveness was associated with a marked reduction in hepatic triglyceride content and an increase in extramyocellular lipid content (EMCL). In obesity an increased in intramyocellular lipid content (IMCL) may cause insulin resistance (Krssak et al. 1999). Rosiglitazone improve insulin sensitivity in patients with T2DM by activating PPAR-? in peripheral adipocytes and promoting adipocyte differentiation (Adams et al. 1997). This results in an increase in smaller and more insulin-responsive adipocytes, which in turn leads to lower circulating plasma fatty acid levels (this evidence may preserve ß-cell function) and a redistribution of lipid (and intracellular fatty acid metabolites) from liver and muscle to peripheral adipocytes. The lower circulating fatty acids are associated with an enhancement of insulin ability to suppress peripheral adipocyte lipolysis (lipolytic effect of HSL is suppressed by insulin).

The improvement in insulin sensitivity is accompanied by enhanced glucose stimulated insulin secretion by pancreatic ß-cell and by falls in fasting plasma insulin, proinsulin, and split proinsulin concentration (Lebovitz et al. 2001; Porter et al. 1999). In vitro, rosiglitazone has been shown to protect human pancreatic islets from the cytostatic effect of free fatty acids (Lupi et al. 2003). Apart from pancreatic ß-cells, evidence of protection of other organs and tissue is suggested by reduced albumin excretion (Bakris et al. 2003). The marked reduction in hepatic triglyceride content in rosiglitazone-treated patients is associated with decreases in serum alkaline phophatase and γ-glutamyl-transpeptidase, both markers of hepatic infiltration that are frequently elevated in nonalcoholic steatohepatitis (NASH). These data suggest that TZD therapy may be useful in patients with NASH, which has been associated with insulin resistance, obesity, and T2DM (Mayerson et al. 2002; Neuschwander-Tetri et al. 2003). Intramuscular triglyceride content is just a marker for another intramyocellular fatty acid metabolite such as fatty acyl CoA, which is actually responsible for event leading to decreased insulin receptor substrate-1 (IRS-1)-associated PI3 kinase activity may results in insulin resistance).

It is also possible that rosiglitazone improves insulin sensitivity in T2DM by altering the concentrations of certain adipocyte derived hormones, such as leptin, TNF-α, adiponectin, or resistin. Rosiglitazone treatment caused a significant increase in EMCL, a finding that is consistent with its effects in promoting adipocyte differentiation and suggests that extramyocellular adipocytes behave similarly to peripheral adipocytes in response to TZDs. Thus, increasing total body fat mass which is exclusively attributable to an increase in peripheral adiposity, while visceral fat stores decreased (Carey et al. 2002). This redistribution of body fat may result from the predilection for certain PPAR-γ agonists to induce pre-adipocytes differentiations in subcutaneous rather than visceral fat depots. Rosiglitazone administration to patients with T2DM is associated with a decrease in concentrations of circulating CRP, fibrinogen, CD-40L, E-selectin, von Willebrand factor and matrix metalloproteinase-9 (MMP-9) and an increase in the anti-inflammatory adipokine adiponectin (Marx et al. 1999).

The lipid profile of rosiglitazone is rather more ambivalent, with a fall in plasma NEFAs and a rise in HDL2-C being offset by increases in apo-B and Lp(a) (Freed et al. 2002; Ko et al. 2003). Whilst LDL-C also increases, there is a shift from small dense LDL particles to a larger and more buoyant form, which may be less readily oxidized and, therefore, less atherogenic (Freed et al. 2002). Rather surprisingly, plasma triglyceride seems to change little in rosiglitazone-treated patients with T2DM (Freed et al. 2002). TZDs currently are approved for adjuvant treatment of T2DM; they reduce insulin resistance, favorable modify several metabolic risk factors. Pioglitazone and rosiglitazone are two available TZDs in Indonesia, even combined tablet consists of rosiglitazone and metformin (R/ Avandamet) has been introduced and widely prescribed.

SUMMARIZED PLEIOTROPIC EFFECTS OF ROSIGLITAZONE

Rosiglitazone (ROS) improves glycemic control in patients with T2DM by increasing glucose uptake in the peripheral tissues (through activation of the PPAR-γ) and, to a laser extent, by inhibiting hepatic glucose production. It improves insulin sensitivity, preserves β-cell function, and lowers fasting plasma insulin, proinsulin, and split proinsulin concentrations. ROS also reduces albumin excretion, ameliorates steatohepatitis in subjects with NASH, and reduces PAI-1 as well as systemic low-grade inflammation. Treatment with rosiglitazone to patients with T2DM is associated with a decrease in concentrations of circulating CRP, fibrinogen, CD40L, E-selectin, von Willebrand factor, MMP-9, and an increase in the anti-inflammatory adipokine adiponectin. The lipid profile of rosiglitazone treated patients show a fall in plasma NEFA and a rise in HDL2-C. In contrast, such benefits are being offset by increases in Apo B and Lp(a). Whilst LDL-C also increases, there is a shift from small dense LDL particles to a larger and more buoyant form, which may be less readily oxidized and, therefore less atherogenic. On the basis of these pleiotropic-effects, rosiglitazone may have potential preclinical and clinical benefits on patients with insulin resistance, prediabetes, the MetS, T2DM, and/or cardiovascular diseases.

PLEIOTROPIC EFFECTS OF METFORMIN

Mounting evidence indicates that metformin may reduce the risk of vascular complications in patients with T2DM. Seven leading articles mentioned below reported summarized cardiovascular benefits of this drug such as (Tjokroprawiro 2004 B) reducing insulin resistance (Giannarelli et al. 2003), beneficial effects on homeostasis and vascular function (Grant 2003), potential contribution to the management of the metabolic syndrome and type 2 diabetes mellitus (Després 2003), antiatherogenic properties (Mamputu et al. 2003), inhibition of glycation processes (Beisswenger et al. 2003), vascular protection (Garber 2003, Libby 2003), prevention of type 2 diabetes mellitus and cardiovascular complications in high-risk subjects (Standl 2003).

Since 1994, Tjokroprawiro (2004 A, B) has collected and summarized 21 metabolic and vasoprotective properties of metformin. Importantly, quadruple effects of metformin in fibrinolysis and antithrombosis are reported such as: to decrease serum levels of fibrinogen, Factor-VII, PAI-1 and Factor-XIIIa. It has been known that Factor-XIIIa is a potent stabilizer of fibrin in which the latter may cause coronary atherosclerosis or acute thrombosis. The outcomes of intensive glycemic therapy reported by UKPDS in 1998 showed significant decreases in risk (compared with conventional therapy), f.e.: diabetes-related death 42%, all cause mortality 36%, any diabetes-related endpoint 32%, myocardial infraction 39%, and stroke 41%.

The Diabetes Prevention Program (DPP) recently reported in 2002 that incidence of diabetes in people with IGT was reduced by 58% with therapeutic lifestyle changes (TLCs) and by 31% with metformin after a mean duration of 2.8 years of intervention. Garber (2003) concluded 10 (ten) pleiotropic effects of metformin in reducing the risk of cardiovascular diseases and classified into 2 groups. First, it improved 5 items: insulin sensitivity, fibrinolysis, nutritive capillary flow, hemorheology, and post ischemic flow; and second, it reduced 5 items: hypertriglyceridemia, AGE-formation, cross-linked fibrin, neovascularization, and oxidative stress.

Metformin is more than an oral antihyperglycemic drug which shows 21 potential pleiotropic properties (Tjokroprawiro 2004 A, B). In carbohydrate metabolism, metformin decreases glucose absorption, decreases fasting blood glucose, decreases 2 hour post prandial blood glucose, increases glycogenesis, increases insulin receptor binding, increases GLUT-5 expression in the gut, activates post-receptor effect, decreases GLP-1 degradation, and prevents ß-cell from gluco-and lipo-toxicity. As lipid modifiers, metformin decreases total cholesterol, and LDL cholesterol, decreases triglyceride, and increases HDL cholesterol. Metformin also provides vasoprotective effects, that is to decrease hyperinsulinemia, decrease platelet aggregation, increases erythrocyte deformability, increase fibrinolysis (decreased fibrinogen, F-VII, PAI-1, and F-XIIIa), increase peripheral arterial blood flow, decrease capillary permeability, decrease carbonyl stress, decrease smooth muscle cell-fibroblast proliferation, and decrease retina neovascularisation. Conclusively, metformin can be used as therapeutic options in the treatment of patients with insulin resistance, IGT, IFG, the MetS, T2DM and CVDs. Importantly, 4 fibrinolytic and antithrombotic effects of metformin should be recognized such as, to decrease fibrinogen, lower F-VII, decrease PAI-1 and lower F-XIIIa.

SUMMARIZED PLEIOTROPIC EFFECTS OF METFORMIN

Metformin shows an antihyperglycemic action by improving insulin sensitivity at the level of the liver and, to a lesser extent, at the peripheral tissues as the

results from multiple actions, such as to increase insulin receptor tyrosine kinase (IRTK) activity, to increase number and activity of GLUT-4 and to enhance glycogen synthesis. At the level of the liver metformin reduces hepatic glucose production by inhibiting gluconeogenesis and possibly, glycogenesis. At muscle tissue metformin increases insulin mediated glucose uptake, glycogen storage, and glucose oxidation. At the adipose tissue level metformin restrains lypolysis.

Metformin protects the pancreatic islet from the insult caused by high level of glucose (glucotoxicity) and/or free fatty acids (lipotoxicity). Metformin treated-patients with T2DM shows a decreased plasma triglycerides and LDL, slight increase in HDL, and reduction of PAI-1. Importantly, metformin shows fibrinolytic and anti-thrombotic effects. It decreased fibrinogen, lowered F-VII, decreased PAI-1, and lowered F-XIIIa. In conclusions, metformin shows improvement (insulin sensitivity, fibrinolysis, nutritive capillary flow, haemorrheology, postischaemic flow), and reduction (hypertiglyceridaemia, AGE formation, cross-linked fibrin, neovascularization, oxidative stress), and hence, reduced CV risk may pursue.

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