

REVIEW

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Updated Review: Improved Glycemic Control with Repaglinide-Metformin in Fixed Combination for Patients with Type 2 Diabetes

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Abstract: As the prevalence of type 2 diabetes continues to rise, new drug therapies will need to be explored to prevent morbidity and mortality associated with diabetes as well as growing health care costs. Type 2 diabetes is characterized by decreased insulin secretion and sensitivity. Numerous oral medications are currently approved for the treatment of type 2 diabetes. A treat-to-failure approach has traditionally been adopted with step-wise additions of oral medications; however, a growing frequency of treatment failures with monotherapy has led to the use of combination therapies earlier in the treatment of type 2 diabetes. One such combination regimen is repaglinide (a prandial glucose optimizer that increases insulin release) plus metformin (an insulin sensitizer that inhibits hepatic glucose output and increases peripheral glucose uptake while minimizing weight gain). Findings from several clinical trials have shown repaglinide plus metformin combination therapy to be superior to either monotherapy with significant reductions in hemoglobin A1C and fasting glucose values. Repaglinide used in combination also has shown less incidence of hypoglycemia compared with other combination therapies such as sulphonylureas plus metformin. Repaglinide plus metformin combination therapy appears to be a valuable therapeutic option for type 2 diabetic patients seeking a less complex drug regimen while potentially achieving better glucose control if currently inadequately controlled on monotherapy.

Keywords: type 2 diabetes, metformin, repaglinide, fixed-dose combination

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Introduction

Diabetes mellitus continues to pose a challenge on a global scale as its prevalence has risen to epidemic proportions with even higher projections expected in the future. With growing prevalence (due to aging population, physical inactivity, and obesity) come higher levels of associated morbidity, mortality, and healthcare costs. Approximately 90 to 95 percent of people with diabetes have type 2 necessitating continued investigation of new as well as existing therapeutic regimens to manage this form of the disease and its complications.

In this review, we examine the benefits of targeting both hepatic gluconeogenesis and insulin deficiency (β -cell dysfunction) through the use of combined oral antidiabetic drugs (OADs). We specifically examined metformin which predominantly acts to decrease hepatic gluconeogenesis and may contribute to weight loss as well as exploring the benefits of repaglinide, a secretagogue, in fixed combination to improve glycemic control in patients with type 2 diabetes.

Pathophysiology

Type 2 diabetes has two defining defects: insulin resistance (IR) which develops in peripheral tissues (mainly adipose tissue and skeletal muscle) and pancreatic beta cell dysfunction which causes a reduction in pancreatic insulin secretion.¹ During the early stages of beta cell dysfunction insulin is unable to suppress hepatic glucose production leading to a rise in postprandial blood glucose levels.² As type 2 diabetes progresses both fasting and postprandial blood glucose values rise due to a progressive decrease in beta cell function with reduced insulin secretion. This is a progressive process that continues until beta cell damage is complete making these patients dependent on peripheral injections of insulin life-long.

The harmful effects of chronic hyperglycemia are not limited to the beta cells alone, as studies have shown that chronic hyperglycemia is also associated with both increased risk of micro- and macrovascular complications.³ The resultant complications from hyperglycemia worsen morbidity and mortality in these patients through increased risk of diseases like coronary artery disease (CAD) and stroke.⁴ Microvascular disease can also produce significant morbidity with 2% of long-standing type 2 diabetic patients developing blindness (retinopathy) and approximately

half of all diabetic patients developing some form of neuropathy. And with diabetes reigning as the leading cause of kidney disease (nephropathy) it becomes evident that the microvascular complications of diabetes indirectly increase mortality as renal failure requiring dialysis carries a high mortality rate.⁵

Treatment Goals

In the treatment of type 2 diabetes the goal is to first achieve good glycemic control, then maintain that control while avoiding hypoglycemic episodes with the sole purpose of minimizing the risk of diabetes associated complications. This can prove to be a daunting task for any healthcare provider especially when avoiding hypoglycemia is high priority. Currently, according to the ADA in 2010 good glycemic control was considered a hemoglobin A1C (A1C) less than seven percent but the guidelines also suggest that A1C goals must be determined on a case-by-case basis as some patients may experience negative outcomes with strict glycemic targets.⁶ The management of type 2 diabetes typically begins with life-style changes (diet, exercise, and weight loss) combined with initiation of metformin as targeted therapy for treating hyperglycemia.⁷

We have learned that combination therapy remains more effective than monotherapy for treating disease because it targets pathological defects at various sites increasing the rate of success. Repaglinide and metformin have been previously approved to be used in a fixed-dose combination (FDC) with the expectation that better glycemic control can be achieved through targeting multiple defects with a single therapy as well as improved compliance.⁸ This drug combination received its approval by the Food and Drug Administration (FDA) in June of 2008 with the purpose of targeting three abnormalities of type 2 diabetes: impaired insulin secretion, insulin resistance and excessive hepatic glucose production. In this article we intend to discuss the advantages and disadvantages of repaglinide-metformin combination therapy and the studies to date that support these opinions.

Meglitinides

The meglitinides, repaglinide and nateglinide are non-sulphonylurea short-acting insulin secretagogues that function through the inhibition of potassium ATP

(K_{ATP}) channels (Fig. 1). These agents are uniquely different from sulphonylureas because they bind to different locations on the potassium channel.⁹ The meglitinides stimulate insulin release in the presence of glucose meaning that these medications should be taken just before or with meals, and because of this mechanism of action they have been shown to improve postprandial hyperglycemia.¹⁰ Although the meglitinides share similar mechanisms of action they remain distinct in that the structures differ and nateglinide has a more selective affinity for pancreatic K_{ATP} than cardiac K_{ATP} while repaglinide remains more non-selective.¹¹ This type of selectivity for cardiac K_{ATP} could potentially lead to impaired cardiac function and increased risk of cardiovascular events with repaglinide use versus nateglinide,¹² however studies do not support this claim.

Compared to sulphonylureas, the meglitinides are thought to reduce the incidence of hypoglycemic events because they promote insulin secretion only in the presence of hyperglycemia, whereas sulphonylureas have been shown to increase insulin secretion at considerably low concentrations of blood glucose.¹³ In addition, studies have shown repaglinide to potentially reduce the risk of diabetes associated complications like macro- and microvascular disease through the reduction of oxidative stress, a potent contributor of vascular dysfunction.¹⁴ This is thought to occur because of repaglinide's effect on postprandial glucose lows.

Changes in qualitative measures like A1C have also been evaluated in past studies of meglitinides showing both repaglinide and meglitinides to be

effective at reducing A1C values in type 2 diabetic patients.¹⁵ When the two agents are compared we find repaglinide to have similar efficacy to sulphonylureas in A1C reduction¹⁶ with nateglinide appearing to be slightly less efficacious.¹⁷ Studies examining the use of repaglinide as monotherapy have shown A1C reductions up to 2.3% with fasting and postprandial reductions of 3.9 mmol/L and 6.4 mmol/L respectively.¹⁸ Repaglinide's ability to effectively target multiple glycemic parameters, especially postprandial hyperglycemia, improves the risk of diabetes-associated complications and therefore reduces mortality risk.¹⁹

The pharmacokinetics of repaglinide includes a bioavailability of 56% (in healthy volunteers) with more than 98% albumin bound and a short half-life of approximately one hour. Drugs inhibiting CYP2C8 and CYP3A4 (ie, gemfibrozil, ketoconazole, and etc.) will alter the pharmacokinetics of repaglinide as these particular CYP enzymes are involved in the metabolism of the drug. Approximately 90% of the drug is cleared in the feces and about 8% is eliminated in the urine.²⁰

Metformin

Metformin has effects mediated by the action of AMP-activated protein kinase and reduces hyperglycemia through inhibition of hepatic glucose production and improvement in insulin sensitivity (Fig. 1).²¹

Metformin targets fasting hyperglycemia through the inhibition of hepatic gluconeogenesis and potential increases in glucagon-like peptide 1 (GLP-1).²¹ Metformin has also been shown to have beneficial effects on cardiovascular risk factors.²² Most patients tolerate metformin with the most common side-effect being gastrointestinal upset which can be reduced with a low starting dose and slow titration to the maximum effective dose. Metformin has been shown to have few drug-drug interactions and since it does not affect insulin secretion, risk of hypoglycemia remains low.

Studies of metformin as monotherapy in type 2 diabetic patients has shown A1C reductions of as much as 2.5%, including reductions in fasting and postprandial glucose values. Weight reduction has also been reported with use of metformin in individuals with type 2 diabetes.²³

Metformin relies on the presence of insulin for its action so as diabetes progresses and insulin levels

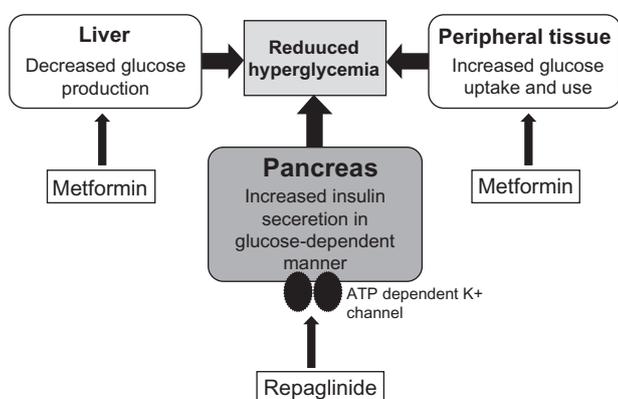


Figure 1. Physiological targets of repaglinide and metformin for the treatment of type 2 diabetes. Adapted from Raskin 2008.²¹



continue to fall achieving tight glucose control when the drug is used as monotherapy becomes more difficult.

The pharmacokinetics of metformin includes a half-life of 6.2 hours and is excreted unchanged in the urine avoiding hepatic or biliary metabolism. Within twenty-four hours of taking metformin approximately 90% of the drug is absorbed and eliminated through the kidneys. Because of metformin's dependence on renal function impaired function increases the risk of metformin-associated lactic acidosis (MALA). Although MALA is a rare (2–9/100,000/year) side-effect it can be fatal with a mortality of more than 50%.²⁴

Repaglinide-Metformin Combination Therapy

The progressive nature of type 2 diabetes makes monotherapy with current OADs difficult because of the limitations making combination therapy a needed alternative for achieving recommended glycemic goals. Repaglinide and metformin have separate but complimentary mechanisms of action targeting different defects in type 2 diabetes that make these drugs ideal choices for use in combination therapy for patients not achieving control with monotherapy (Fig. 1).

Clinical experience with repaglinide-metformin combination therapy

Studies evaluated in a previous review article showed repaglinide-metformin combination to be well tolerated and effective at reducing A1C and fasting blood glucose levels suggesting combination therapy

to be more effective than monotherapy.²¹ Several randomized double-blind studies have looked at repaglinide-metformin combination therapy in type 2 diabetic patients with results presented in Table 1.

In these studies patients ranged from 55–65 years of age with male predominance and body mass indices (BMI) from 31–33 kg/m² and carried a diagnosis of diabetes for 6–9 years with unknown complications. These patients were treated with repaglinide doses ranging from 0.5–4 mg titrated as tolerated before meals with combined metformin at 2 grams daily.

Combining repaglinide and metformin for the treatment of poorly controlled type 2 diabetic patients has been shown to be more effective than monotherapy with either of these agents alone. Moses and colleagues demonstrated just how effective combination therapy was through a randomized controlled study showing a greater number of repaglinide-metformin treated patients reaching A1C goals of 7.1% compared to monotherapy.²⁵ Upon follow-up after 3 months of therapy both monotherapy groups showed similar A1C reductions, whereas in the combination therapy group there was a statistically significant reduction in A1C values (from 8.3 to 6.9%; $P = 0.0016$). By the end of the study approximately 60% of patients in the repaglinide-metformin combination arm achieved an A1C of less than 7% with inferior reductions displayed in the monotherapy arms (Fig. 2).

In addition, a study by Shapiro et al evaluating poorly controlled type 2 diabetic patients following 16 weeks of combination therapy with repaglinide plus metformin also showed significant reductions in

Table 1. Efficacy of combination therapy with repaglinide and metformin vs. monotherapy in randomized double-blind studies.

Reference	Study design	Baseline A1C	Mean reductions in A1C
Moses et al ²⁵ and Moses et al ²⁶	4–5 months of treatment with: Repaglinide + placebo (n = 29) Placebo + metformin (n = 27) Repaglinide + metformin (n = 27)	8.3	1.4%
Reboussin et al ²⁷	16 weeks of treatment with: Repaglinide (n = 44) Repaglinide + metformin (n = 42)	8.3	1.0% 1.7%
Raskin et al ¹⁷	16 weeks of treatment with: Repaglinide + metformin (n = 96) Nateglinide + metformin (n = 96)	8.4 8.2	1.3% 0.7%

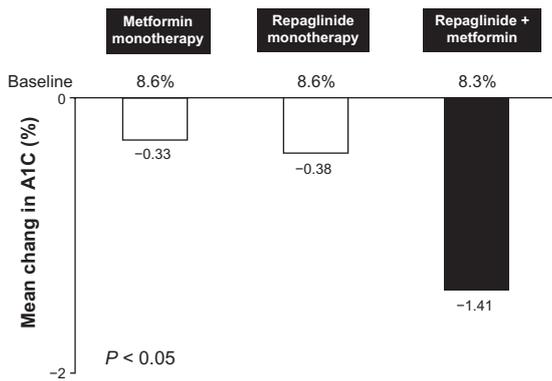


Figure 2. Mean change in A1C levels from baseline in patients receiving metformin or repaglinide monotherapies versus repaglinide + metformin combination therapy. Drawn from data of Moses et al 1999.²⁵

A1C and an increased number of these patients reaching A1C goals of less than 7% compared to repaglinide monotherapy.²⁸ In this study the majority of patients were 56–65 years of age with unknown duration of disease and complications. Patients were treated with repaglinide starting at a dose of 0.5 mg before each meal and titrated according to blood glucose values. Reboussin and colleagues also showed a significant reduction in A1C in the repaglinide-metformin arm compared to the repaglinide monotherapy arm as well as greater improvements in fasting glucose levels with combination therapy (Table 1).²⁷

Dosing strategies

Studies have also evaluated the effectiveness of using various dosing strategies with repaglinide + metformin combination therapy to determine if twice daily versus three times daily dosing demonstrated improved benefit in treating type 2 diabetes. Results from a 26 week study comparing these two dosing strategies showed similar reductions in A1C of -0.99% and -1.02% from baseline in the twice and three times daily arms, respectively²⁹ (Fig. 3). This study showed no statistically significant difference between the two arms proving that twice daily dosing was non-inferior to the three times daily dosing regimen (confidence interval [CI]: -0.104 to 0.349). There were also further similarities in the two groups with 42.9% and 48.9% of patients at 26 weeks reaching target A1C goals of less than 7% in the twice and three times daily groups respectively. Essentially there was no significant difference between the treatment regimens in terms of the number of patients reaching the target A1C

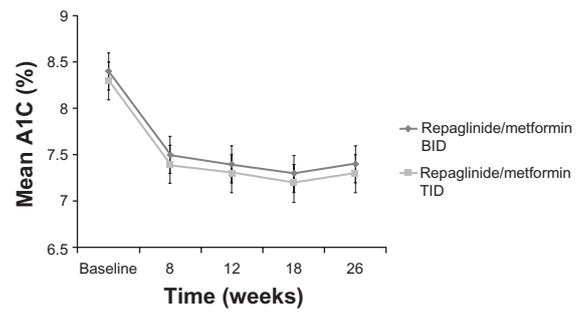


Figure 3. Mean change in A1C levels from baseline to 26 weeks in patients receiving repaglinide/metformin twice daily (BID) and three times daily (TID) fixed-dose combination regimens. Drawn from data of Raskin et al 2009.²⁹

goals. The two groups also showed similar reductions in fasting glucose levels with mean reductions of -1.13 mmol/L and -1.10 mmol/L for the twice and three times daily regimens, respectively. These results suggest that patients would benefit most from twice daily dosing versus three times daily dosing as this regimen provides the most benefit with the lowest risk of adverse events.

Safety and side-effects

Data addressing the safety and side-effects of repaglinide and metformin combination therapy have shown this drug combination to be as safe with no increased risk of side-effects compared to monotherapy with either agent. Moses et al has shown a comparable incidence of gastrointestinal complications (ie, nausea, vomiting, diarrhea) compared with metformin monotherapy.²⁵ The complimentary actions of repaglinide and metformin may help reduce the possible side-effects that higher doses of metformin would cause by decreasing the need for high dose metformin therapy.²⁵ Soegondo and colleagues demonstrated a low incidence of hypoglycemia (approximately 9%) in a study of repaglinide and metformin combination therapy in type 2 diabetic patients.³⁰ These episodes of hypoglycemia were also shown to be mild.²⁵ Studies have shown long-term weight-neutrality with the use of repaglinide and metformin combination therapy in the treatment of type 2 diabetes.³⁰

Repaglinide and metformin combination therapy should be avoided in patients with kidney and liver disease and those prone to malabsorption of vitamin B12 as this medication regimen increases the risk of lactic acidosis and megaloblastic anemia in patients with these co-morbidities. This medication should



also be avoided in breast-feeding women as no studies have been done to assess whether this drug passes into breast milk and the effect on a nursing infant is unknown. Repaglinide and metformin combination therapy should also be avoided in patients taking gemfibrozil and itraconazole together as this combination has been shown to significantly increase the plasma concentration of repaglinide.³¹ Other medications, such as cyclosporine, trimethoprim, itraconazole, clarithromycin, erythromycin, rifabutin, and St. John's wort also affect the removal of repaglinide from the body increasing a patient's risk of adverse events and should be avoided while taking this combination regimen.

Repaglinide and Metformin Combination Versus Other Metformin-Containing Combination Regimens

Multiple studies have evaluated the efficacy of combination therapy with various OADs [ie, secretagogues, thiazolidinediones (TZDs), α 1-glucosidase inhibitors, and DPP-4 inhibitors] and metformin but specific studies have been chosen for the purpose of discussion and outlined in Table 2. Safety data shows metformin combined with nateglinide or DPP-4 inhibitors (ie, vildagliptin and sitagliptin) is well tolerated, but when metformin was combined with glyburide, 74% of patients reported hypoglycemic episodes.²¹ Metformin combined with the TZDs (ie, rosiglitazone and pioglitazone) has been shown to be well tolerated by patients with common side-effects

including worsening edema, congestive heart failure, and weight gain.³²

Yet despite their effectiveness and tolerability, their popularity has decreased greatly due to cardiovascular safety concerns and increased risk of fractures. With a carbose and metformin combination gastrointestinal side effects associated with acarbose (ie, abdominal pain, diarrhea, and flatulence) may limit its use, especially in conjunction with metformin which can have significant gastrointestinal side effects. However, commonly in clinical practice, α 1-glucosidase inhibitors are not considered first line therapy.

Studies have been performed comparing repaglinide and metformin combination therapy to metformin combined with other secretagogues (ie, nateglinide and glyburide). In one 16 week study of repaglinide/metformin combination therapy results showed this regimen to be superior at reducing A1C and fasting glucose levels compared to nateglinide/metformin combination in adults ≥ 18 years old with type 2 diabetes for at least 3 months and BMI values of 24–42 kg/m². This was a statistically significant difference ($P < 0.05$) between the two arms (Fig. 4).¹⁷ Both regimens were found to be equally safe in patients. In another study looking at hypoglycemic events in repaglinide/metformin combination versus glyburide/metformin combination, repaglinide/metformin combination demonstrated less hypoglycemic episodes with fewer events of glucose values < 55 mg/dL. The results of these studies suggest that repaglinide/metformin combination is as effective as other combination therapies

Table 2. Efficacy data from important combination therapy clinical trials using metformin.

Studies	Previous therapy (baseline A1C,%)	Mean A1C reduction (%)	Proportion of patients with A1C levels $< 7.1\%$ (%)	Mean fasting plasma glucose reduction (mmol/l)
Repaglinide plus metformin ^{17,27,33}	OAD therapy (8.2–8.4)	1.3–1.7	59–71	2.2–4.7
Nateglinide plus metformin ^{17,34–36}	OAD therapy (7.7–8.2)	0.4–0.7	47–58	0.6–1.2
	Treatment naive (8.2–8.4)	1.5–1.6	70	1.6–2.3
Pioglitazone/rosiglitazone plus metformin ^{37,38}	OAD therapy (8.8)	0.9–1.3	28–64	0.4–2.9
Acarbose plus metformin ^{39,40} Fixed-dose glyburide– Metformin ³⁷	OAD therapy (8.0–8.5)	0.2–0.7	36–42	0.7–1.0
	OAD therapy	1.5	60	2.6
	Treatment naive (8.8)	2.3	79	3.5
Vildagliptin/sitagliptin plus metformin ^{34,41,42}	OAD therapy (7.6–8.0)	0.5–0.7	42–47	0.5–1.2

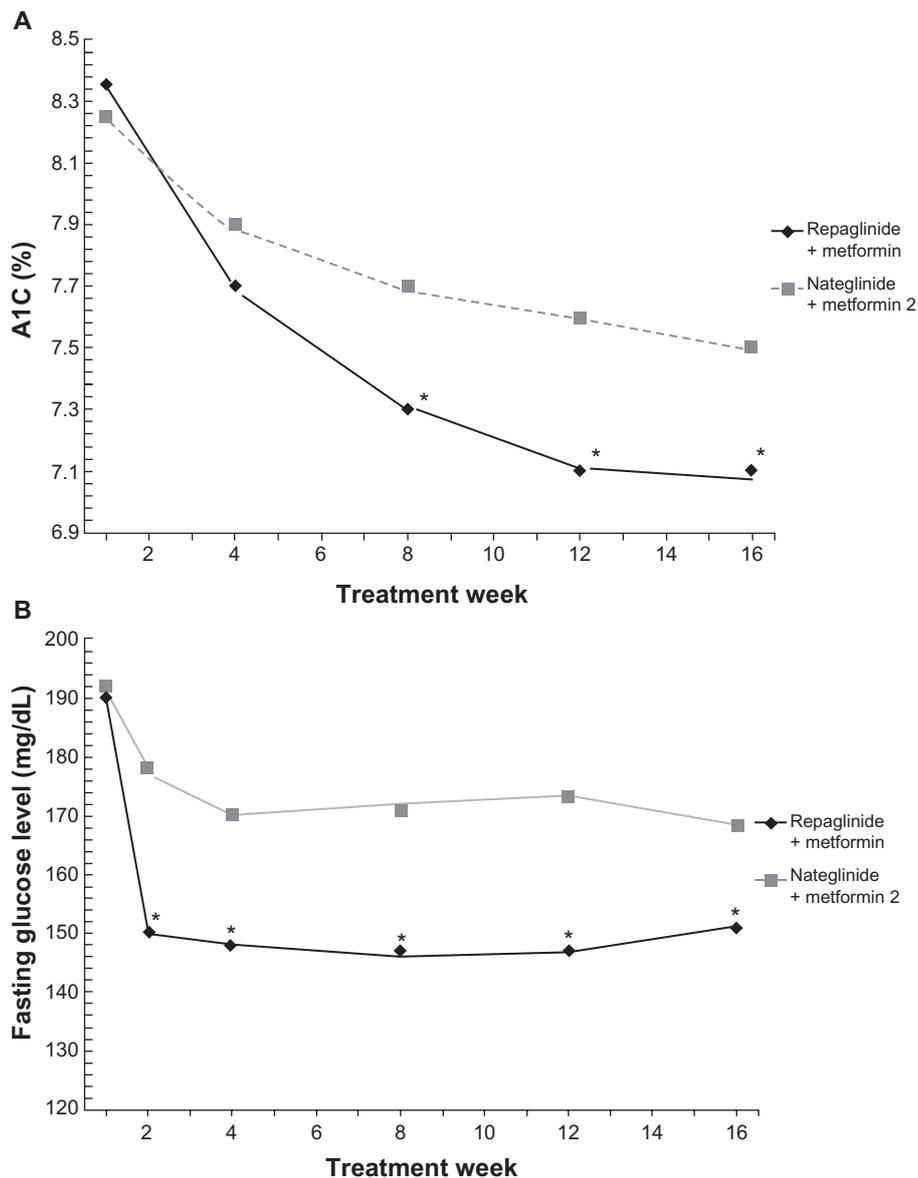


Figure 4. Reduction in A1C (A) and fasting glucose levels (B) after treating patients with repaglinide plus metformin combination therapy compared with nateglinide plus metformin combination therapy. Drawn from data of Raskin et al 2003.¹⁷

in treating type 2 diabetes and may deliver treatment more safely compared to other therapies.

Repaglinide and Metformin Therapy Provides Economic Benefits

The use of combination therapy affords many benefits including: less side-effect related to higher dosing of medications, improvements in patient compliance, and reductions in overall cost of therapy. When evaluating improvements in patient compliance, especially in fixed-combination agents, a meta-analysis of studies

(two studies of diabetic patients) showed a 26% decrease in non-compliance risk with combination therapy versus using the drugs individually in combination.⁴³ A study by Palmer and colleagues has even suggested that the use of repaglinide/metformin combination provides improved quality of life and life expectancy in type 2 diabetic patients compared to treatment with nateglinide/metformin combination therapy.⁴⁴ ENREF_51_ENREF_52_ENREF_51_ENREF_53_ENREF_53_ENREF_53. This study also suggested an estimated savings of >\$3600



per patient over a 30 year period with repaglinide/metformin combination versus nateglinide/metformin combination therapy.

Conclusions

In the treatment of type 2 diabetes, lifestyle modification combined with metformin as a monotherapy is recommended as first-line therapy. But as type 2 diabetes progresses with worsening beta cell function and subsequent hyperglycemia, failure of therapy is inevitable, making combination therapy vital to improving treatment success rates. As a combination therapy, the addition of repaglinide to metformin is a good choice given their complementary mechanisms of action. Repaglinide (an insulin secretagogue) addresses meal-time glucose variations while metformin (an insulin sensitizer) acts as a basal glucose stabilizer through its inhibition of hepatic glucose production and increased peripheral glucose uptake. Together these medications provide patients with the possibility of sustained glycaemic control compared with repaglinide and metformin monotherapy which has been shown to be inferior to combination therapy.

Data from multiple studies have shown repaglinide/metformin combination therapy to be more effective and better tolerated than other approaches to treatment with improved glucose control (reductions in A1C and fasting glucose levels), less side-effects (hypoglycemia), and improved compliance and cost. Diabetes is a complex disease with increasing complexity of treatment options making the need for an effective yet simpler therapy necessary to potentially improve adherence and quality of life. And based on current studies there also appears to be some economic benefits to repaglinide/metformin combination use as well.

In conclusion, repaglinide/metformin combination therapy appears to be a valuable therapeutic option for type 2 diabetic patients seeking a less complex drug regimen while potentially achieving better glucose control if currently inadequately controlled on monotherapy.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not

been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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