

Disparity in Response to Metformin among Obese versus Non-Obese Patients with Type 2 Diabetes

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ABSTRACT

OBJECTIVES: The UK Prospective Diabetes Study (UKPDS) demonstrated that intensive glucose control with metformin may decrease the risk of diabetes-related adverse outcomes among obese patients with type 2 diabetes. Therefore, metformin is frequently first-line pharmacotherapy in obese patients. We examined whether there were differences in metformin response between obese (BMI > 30) versus non-obese (BMI < 30) patients.

METHODS: This was a Phase III, 24-week, randomized, double-blind, active-controlled, fixed-dose trial comparing immediate-release metformin (MIR) 1,500 mg/day, b.i.d. (MIR-1500B) versus extended-release metformin (MER) at three doses [1,500 mg/day q.d. (MER-1500Q), 1,500 mg/day b.i.d. (MER-1500B), or 2,000 mg/day q.d. (MER-2000Q)] among adults with type 2 diabetes who were medication naïve or received prior oral anti-diabetic monotherapy. Analyses were conducted on the intent-to-treat (ITT) sample, defined as those receiving at least one dose of medication and at least one A1C follow-up from baseline.

RESULTS: There were 217 non-obese and 428 obese participants. Obese patients achieved significantly greater reduction in A1C from baseline to study end with metformin ER (pooled results across doses) versus MIR-1500B (mean change in A1C percentage points: -1.10 versus -0.75, p=0.0082); there were no significant differences between treatment groups among non-obese patients. Follow-up t-tests indicated that obese patients achieved a significantly greater mean reduction in A1C from baseline to study end with MER-2000Q versus MIR1500B (mean change in A1C percentage points: -1.19 versus -0.75, p=0.006) or MER1500B compared to MIR1500B (mean change in A1C percentage points: -1.16 versus -0.75, p=0.0125).

CONCLUSIONS: Findings demonstrate differential responses to metformin by obesity status.

BACKGROUND

Diabetes mellitus is a metabolic disorder characterized by the presence of chronic hyperglycemia (high blood glucose) due to defects in insulin secretion, insulin action, or both. Type 2 diabetes, which accounts for 90-95% of all diabetes cases, occurs in response to impaired insulin secretion, insulin resistance, or excessive hepatic glucose production. Risk factors include obesity and physical inactivity. Long-term micro- and macrovascular complications, including retinopathy, neuropathy, nephropathy, and cardiovascular disease, may be mitigated by intensive glycemic control.^{3,5}

The glycosylated hemoglobin (A1C) laboratory test provides a long-term (3 to 4 month) measure of average glycemic control and predicts the risk for diabetes-related microvascular and macrovascular complications.

A consensus algorithm recently set forth by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends lifestyle changes with metformin medication as the first step to intensive control of type 2 diabetes.⁶

OBJECTIVES

We sought to answer the following questions:

- Are there differences in persistence rates associated with immediate-release metformin (MIR) versus a novel extended-release metformin (MER) formulation?
- If there are differences in persistence, do these differences affect A1C outcomes?

METHODS

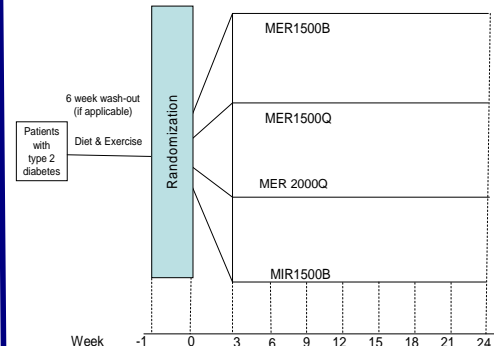
This was a multicenter, randomized, double-blind (double-dummy), active-controlled, dose-ranging, non-inferiority, parallel-group clinical study designed to compare the efficacy and safety of a novel metformin extended-release (MER) formulation at doses of 1500 once daily (MER1500Q), 500 mg in the morning and 1000 mg in the evening (MER1500B), and 2000 once daily (MER 2000Q), to immediate-release metformin 500 mg in the morning and 1000 mg in the evening (MIR 1500B).

The MIR dosage was chosen because it is the most commonly used dosage of metformin and is accepted as being safe and effective with a tolerable side effect profile. The MIR dose regimen used was as described in the product insert. The MER1500Q and MER 1500B dosages were chosen to examine the possible advantages of once-daily vs. twice-daily doses of MER at a comparable dose to that of the control group. The MER2000Q dose was designed to compare the safety and efficacy of this higher dosage to the standard MIR dose.

We report A1C change from baseline across the 4 treatment groups (MER 1500Q, 1500B, MER 2000Q, and MIR 1500B).

Participants were adults with type 2 diabetes who were drug naïve or previously treated with anti-hyperglycemic agents.

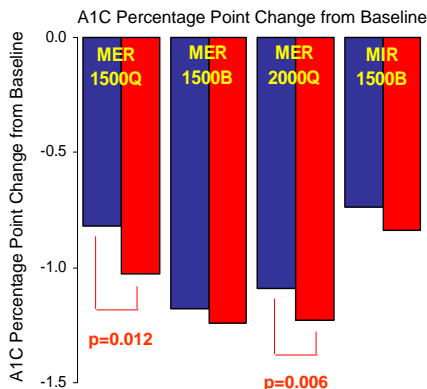
Figure 1. Study Design



RESULTS

Baseline Characteristics

| | MER 1500Q | MER 1500B | MER 2000Q | MIR 1500B |
|------------------------|-----------|-----------|-----------|-----------|
| Mean Age (SD) | 54 (11) | 54 (12) | 55 (12) | 54 (12) |
| Male % | 47% | 61% | 53% | 55% |
| Caucasian % | 60 | 64 | 62% | 64% |
| Mean Yrs Diabetes (SD) | 3.9 (4.5) | 4.5 (4.9) | 3.9 (4.3) | 4.4 (5.4) |
| Drug naïve % | 45% | 47% | 49% | 50% |
| BMI ≥30 % | 25% | 26% | 24% | 25% |
| Mean Baseline A1C (SD) | 8.3 (1.5) | 8.5 (1.5) | 8.2 (1.4) | 8.4 (1.4) |



CONCLUSION

Obesity is a strongly associated with type 2 diabetes. Fifty percent of men and 82% of women with type 2 diabetes exceed their desirable weight by 120%⁷

Given the high likelihood of coexisting type 2 diabetes with obesity, it is important to understand the interaction between BMI and responses to metformin formulations by obesity status.

Our findings indicate that among non-obese type 2 diabetic patients, there were no differences in A1C responses to metformin extended release versus immediate release formulations. However, among obese patients with type 2 diabetes, patients who received once-daily extended release metformin showed significantly better A1C results at study end than those who received immediate release metformin.

REFERENCES

1. Cramer JA. A systematic review of adherence with medications for diabetes. Diabetes Care 2004;27(5):1218-24.
2. Stephens JM, Botteman MF, Hay JW. Economic impact of antidiabetic medications and glycemic control on managed care organizations: a review of the literature. J Manag Care Pharm 2006;12(2):130-42.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352(9131):837-53.
4. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329(14):977-86.
5. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353(25):2643-53.
6. Nathan DM, Buse JB, Davidson MB, et al. Management of Hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and European Association for the Study of Diabetes. Diabetes Care 2006;29(8):1963-1972.
7. National Diabetes Data Group. Diabetes in America, 2nd Edition. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 1995. Report No.: NIH Publication No. 95-1468.

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