Glycemic Control in Patients with Type 2 Diabetes Mellitus Switched from Twice-Daily Immediate-Release Metformin to a Once-Daily Extended-Release Formulation

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ABSTRACT

Background: The extended-release formulation of metformin (MXR) prolongs drug absorption in the upper gastrointestinal tract and permits once-daily dosing in patients with type 2 diabetes mellitus. This newer formulation may enhance patient compliance with oral therapy and improve long-term control of diabetes compared with the conventional immediate-release formulation of metformin (MIR).

Objective: The goal of this study was to determine the effects on glycemic control of a switch to MXR therapy in patients with type 2 diabetes currently treated with MIR.

Methods: This was a multicenter, randomized, double-blind, parallel-group study in patients with established type 2 diabetes. Eligible patients were to have a glycated hemoglobin (HbA1c) value ≤8.5% and mean fasting plasma glucose (FPG) concentrations ≤200 mg/dL while receiving MIR 500 mg BID for at least 8 weeks. After a 2-week, single-blind lead-in period, patients were randomly assigned to receive MXR 1000 or 1500 mg QD for 24 weeks or to continue MIR 500 mg BID for 24 weeks. The primary efficacy variable was change in HbA1c from baseline to week 12. Other variables included change in FPG levels; change in HbA1c; distribution of HbA1c values; mean daily blood glucose concentrations (self-monitored); levels of fructosamine, serum insulin, and lipids; and body weight.

Results: Two hundred seventeen patients were randomized to treatment. The mean change from baseline in HbA1c values at weeks 12 and 24 were small and
similar in the 3 treatment groups. At week 12, the mean change from baseline in HbA1c was 0.15% for MIR, 0.23% for MXR 1000 mg, and 0.04% for MXR 1500 mg. The corresponding mean changes at week 24 were 0.06%, 0.25%, and 0.14%.

Conclusions: In this study, patients with type 2 diabetes who had been receiving twice-daily MIR achieved comparable glycemic control when therapy was switched to once-daily MXR at the same or a greater total daily dose. (Clin Ther. 2003;25:515–529) Copyright © 2003 Excerpta Medica, Inc.

Key words: compliance, diabetes, efficacy, extended-release, immediate-release, metformin.

INTRODUCTION
The biguanide oral antihyperglycemic agent metformin is well established as a therapeutic agent in patients with type 2 diabetes mellitus.1-3 It has a unique mechanism of action,4,5 proven efficacy,6,7 and a favorable safety profile.6,7 Metformin produces clinically significant improvements in glycemic control in patients with type 2 diabetes through its insulin-sensitizing actions on both the liver, where it reduces hepatic glucose overproduction, and peripheral tissues (particularly skeletal muscle), where it enhances glucose uptake.4,5,8-10

Pharmacokinetic studies of the conventional immediate-release formulation of metformin* (MIR) have shown that this agent is absorbed into the upper gastrointestinal tract, with only minimal absorption occurring in the colon.11 The extent of absorption is improved when gastrointestinal motility is slowed.12 An extended-release formulation of metformin† (MXR) has been developed to allow once-daily dosing. This newer formulation releases the active drug through hydrated polymers, which expand after uptake of fluid. This prolongs gastric residence time, which produces slower drug absorption in the upper gastrointestinal tract and allows once-daily dosing.13

Pharmacokinetic investigations in patients with type 2 diabetes have shown that steady-state peak plasma concentrations were higher with MXR than with MIR (MXR 1000 mg:MIR 500 mg ratio, 1.25) and were achieved later (time to maximum concentration delayed 3–5 hours relative to MIR).13 Additionally, the extent of absorption of MXR given once daily in healthy volunteers was similar to that of MIR given twice daily at the same total daily dose, as measured by area under the plasma concentration–time curve (AUC).14 Mean steady-state AUC values were identical after administration of MXR 2000 mg QD and MIR 1000 mg BID (20.5 μg·h/mL).14 This finding suggests the feasibility of once-daily therapy

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*Trademark: Glucophage® (Bristol-Myers Squibb Company, Princeton, New Jersey).
†Trademark: Glucophage® XR (Bristol-Myers Squibb Company).
with MXR and a potential advantage for MXR over conventional MIR in terms of improved patient compliance, as has been reported with other long-acting medications that require less-frequent dosing.\textsuperscript{15–17} Improved compliance with antidiabetic therapy might be expected to result in better glycemic control and a reduced risk of the long-term complications associated with diabetes.\textsuperscript{1,18,19}

To examine whether a switch from twice-daily MIR to once-daily MXR would achieve comparable degrees of glycemic control in patients with type 2 diabetes, investigators conducted a study of the efficacy and tolerability of MXR in patients with type 2 diabetes who had achieved moderate or good glycemic control with MIR.

\textbf{PATIENTS AND METHODS}

\textit{Inclusion and Exclusion Criteria}

Eligible patients had been receiving MIR 500 mg BID for the treatment of type 2 diabetes for at least 8 weeks. They were required to have a glycated hemoglobin (HbA\textsubscript{1c}) value $\leq$8.5\% and mean fasting plasma glucose (FPG) concentrations $\leq$200 mg/dL. The inclusion of patients who had achieved moderate or good glycemic control at moderate doses of MIR was intended to preselect patients who were likely to respond to once-daily MXR.

Patients were also required to be free of symptomatic type 2 diabetes, diabetic ketoacidosis, hyperosmolar nonketotic coma, significant renal disease/dysfunction (serum creatinine level $\geq$1.5 mg/dL for men, $\geq$1.4 mg/dL for women), hepatic dysfunction (serum aspartate aminotransferase or alanine aminotransferase $\geq$2 times the upper limit of normal or total bilirubin $\geq$2 times the upper limit of normal), congestive heart failure, major psychiatric disorders, alcohol and/or substance abuse, seizure disorders, or a history of malignancy. Additionally, patients could not be receiving long-term insulin therapy or any other antihyperglycemic therapy apart from MIR, anticoagulants, antiepileptic drugs, or oral steroids. Pregnant or breast-feeding women were excluded from the study.

\textit{Study Design}

This was a randomized, double-blind, parallel-group clinical trial conducted at 42 centers in the United States between July 1998 and June 1999. The study enrolled patients between the ages of 27 and 77 years who had had type 2 diabetes for >2 months to <10 years. During a 2-week, single-blind lead-in period, all patients followed an American Diabetes Association weight-maintenance diet and received MIR 500 mg BID. At the end of this period, patients who were at least 80\% compliant with drug treatment (as determined by tablet counts and interviews) were randomly assigned in equal groups to receive 1 of 3 regimens for 24 weeks: (1) MXR 1000 mg QD administered with the evening meal; (2) MXR 1000 mg QD administered with the evening meal for 1 week, followed by an increase
to 1500 mg QD; or (3) continuation of MIR 500 mg BID with the morning and evening meals. After 12 weeks, the daily dose could be increased by 500 mg in any group if HbA₁c was ≥8% at that time.

To ensure that double-blinding was maintained, all patients received a similar number of tablets daily; placebo tablets were indistinguishable from MIR and MXR tablets. Patients were instructed to continue following the prescribed eucaloric diet throughout the study and were provided with blood glucose meters for measuring and monitoring their glucose concentrations.

All patients gave written informed consent before undergoing any study procedures.

Study Assessments

Initial assessments were conducted at the screening visit and during the lead-in period at weeks -2, -1, and baseline (week 0). Baseline measurements included HbA₁c, FPG, mean daily blood glucose concentrations, serum lipid profile (total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglyceride concentrations), fructosamine and serum insulin levels, standard laboratory tests (hematology, serum chemistry profile, urinalysis), body weight, vital signs, and electrocardiography (ECG). All laboratory tests were conducted after a minimum fast of 8 hours. Laboratory measurements were performed by a central laboratory (UCT International, New York, New York). Some or all of these measurements were repeated at assessments during the double-blind treatment period (weeks 1, 4, 8, 12, 16, 20, and 24).

Compliance was assessed by reviewing the tablet counts conducted at each study visit. Additionally, patients were asked to confirm their compliance with therapy at each visit. Acceptable compliance was defined as ≥80% of expected study drug consumption.

Efficacy Assessment

The primary efficacy variable was the degree of glycemic control with the switch from MIR to MXR, as determined by the mean change from baseline in HbA₁c at week 12. Secondary efficacy variables included the change from baseline in HbA₁c at week 24; the distribution of HbA₁c values between 3 categories (<7%, 7%–<8%, and ≥8%) at weeks 12 and 24; changes from baseline in FPG concentrations, mean daily blood glucose concentrations (self-monitored), fructosamine levels, serum insulin levels, lipid levels, and body weight at weeks 12 and 24; and the proportion of patients in each group who discontinued treatment due to inadequate glycemic control. Additionally, a post hoc analysis was conducted to assess the distribution of HbA₁c values at weeks 12 and 24 by baseline HbA₁c category in each treatment group.
Safety Assessment
The tolerability of MXR was assessed by analysis of clinical adverse events reported by patients or detected by investigators. In addition to their spontaneous reports, patients were questioned directly at each visit about adverse events occurring since the last visit. Changes in standard laboratory parameters, vital signs, findings on physical examination, and ECG findings were also monitored. Adverse events were recorded on patients' clinical report forms without regard to causality and were subsequently classified by the investigators as either related or unrelated to study medications. An assessment of selected treatment-emergent gastrointestinal adverse events was conducted separately. These events included abdominal pain, anorectal disorder, constipation, decreased appetite, diarrhea, distention of the abdomen, dyspepsia/heartburn, flatulence, gastroenteritis, gastroesophageal reflux, and nausea/vomiting. Investigators and laboratory personnel remained blinded to treatment assignment when assessing clinical adverse events and laboratory findings.

Statistical Analysis
For the primary efficacy variable, mean change in HbA1c from baseline to week 12, 95% CIs were constructed within each randomly assigned treatment group. Similarly, secondary efficacy parameters at weeks 12 and 24 were summarized for each treatment group with the use of 95% CIs. Whenever data were not available for secondary end points at week 12 or 24, a last-observation-carried-forward analysis of change was performed using the last measurement obtained before these time points. Rates of adverse events were described by body system.

RESULTS
Two hundred seventeen patients were randomly assigned to treatment, and 191 completed the double-blind treatment phase. Among the 26 patients who did not complete the 24-week treatment period, the most common reasons for discontinuation were patient's request (n = 12), adverse events (n = 8), and loss to follow-up (n = 3).

Patients' demographic and baseline clinical characteristics are summarized by treatment group in Table I. Most patients were overweight or obese, with only 12% of the study population having a body mass index <25 kg/m². Diabetes characteristics and lipid levels were balanced between treatment groups at baseline, with a mean disease duration of 3 years, mean baseline HbA1c value of ~7.0%, and mean LDL-C levels ranging from 116 to 124 mg/dL. The mean duration of exposure to study medications was similar between treatment groups (MIR, 158 days; MXR 1000 mg, 156 days; MXR 1500 mg, 160 days). Compliance with treatment was rated as acceptable (≥80%) in all groups.
### Table I. Demographic and baseline clinical characteristics of the study population. Values are mean (SD) unless otherwise noted.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MIR 500 mg BID (n = 71)</th>
<th>1000 mg QD (n = 75)</th>
<th>1500 mg QD (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>54</td>
<td>54</td>
<td>55</td>
</tr>
<tr>
<td>Sex, no.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>40</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>Male</td>
<td>31</td>
<td>34</td>
<td>28</td>
</tr>
<tr>
<td>Mean body weight, kg</td>
<td>96</td>
<td>92</td>
<td>88</td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>33</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Mean duration of diabetes, y</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>HbA₁c, %</td>
<td>7.1 (0.8)</td>
<td>7.0 (0.8)</td>
<td>7.0 (0.7)</td>
</tr>
<tr>
<td>FPG, mg/dL*</td>
<td>128 (27)</td>
<td>132 (29)</td>
<td>132 (22)</td>
</tr>
<tr>
<td>Mean daily blood glucose, mg/dL†</td>
<td>146 (30)</td>
<td>149 (30)</td>
<td>151 (25)</td>
</tr>
<tr>
<td>Fructosamine, μmol/L</td>
<td>264 (40)</td>
<td>267 (42)</td>
<td>275 (38)</td>
</tr>
<tr>
<td>Serum insulin, μU/mL</td>
<td>23 (18)</td>
<td>20 (18)</td>
<td>17 (10)</td>
</tr>
<tr>
<td>Lipid profile, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>199 (34)</td>
<td>202 (38)</td>
<td>201 (39)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>122 (30)</td>
<td>124 (33)</td>
<td>116 (34)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>42 (9)</td>
<td>42 (10)</td>
<td>45 (11)</td>
</tr>
<tr>
<td>TG</td>
<td>181 (113)</td>
<td>187 (200)</td>
<td>201 (137)</td>
</tr>
</tbody>
</table>

MXR = extended-release formulation of metformin; MIR = immediate-release formulation of metformin; BMI = body mass index; HbA₁c = glycated hemoglobin; FPG = fasting plasma glucose; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides.

*Laboratory measured (to convert to mmol/L, multiply value in mg/dL by 0.0551).
†Self-monitored by patients.

### Efficacy Outcomes

#### Glycemic Control

Only small increases from baseline in mean HbA₁c were observed at weeks 12 and 24 in the 3 treatment groups (Figure 1). At week 12, HbA₁c values had increased slightly from baseline, with mean changes of 0.15% for MIR, 0.23% for MXR 1000 mg QD, and 0.04% for MXR 1500 mg QD. The corresponding changes at week 24 were 0.06%, 0.25%, and 0.14%. The distribution of HbA₁c values in the specified categories (<7.0%, 7.0%–<8.0%, and ≥8.0%) was not significantly different between groups during the study. Post hoc analysis of the distribution of HbA₁c values by baseline value showed that similar proportions of patients with initial values of <7.0% and 7.0% to <8.0% remained in these categories at weeks 12 and 24 (Figure 2). In those with baseline values ≥8.0%, more patients...
in the MXR groups progressed to a lower HbA\(_{lc}\) category compared with the MIR group; however, this finding should be interpreted with caution, as the number of patients involved was small. Two patients in the MIR group and 4 in each of the MXR groups had ≥1% increases in HbA\(_{lc}\) from baseline at week 24.

Mean FPG concentrations had also increased in all 3 treatment groups at weeks 12 and 24. The mean increases were smaller in the MXR groups compared with the MIR group (Figure 3). Other measures of glycemic control, including mean daily blood glucose concentration, fructosamine and serum insulin levels, and body weight, showed similar mean changes at weeks 12 and 24 in each group. Only 1 patient (in the MIR group) required discontinuation of treatment because of inadequate glycemic control.

**Lipid Response**

Changes in lipid profiles by treatment group are presented in Table II. No clinically significant changes from baseline were seen in HDL-C or TC levels at week 24 in any treatment group. LDL-C levels at week 24 decreased in all 3 treatment groups, with a mean change of -4 mg/dL with MIR (95% CI, -9 to 1) and -6 mg/dL in both MXR groups (1000 mg, 95% CI, -11 to -1; 1500 mg, 95% CI, -12 to 0). Whereas only small increases from baseline in triglyceride levels were observed at week 24 in pa-
Figure 2. Percentage (SE) of patients in each treatment group with glycated hemoglobin (HbA1c) values in the <7.0% or 7.0% to <8.0% category at baseline that remained in the same category at weeks 12 and 24. MIR = immediate-release metformin; MXR = extended-release metformin.

Patients receiving MIR (mean change, 1 mg/dL; 95% CI, −14 to 17), statistically significant increases of 34 mg/dL (95% CI, 15 to 53) and 42 mg/dL (95% CI, 6 to 78) were seen at week 24 in the groups that received MXR 1000 and 1500 mg, respectively.

**Tolerability**

All 217 patients who were randomly assigned to treatment and received ≥1 dose of study medication were included in the tolerability analysis. Discontinuation due to adverse events occurred in 1 of 71 patients who received MIR, compared with 7 of 146 who received either dose of MXR. One MIR-treated patient discontinued treatment prematurely because of increased urinary protein concentrations; the study investigator considered this event unrelated to treatment. Reasons for early withdrawal in the group that received MXR 1000 mg included pancreatitis (unrelated to treatment), eosinophilia (possibly related), abdominal pain (possibly related), neuropathy (unrelated), rash (probably related), and gastroesophageal reflux (unrelated). In the group that received MXR 1500 mg, 1 pa-
Figure 3. Mean (SE) fasting plasma glucose (FPG) levels at baseline, week 12, and week 24. MIR = immediate-release metformin; MXR = extended-release metformin.

Table II. Changes in lipid profiles from baseline to week 24 (N = 204).

<table>
<thead>
<tr>
<th>Lipid Parameter</th>
<th>MIR 500 mg BID</th>
<th>MXR 1000 mg QD</th>
<th>MXR 1500 mg QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>Mean (SE) Change 95% CI</td>
<td>Mean (SE) Change 95% CI</td>
<td>Mean (SE) Change 95% CI</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HDL-C</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TG</td>
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</tbody>
</table>

MIR = immediate-release metformin; MXR = extended-release metformin; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides.
patient discontinued treatment after a single episode of mild diarrhea that was considered probably associated with treatment.

Table III presents the incidence of treatment-emergent clinical adverse drug experiences occurring in ≥3% of patients in any treatment group that were considered certainly, probably, or possibly related to study medication or for which the relationship to study medication was unaevaluable. Drug-related experiences were reported in 18 of 71 (25%) MIR recipients, 22 of 75 (29%) MXR 1000 mg recipients, and 24 of 71 (34%) MXR 1500 mg recipients. Although the trial was not statistically powered to detect differences in tolerability between groups, patients in the MXR 1000 mg group had a 10% lower incidence of the selected treatment-emergent gastrointestinal adverse events compared with patients in the MIR group (29% vs 39%), who were receiving an equivalent daily dose (Figure 4).

Eight of 146 (5%) patients who received MXR experienced a serious adverse event, compared with 2 of 71 (3%) patients who received MIR. In the MXR group, serious adverse events included pancreatitis, malignant neoplasm, angina and heart failure, cerebrovascular accident, pulmonary infection (followed by lactic acidosis, myocardial infarction, cardiovascular shock, electromechanical dissociation, and death in a patient receiving MXR 1500 mg), chest pain and gallbladder disorder, hypertension, ventricular rhythm disturbance, and urologic/rectal surgery. In the MIR group, serious events included pulmonary infection and renal abnormality. The investigators considered none of these serious adverse events, including the death, related to receipt of metformin. Additionally, there

| Table III. Number (%) of treatment-emergent clinical adverse drug experiences* (ADEs) occurring in ≥3% of patients. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| | MIR | | MXR | |
| | 500 mg BID | 1000 mg QD | 1500 mg QD | Total |
| All ADEs | 18 (25) | 22 (29) | 24 (34) | 46 (32) |
| Diarrhea | 2 (3) | 4 (5) | 11 (15) | 15 (10) |
| Flatulence | 1 (1) | 3 (4) | 2 (3) | 5 (3) |
| Abdominal pain | 1 (1) | 3 (4) | 1 (1) | 4 (3) |
| Nausea/vomiting | 3 (4) | 2 (3) | 2 (3) | 4 (3) |
| Headache | 3 (4) | 3 (4) | - | 3 (2) |
| Dyspepsia/heartburn | 4 (6) | 2 (3) | - | 2 (1) |

MXR = extended-release metformin; MIR = immediate-release metformin.
*Includes events rated certainly, probably, or possibly related to study medications and those for which the relationship was unaevaluable.
Figure 4. Percentage (SE) of patients with selected treatment-emergent gastrointestinal clinical adverse events (abdominal pain, anorectal disorder, constipation, decreased appetite, diarrhea, distention of the abdomen, dyspepsia/heartburn, flatulence, gastroenteritis, gastroesophageal reflux, and nausea/vomiting). MIR = immediate-release metformin; MXR = extended-release metformin.

were no clinically significant changes in vital signs or physical examination findings during the study. Only 2 hypoglycemic events were recorded—one with MIR and 1 with MXR 1000 mg; neither event was considered severe.

Investigator-identified laboratory adverse events occurred in 4 of 71 (6%) patients in the MIR group and 11 of 146 (8%) patients in the combined MXR groups (Table IV). Apart from increases in triglyceride levels (MIR, 0 patients; combined MXR, 3 patients) and urinary protein (MIR, 2 patients; combined MXR, 0 patients), the incidence of other laboratory adverse events was similar during treatment and between groups. Only 2 marked laboratory abnormalities occurred during double-blind treatment—a low serum sodium level in a patient receiving MXR 1500 mg, and low neutrophils and bands in a patient receiving MIR.

**DISCUSSION**

Because metformin targets key defects underlying type 2 diabetes, it is an effective therapeutic agent, producing reductions in HbA1c ranging from 0.8% to 2.0% when administered as monotherapy. It has been used increasingly as a first-line
agent for the treatment of type 2 diabetes, both as monotherapy and as a component of combination regimens.¹⁻³ Until recently, the conventional MIR formulation administered BID or TID has been used as first-line therapy, but this formulation may be less than optimal in terms of patient compliance with daily therapy. In the present randomized, double-blind study, the newer once-daily MXR formulation demonstrated a comparable efficacy and tolerability profile to MIR given BID. Specifically, in this population of patients with type 2 diabetes who had achieved moderate or good glycemic control with MIR therapy, glycemic control was maintained with a switch to once-daily MXR therapy at the same total daily dosage. Thus, once-daily administration of MXR was effective in this study population and might be anticipated to enhance patient compliance with treatment.¹⁷ Increased compliance with the therapeutic regimen may be an important step toward achieving better long-term control of diabetes and fewer diabetes-related complications, as has been documented in landmark studies in patients with type ¹¹ and type ²¹ diabetes.

This study was designed to assess glycemic control, as measured by change in HbA₁c from baseline to week 12, after a switch from MIR 500 mg to 1 of 2 doses of MXR given once daily. Patients enrolled in the study had established type 2 diabetes, an HbA₁c value ≤8.5% while receiving MIR 500 mg BID for ≥8 weeks,
and a mean FPG concentration \( \leq 200 \text{ mg/dL} \). Patients who were switched to MXR 1000 or 1500 mg once daily achieved indices of glycemic control that were comparable to those of patients who continued MIR therapy. Changes in \( \text{HbA}_{1c} \) from baseline at weeks 12 and 24 were minimal in all 3 treatment groups, as were changes in most other indices of diabetes control, including FPG, blood glucose concentrations, fructosamine levels, serum insulin levels, and body weight. This finding of good to excellent glycemic control with MXR is congruent with the findings of other studies of MXR in patients whose type 2 diabetes was not well controlled with diet and exercise alone.\(^{21,22}\)

In the present study, MXR appeared to have an overall positive effect on lipid profiles. Both MXR groups had statistically significant decreases from baseline in serum LDL-C concentrations at week 24. No clinically significant changes in TC or HDL-C levels were observed in any group. The reductions in LDL-C levels with MXR agree with earlier findings\(^{21,22}\); however, the significant increase in triglyceride levels seen in both MXR groups was not consistent with observations from other placebo-controlled trials of MXR.\(^{21,23}\) The significance of this effect is uncertain. Although glycemic control was maintained with the switch to MXR in this study, it is possible that once-daily dosing may not achieve the triglyceride-lowering benefit associated with use of MIR. In the other placebo-controlled studies,\(^{21,23}\) reductions from baseline triglyceride values were accompanied by significant decreases in \( \text{HbA}_{1c} \) (\(-0.4\% \) to \(-1.1\% \); \( P < 0.001 \)), perhaps accounting for the divergent findings in this study. Inherent variability in triglyceride levels may also have played a part.

Because the dual hydrophilic polymer system of MXR releases metformin slowly, this formulation may provide favorable tolerability benefits compared with MIR. Although this trial was not powered to identify differences in adverse-event rates between MXR and MIR, the overall rate of treatment-emergent clinical adverse drug experiences was similar between the formulations. No serious drug-related adverse experiences were reported in any treatment group. Although the investigators were blinded to study drug assignment, the trial design was limited by all patients’ having received metformin. Accordingly, it is possible that there was some bias in evaluating the causation of treatment-emergent adverse experiences.

**CONCLUSION**

In this multicenter, randomized, double-blind, parallel-group study, comparable glycemic control was observed after a switch to therapy with MXR 1000 or 1500 mg QD in patients with type 2 diabetes who had achieved moderate or good glycemic control (\( \text{HbA}_{1c} \leq 8.5\% \), FPG \( \leq 200 \text{ mg/dL} \)) with MIR 500 mg BID.

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