Long-Term Titrated-Dose α-Glucosidase Inhibition in Non-Insulin-Requiring Hispanic NIDDM Patients

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OBJECTIVE — To assess the long-term safety and effectiveness of a titrated dose of the α-glucosidase inhibitor miglitol (BAY m 1099) in Hispanic NIDDM patients.

RESEARCH DESIGN AND METHODS — A 1-year double-blind randomized placebo-controlled study in which diet-treated or diet plus sulfonylurea–treated Hispanic NIDDM patients received either placebo (n = 131) or miglitol in doses of 50, 100, 150, or 200 mg t.i.d. (n = 254), up-titrated and down-titrated based on tolerability. Efficacy parameters included changes from baseline in HbA_{1c}, fasting and 2-h postprandial plasma glucose and serum insulin, fasting serum lipids, and urinary albumin-to-creatinine ratio (ACR). Safety assessments consisted primarily of tabulation of adverse events and intercurrent illnesses, and of periodic laboratory determinations.

RESULTS — Reductions from baseline in HbA_{1c} levels at the 6-month (primary efficacy) endpoint were significantly greater by 0.83% in the miglitol group than in the placebo group. HbA_{1c} reductions in the miglitol treatment group significantly exceeded those in the placebo group by 0.63, 0.73, and 0.92% at 3, 9, and 12 months of treatment, respectively. Reductions in 120-min postprandial glucose and insulin levels were significantly greater in the miglitol group than in the placebo group at all postbaseline visits. There was little difference between treatments for changes in fasting insulin or lipid levels. Miglitol-associated reductions versus placebo in fasting plasma glucose (P = 0.0587 at 6 months) and in ACR (P = 0.0541 at 1 year) were nearly statistically significant. These efficacy results were not notably different between the 6-month endpoint, at which time the mean miglitol dose was 100 mg t.i.d., and the 1-year visit, when the mean miglitol dose was 149 mg t.i.d. Notable adverse events seen significantly more often in the miglitol group than in the placebo group were flatulence and diarrhea (or soft stools). The incidence of these gastrointestinal adverse events appeared to be dose dependent.

CONCLUSIONS — Miglitol treatment of non–insulin-requiring Hispanic NIDDM patients at doses from 50 to 200 mg t.i.d. produced statistically and clinically significant reductions of HbA_{1c}, primarily associated with reduction of glucose and insulin levels in the postprandial period, which were sustained over a year of treatment. Adverse events related to the drug's mechanism of action were common, but generally well tolerated. Doses above 100 mg t.i.d. were not associated with notably enhanced efficacy in most patients.

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Abbreviations: ACR, urinary albumin-to-creatinine ratio; ADA, American Diabetes Association; ANOVA, analysis of variance; DCCT, Diabetes Control and Complications Trial; HHANES, Hispanic Health and Nutrition Examination Survey; UKPDS, U.K. Prospective Diabetes Study.

Type 2 diabetes and its complications are highly prevalent among Hispanic individuals, the fastest-growing ethnic group in the U.S. Reasons for this prevalence include genetic and environmental tendencies toward diabetes and obesity in this population, as well as suboptimal communication with health care providers and substandard levels of care, leading to late diagnosis and inadequate follow-up (1). The Hispanic Health and Nutrition Examination Survey (HHANES) of 1982–1984 described a prevalence of diagnosed NIDDM in Hispanic subjects approximately twice that of non-Hispanic subjects (2). In the San Antonio Heart Study (3), a higher prevalence of microvascular complications associated with NIDDM was seen in Mexican-American individuals as compared with non-Hispanic white individuals: two- to threefold higher for diabetic retinopathy and sixfold higher for nephropathy. The treatment of Hispanic individuals with diabetes emerges as a large public health problem because these patients have typically been underserved by the U.S. health care system and underrepresented in clinical trials of new treatments and therapies.

A common and difficult problem in diabetes treatment is the large increase in blood glucose that typically occurs after meals. Lifestyle interventions, sulfonylureas that enhance endogenous insulin secretion, biguanides, and even insulin therapy have not provided an optimal solution to this problem. α-Glucosidase inhibitors, including acarbose and the desoxynojirimycin derivative miglitol (BAY m 1099), blunt postprandial blood glucose surges in diabetes by delaying the breakdown and absorption of polysaccharides from the small intestine. In the present study, the effects of miglitol at a dose titrated at 13-week intervals among four levels (50, 100, 150, and 200 mg t.i.d.) based on tolerability were studied in a large balanced population of Hispanic NIDDM patients drawn principally from Mexican-American, Puerto Rican–American, and Cuban-American subgroups.

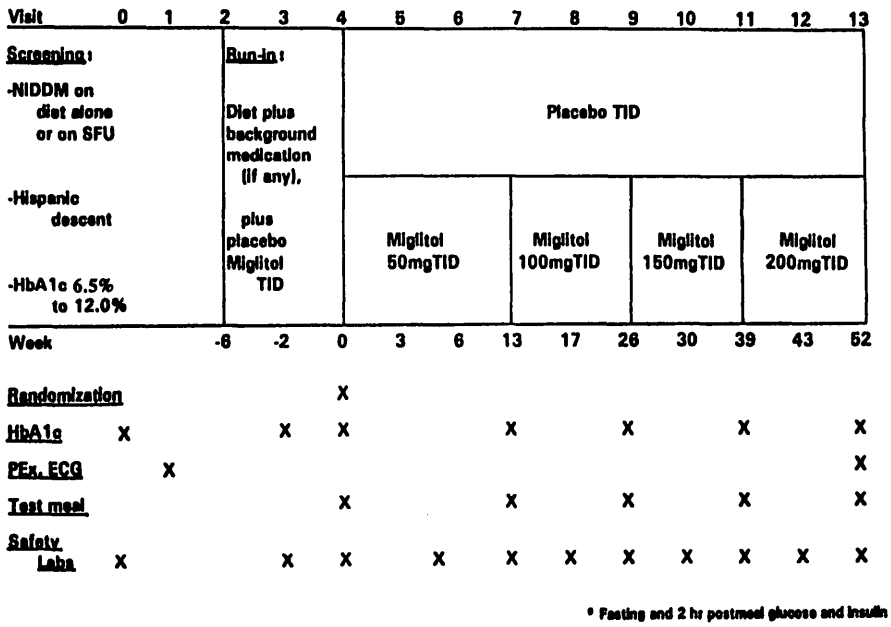

Figure 1—*Design of the study, showing treatment and dose-titration phases and timing of principal assessments made. Patients were allowed to up-titrate and back-titrate their miglitol or placebo dose at any time during double-blind treatment, although dose increases occurred primarily at weeks 13, 26, and 39.*

RESEARCH DESIGN AND METHODS

Study design

The study population consisted of Hispanic NIDDM patients, that is, patients from either a Mexican-American or Cuban-American ethnic group, or patients with ancestry from Puerto Rico, the Dominican Republic, or Central/South America. The locations of the 15 study centers were chosen so that the distribution of study patients by subethnicity would correspond to that of the U.S. Hispanic NIDDM population as a whole, that is, a majority of centers were in the Southwest U.S., with the others divided between the Northeast and Florida.

Patients were required to have had stable treatment for their NIDDM (either diet or diet plus sulfonylurea at a fixed dose) for at least 12 weeks prior to randomization. No chronic insulin treatment was given within 6 months of randomization. HbA_{1c} levels before randomization were required to be in the range of 6.5–12%, and patients had no debilitating or critical illness that would interfere with study participation. Eligibility for study inclusion was based on the results of medical history, a physical examination, laboratory testing, baseline electrocardiogram, and recent chest X-ray results.

The study design is diagrammed in Fig. 1. Informed consent was obtained (in Spanish, if necessary) at the first screening visit in accordance with the guidelines of the various study center institutional review boards. Enrolled patients received instruction in a diabetic diet consisting of at least 50% carbohydrate, designed by a nutritionist and the patient. This diet was intended to maintain weight in nonobese patients and to produce a gradual (1 lb/week) weight loss in obese or overweight patients.

For the patients to become accustomed to the dosage schedule and for compliance to be assessed, at visit 2 they began to take single-blind placebo miglitol three times a day with the first bite of each main meal. Compliant patients (those who took at least 80% of the prescribed drug based on tablet counts) who satisfied the enrollment criteria at visit 3 were randomized at visit 4 to receive, in double-blind fashion, either 50 mg t.i.d. miglitol or its placebo with the first bite of each main meal. In general, patients in either the miglitol or placebo groups tolerant of a lower dose were asked to titrate their doses to 100 mg t.i.d. at 13 weeks, and to 150 and 200 mg t.i.d. at 26 and 39 weeks, respectively, by increasing the number of 50-mg tablets taken with each meal. Patients were permitted to up-titrate and back-titrate their doses at any time during the double-blind treatment phase, although, in general, first-time dose increases to 100, 150, or 200 mg t.i.d. occurred at the designated 13-, 26-, and 39-week visits, respectively.

Patients' background treatment (either diet alone or diet plus sulfonylurea) was continued without change for the entire course of the double-blind treatment, if possible. Background sulfonylurea dose reductions were permitted at any time for threatened or actual hypoglycemia, and sulfonylurea dose increases were permitted after the first 6 months of double-blind treatment when necessary. Randomization, performed independently at each center, was two-to-one, i.e., twice as many patients were allocated to miglitol treatment as to placebo treatment, and was stratified by background treatment (diet only in stratum 1, diet plus sulfonylurea in stratum 2) to help ensure a balanced representation of both strata between study treatments.

Analysis of efficacy

The primary efficacy criterion in this study was the change from baseline to the 6-month visit in HbA_{1c}. HbA_{1c} levels, along with other efficacy parameters, were assessed at baseline and at every 13 weeks of double-blind treatment, as well as at treatment endpoint. Secondary efficacy parameters consisted of fasting lipid levels (triglycerides and total, LDL, and HDL cholesterol), plasma glucose and serum insulin levels at both fasting and 120 min after the start of a standard 483-kcal 51% carbohydrate mixed-meal breakfast, and the ratio of albumin to creatinine in a fasting urine specimen (assessed at baseline and at double-blind endpoint only), which was used lieu of 24-h urine collections as an index of normalized urinary albumin excretion (4). Analyses of log-transformed values for fasting triglycerides and urinary albumin-to-creatinine ratios (ACRs) were performed because of departures from normality in these data. In addition, incidence rates of treatment failure (defined as dropout due to lack of efficacy), treatment response (a decrease in HbA_{1c} of at least one percentage point or a decrease to 7%, provided a drop of at least 0.5% had occurred), sulfonylurea dose increases for hyperglycemia, and sulfonylurea dose reductions for hypoglycemia were compared between the two treatment groups.

To minimize variability and permit pooling of results across centers, central laboratories were used during the study for the performance of efficacy and safety laboratory measurements. HbA_{1c} levels were assayed by the University of Missouri (Dr. David Goldstein), and all other blood and urine assays were performed by SmithKline Beecham Clinical Laboratories (Van Nuys, CA).

Table 1—*Baseline demographic and disease characteristics*

	Placebo	Miglitol
n	120	220
Least squares mean		
BMI (kg/m²)	30.6	31.8
Age (years)	53.9	52.9
Weight (kg)	82.9	85.8
Duration of NIDDM (years)	4.8	5.7
Baseline HbA_{1c} (%)	8.53	8.70
Baseline FPG (mmol/l)	11.1	11.0
Baseline FSI (pmol/l)	123.6	130.8
Percent		
Male	52	60
Mexican/ Mexican-American	65	60
Puerto Rican	18	17
Cuban/Cuban-American	11	8
Central/South American	5	12
Other	1	3

FPG, fasting plasma glucose; FSI, fasting serum insulin.

Table 2—*Changes from baseline in efficacy variables*

	Least-squares mean changes		
	Placebo	Miglitol	*P* value
HbA_{1c}	0.57*	−0.26	0.0001
Fasting plasma glucose (mmol/l)	0.59	−0.10	0.0587
120-min plasma glucose (mmol/l)	0.53*	−1.41	0.0001
Fasting serum insulin (pmol/l)	−11.1	−14.6	0.6520
120-min serum insulin (pmol/l)	−32.3*	−108	0.0004
Fasting triglycerides†	0.99	0.97	0.7473
Total cholesterol (mmol/l)	0.12	0.19	0.3602
HDL cholesterol (mmol/l)	0.03	0.01	0.5275
LDL cholesterol (mmol/l)	0.02	0.14	0.0936
ACR‡	0.92	0.70	0.0541

*Significantly different from miglitol; †geometric least-squares mean of the ratio of the 6-month value to the baseline value; ‡geometric least-squares mean of the ratio of the 1-year value to the baseline value.

The primary efficacy endpoint was the 6-month (week 26) visit, at which time most study patients were taking active or placebo miglitol 100 mg t.i.d. Patients were valid for the primary efficacy analysis provided they had valid efficacy data at this visit. An additional (1-year) efficacy analysis included data from all patients who had satisfactorily completed at least 39 weeks of double-blind treatment.

Analysis of safety

Tabulation of adverse events and intercurrent illnesses, as well as periodic laboratory evaluations, comprised the majority of the safety data in this study. Physical exam and electrocardiogram findings at baseline and at double-blind endpoint were also captured, as well as dropout rates for multiple causes, including adverse events and insufficient therapeutic effect.

Statistical analysis

All significance tests were two-tailed and were performed at an α-level of 0.05. The primary efficacy variable was the change from baseline in HbA_{1c} at the 6-month visit. Continuous variables were analyzed by analysis of variance (ANOVA). The ANOVA model included effects for treatment, investigator, and stratum. All paired comparisons were based on the least-squares means estimated by the model. Incidence rates of adverse events and abnormal laboratory values were analyzed by χ^2 or Fisher's exact tests, depending on cell sizes.

RESULTS — The two treatment groups were comparable at baseline with respect to the demographic and metabolic variables listed in Table 1, and with respect to all efficacy variables except geometric mean fasting triglycerides, which were significantly lower at baseline in the miglitol-treated group (169 mg/dl) than in the placebo-treated patients (196 mg/dl).

Of 131 patients randomized to placebo treatment, 117 (82%), and 199 of 254 patients randomized to miglitol (78%), were treated with sulfonylurea at baseline (stratum 2); 39 and 37% of these patients, respectively, took the maximum dose. Glyburide and glipizide were the most commonly used sulfonylureas, and the mean baseline doses of both sulfonylureas were similar in both treatment groups. Mean miglitol doses in the miglitol group at visits 7, 9, 11, and 13 were 50, 95, 126, and 149 mg t.i.d., respectively.

Efficacy

Miglitol was significantly superior to placebo ($P = 0.0001$) in the primary analysis (HbA_{1c} change from baseline to the 6-month visit in patients valid for efficacy) with a mean placebo-subtracted HbA_{1c} change from baseline (HbA_{1c} treatment effect) of −0.83% (Table 2).

Mean HbA_{1c} levels over time are plotted in Fig. 2. At each visit, miglitol was

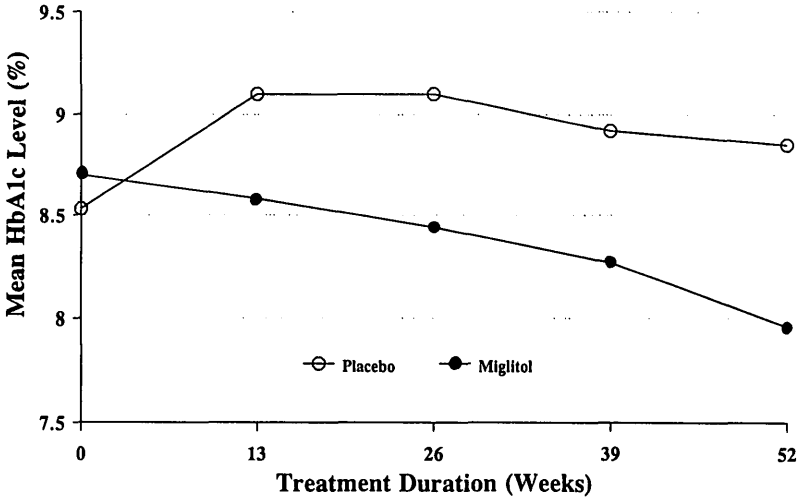

Figure 2—*Mean HbA_{1c} levels at double-blind treatment time points for patients valid for efficacy in the miglitol (●) and placebo (○) groups. The mean doses of miglitol taken by patients in the active treatment group were 50, 95, 126, and 150 mg t.i.d. at weeks 13, 26, 39, and 52, respectively.*

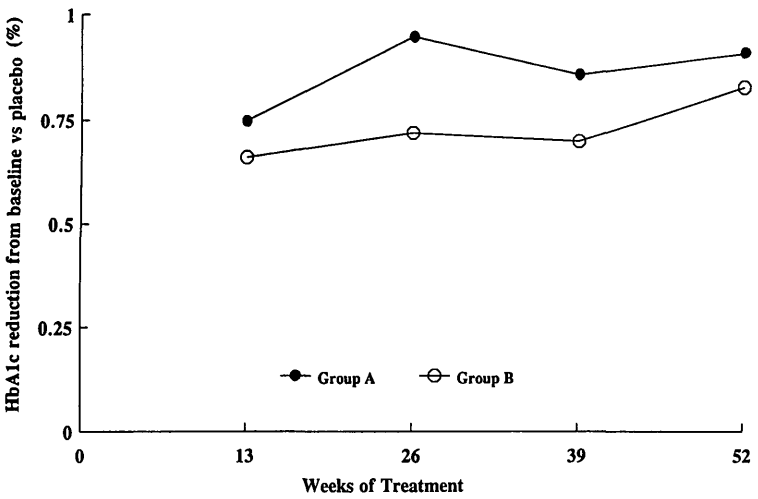

Figure 3—*Placebo-subtracted reduction in HbA_{1c} from baseline to the 13-week study visit in miglitol-treated patients who completed the study and whose dose at 1 year was either 200 mg t.i.d. (group A, n = 75, ●) or <200 mg t.i.d. (group B, n = 98, ○).*

superior to placebo ($P = 0.0001$). The treatment effects ranged from −0.63% (SE 0.10) at week 13 to −0.92% (SE 0.20) at week 52. The treatment effect at the last value for each patient (from weeks 6–52) was −0.99% (SE 0.17).

For the secondary efficacy variables, the least-squares mean changes are summarized in Table 2 for the population of patients valid for efficacy. With respect to changes from baseline in plasma glucose and serum insulin, miglitol was significantly superior to placebo for the 120-min postprandial value in each case. There was a trend toward a significant difference for fasting plasma glucose but no difference between treatments for fasting serum insulin. There was little difference in the fasting lipid levels between treatments.

With respect to ACR, a smaller geometric mean ratio of the 1-year value to the baseline value was observed in the miglitol group as compared with the placebo group. The difference between treatments approached statistical significance. There was a significantly greater incidence of treatment-emergent initiation of antihypertensive medication in the miglitol group (11%) compared with the placebo group (1%). When ACR changes were analyzed in the group of placebo and miglitol patients who did not initiate antihypertensive treatment during the study, the geometric means of the ratio of endpoint to baseline levels of ACR (0.96 vs. 0.83 in the placebo and miglitol groups, respectively) were not as low in either treatment group as the corresponding figures for the "all patient" treatment groups (0.92 vs. 0.70). The 11 miglitol-treated patients who had baseline and endpoint ACR assessments and who began antihypertensive treatment during the study had a higher mean baseline ACR (327 mg albumin/creatinine) than those miglitol-treated patients ($n = 132$) with the same assessments who did not begin antihypertensive therapy during the study (209 mg albumin/creatinine). These 11 patients experienced a mean 54% reduction in their baseline ACR over the course of the study.

No baseline demographic or metabolic variables such as age, sex, BMI, duration of diabetes, or baseline HbA_{1c}, fasting glucose, or insulin levels, were found to be correlated with treatment changes in HbA_{1c} at the 6-month endpoint.

In this study, the great majority of patients were sulfonylurea treated. For the few diet-treated patients (10 placebo, 19 miglitol), the miglitol HbA_{1c} treatment effect at 6 months was −1.04%, vs. −0.80% for the 90% of the patients in the study who were sulfonylurea treated. The majority of stratum 2 patients in both treatments were taking glyburide. The HbA_{1c} treatment difference ranged from −0.70% for the stratum 2 subgroup on submaximal glyburide to −0.97% for the subgroup on maximal glyburide. With respect to any sulfonylurea, the treatment difference was also −0.70% for the subgroup on submaximal sulfonylurea and −0.97% for the subgroup on maximal sulfonylurea.

There was a significantly greater proportion of patients valid for efficacy at the 6-month visit in the miglitol group than in the placebo group who were treatment responders, as defined above (27 vs. 10%, respectively). There were no significant differences between treatments either for the incidence of sulfonylurea increase due to hyperglycemia or for the incidence of sulfonylurea decrease due to hypoglycemia.

Although the design of the study was not that of a classical dose-response (fixed-dose) trial, analyses were performed to investigate a possible dose response for HbA_{1c}. As Fig. 3 shows, placebo-subtracted HbA_{1c} reductions at each 13-week visit were greater in the group of miglitol-treated patients (group A, $n = 75$) who completed the study taking 200 mg t.i.d. at the 1-year visit than in the group of study completers (group B, $n = 98$) in the miglitol group taking less than 200 mg t.i.d. at the 1-year visit. The differences between groups A and B were similar at each visit, even at 13 and 26 weeks, when their mean miglitol doses were quite comparable. In neither group did the HbA_{1c} treatment effect increase or decrease notably over the last 6 months of treatment.

A repeated measures model was applied to additionally describe the dose response. The repeated measures model assessed the change in HbA_{1c} response to change in dose, while taking into account differences among visits and the correlations between measurements within a patient. The predicted mean placebo-subtracted differences were −0.54, −0.83, −0.87, and −0.91% for the 50, 100, 150, and 200 mg t.i.d. doses, respectively. An increasing effect at increased dose was predicted, but at a decreasing rate.

Safety

The incidence rates of adverse events for which the differences between placebo and miglitol were statistically significant are listed in Table 3. In each case, incidence reflected the occurrence of any event, no matter how mild or transient.

Of these, flatulence and diarrhea were the most frequently reported events in the miglitol group. The incidences of diarrhea, flatulence, and pharyngitis were statistically significantly greater in the miglitol group than in the placebo group.

The events for which the incidence was greater in the placebo group than in the miglitol group were hypoesthesia, paresthesia, vaginal moniliasis, and hematuria.

The differences between treatments in the percent of patients experiencing diarrhea as a treatment-emergent event increased

Table 3—*Adverse events where incidence was significantly different between treatment groups*

Adverse event	Placebo	Miglitol
Diarrhea	18/130 (14)	141/250 (56)
Flatulence	35/130 (27)	150/250 (60)
Pharyngitis	15/131 (11)	49/250 (20)
Hypoesthesia	10/131 (8)	7/250 (3)
Paresthesia	5/131 (4)	2/250 (1)
Vaginal moniliasis	5/131 (4)	0/250 (0)
Hematuria	3/131 (2)	0/250 (0)

Data are *n*/total (%).

with increasing duration of double-blind treatment, as patients' mean miglitol dose also increased. The difference between treatments in the percent of patients with flatulence increased after the first 3 months of treatment, when most patients on active miglitol increased their dose from 50 to 100 mg t.i.d. Thereafter, the differences were relatively constant.

There was a greater rate of discontinuation due to adverse events in the miglitol group as compared with the placebo group: 9 vs. 5%, respectively (NS). Diarrhea and flatulence were the only adverse events associated with a significantly greater number of patients who left the study prematurely. This significant discontinuation occurred because of diarrhea in 4% of the miglitol group and because of flatulence in 5% of the miglitol group. Abdominal pain led to study discontinuation in 2% of miglitol-treated patients. No placebo patient withdrew prematurely for any of these three gastrointestinal adverse events, but a greater percentage of placebo patients withdrew from the study because of insufficient therapeutic effect or hyperglycemia (3%) than in the miglitol group (1%). There was one death in the study, in the placebo group.

There was only one laboratory abnormality for which there was a statistically significant difference between treatments; there was a higher incidence of treatment-emergent abnormal urine glucose levels in the placebo group as compared with the miglitol group: 25/49 (51%) vs. 16/68 (24%), respectively.

There were no statistically significant differences between treatments with respect to changes from baseline in vital signs at any visit. Both treatments showed mean reductions from baseline in fasting weight after visit 5. While the reductions tended to be greater in the miglitol group as compared with the placebo group, the difference was not statistically significant.

CONCLUSIONS

Efficacy

HbA_{1c}. In the present study, there appeared to be no demographic or metabolic features associated with an enhanced HbA_{1c} treatment effect. The greater HbA_{1c} treatment effect in the diet-only patients (stratum 1) as compared with sulfonylurea-treated patients (stratum 2) may reflect an improved treatment response in those with less severe disease, although associations of HbA_{1c} treatment effect with duration of disease, or with baseline HbA_{1c}, glucose, or insulin levels, were not evident. Age, sex, or body habitus did not predict response. Neither baseline nor ongoing assessments of patients' diets were performed, but in other studies (5,6), no relationship between patients' carbohydrate intake and HbA_{1c} response to miglitol has been found.

Approximately 35–40% of the sulfonylurea-treated patients were taking maximal-dose sulfonylurea during the study, and in these patients, the HbA_{1c} treatment difference was −0.97%. This compares favorably with the recent results of a 1-year fixed-dose dose-ranging study of miglitol treatment of a broadly based population of U.S. NIDDM patients treated with maximal-dose sulfonylurea, in which the HbA_{1c} treatment effects for miglitol 50 and 100 mg t.i.d. were −0.62 and −0.73%, respectively (6). The HbA_{1c} treatment effects in this study are echoed by the responder analysis results.

As a titration study, this trial was not designed to compare the efficacy of the different doses of miglitol used, but in fact there was little notable difference between miglitol-associated placebo-subtracted HbA_{1c} changes from baseline at the end of the second, third, and fourth 13-week treatment periods. After week 26, HbA_{1c} treatment differences did not notably increase with increasing dose in the 46% of study patients who tolerated miglitol 200 mg t.i.d. Hence, patients who were able to tolerate 150 and 200 mg t.i.d. miglitol might have ultimately had as great an HbA_{1c} effect had they stayed on 50 or 100 mg t.i.d. for the full year, rather than increasing their dose. In formal fixed-dose dose-response studies (6), no loss of miglitol's HbA_{1c} treatment effect occurred at either the 50 or the 100 mg t.i.d. doses over 1 year of treatment. It is thus unlikely that the preservation of miglitol's HbA_{1c} treatment effect over 1 year in this study depended on miglitol dose increases that occurred every 13 weeks. The results of the repeated measures model analysis of the response of HbA_{1c} to different doses of miglitol in this study are consistent with the apparently modest enhancement of efficacy achieved at the 200 mg t.i.d. dose compared with the 100 mg t.i.d. dose.

It is apparent from Fig. 3 that mean HbA_{1c} reductions for those patients who tolerated the highest dose of miglitol were slightly greater numerically at each visit listed, despite the fact that at the earlier visits (weeks 13 and 26), the mean miglitol dose in the two groups was practically identical. Although it is possible that many group A patients may simply have been more compliant with treatment and/or diet than their group B counterparts, study drug compliance was numerically greater in group B patients at every visit, based on tablet counts (but >90% in each group at each visit). The similar treatment effects in groups A and B on 120-min postprandial plasma glucose at week 28 (−36.6 mg/dl for group A, −38.5 mg/dl for group B), at which time both groups were taking a mean dose of 100 mg t.i.d., does not support the existence of a better drug effect in group A patients because postprandial glucose reduction is the primary effect of the drug.

Glucose and insulin. Miglitol treatment was associated with a modest mean reduction in fasting glucose levels that approached statistical significance and with significant reductions in both 2-h postmeal glucose and insulin levels similar in magnitude to those seen in other studies (5,7). These glucose and insulin treatment effects tended to increase with time (and with higher mean miglitol dose) over the year of treatment. Postprandial insulin reductions are potentially significant from the standpoints of reduction in macrovascular disease risk (8) and of a possible pancreas-sparing effect on residual insulin secretion (9) in these predominantly sulfonylurea-treated NIDDM patients.

Urinary ACR. The ratio of the 1-year to baseline values (geometric means) was reduced in the miglitol group in comparison to placebo to a degree approaching statistical significance (P = 0.0541), and these reductions occurred in the miglitol group at each of four levels (quartiles) of severity of baseline ACR.

While initiation of antihypertensive treatment in a subset of study patients had

some effect to reduce mean ACR in the miglitol treatment group as a whole, the relatively greater ACR reduction seen with the α-glucosidase inhibitor was not completely the result of a disproportionate treatment with antihypertensives (such as ACE inhibitors). Whether the miglitol-associated ACR reductions were simply due to reduction of overall hyperglycemia (10,11) or whether there may be effects of postprandial glucose excursions on urinary albumin excretion in NIDDM beyond those that could be anticipated from the effects of postprandial elevations on HbA_{1c} levels alone is a matter for further study.

Safety

Gastrointestinal adverse events. Flatulence and diarrhea were significantly more common among miglitol-treated patients than placebo-treated patients, as other miglitol trials have consistently demonstrated (5,6,12). These side effects are shared by all α-glucosidase inhibitors. Flatulence and abdominal pain are the result of gas production from the metabolism of unabsorbed carbohydrate by intestinal microflora, and soft stools (much more commonly than watery diarrhea) result from the osmotic effect of this unabsorbed carbohydrate. Although complaints of flatulence and diarrhea were quite common among miglitol-treated patients (as was flatulence in the placebo group), they were generally well tolerated, as evidenced by the low dropout rates: 5% for flatulence and 4% for diarrhea in the miglitol group.

Rates of abdominal pain complaints, though initially greater in miglitol-treated patients, tended to equalize between the two groups by the last 3 months of the study, despite the increasing mean dose of miglitol from quarter to quarter. Complaints of diarrhea and flatulence remained more common in the miglitol group throughout the year of treatment, and, in the case of diarrhea, the gap between the miglitol and placebo group incidences appeared to widen somewhat in the last 6 months of the study. The difference between the miglitol and placebo groups in the rates of complaints of flatulence reached a maximum during the 2nd quarter of the year of double-blind treatment and did not widen further in the last 6 months of the study. The relationship of these adverse events to time was unlikely to have been affected by dropouts, as the same relationships are evident for the population of all patients who completed the study.

Although the incidence of these gastrointestinal adverse events was greater in the miglitol group throughout the year of treatment, the notable incidence and persistence of these symptoms in the placebo group would have made it difficult to establish with a high degree of certitude which patients received placebo and which received active miglitol. Thus the study blinding, while weakened by the prominence of these adverse events and their association with α-glucosidase inhibitor treatment (well-known to both investigators and patients before randomization), was not invalidated.

Thus, while efficacy does not appear to improve at miglitol doses >100 mg t.i.d., the diarrhea, or softer more frequent stools, associated with miglitol use does seem to lead to reduced tolerability of the higher doses. While common, abdominal pain, diarrhea, and flatulence are relatively benign in severity, quick to appear at a given dose, and quick to resolve once the drug is stopped or reduced in dose. In many cases, tolerance improves with continued treatment. These adverse events led to discontinuation in relatively few instances and to serious or permanent morbidity in no patients.

Other adverse events. Hypoesthesia and paresthesia (Table 3) may have been less common in the miglitol-treated group because of improved metabolic control in that group, since these are both common features of diabetic peripheral neuropathy that can improve with better (or worsen with poorer) glycemic regulation. Likewise, better metabolic control is associated with reduction in the incidence of vaginal yeast and urine infections, to which the decreased incidences of moniliasis and hematuria in the miglitol group attest. Pharyngitis appeared significantly more often among miglitol-treated patients despite their improved metabolic control; this finding appears to be without clinical relevance and its statistical significance is probably an artifact of multiple significance testing.

Laboratory abnormalities. Treatment-emergent elevated urine glucose was seen in 25 of 49 (51%) placebo-treated patients, compared with 16 of 68 (24%) miglitol-treated patients, a direct reflection of the preservation or relative improvement of metabolic control in the miglitol group.

Other safety parameters. There were no vital sign parameters for which significant changes from baseline were seen between the miglitol and placebo groups. Despite the significantly more frequent treatment-emergent initiation of antihypertensive treatment in the miglitol group, there was no indication of an increase above baseline in mean systolic or diastolic blood pressure in the miglitol group compared with the placebo group in any study visit. Decreases from baseline in body weight of <1 kg were seen in both groups at various double-blind time points, but these changes were not significantly different between treatment groups at any time point.

Summary

In a position statement on the results of the Diabetes Control and Complications Trial (DCCT) on IDDM, which demonstrated that tighter metabolic control substantially reduces both the development of new, and the progression of established, microvascular complications (13), the American Diabetes Association (ADA) added caveats regarding attempts at better blood glucose control in NIDDM because of the tendency of then-available pharmacologic treatments to produce weight gain, hyperinsulinemia, and hypoglycemia. Miglitol-associated improvements in postprandial and mean day-long blood glucose levels have been achieved with reductions in postprandial serum insulin levels and without weight gain or an increased incidence of hypoglycemia. These features of α-glucosidase inhibitors address the principal reservations of the ADA concerning tight blood glucose control in NIDDM.

Hispanic patients will comprise 50% of the newly diagnosed U.S. NIDDM population by the year 2000. They seem to develop NIDDM at a younger age, have more poorly controlled disease, and are prone to more severe microvascular complications than their non-Hispanic NIDDM counterparts in the U.S. (2,14). If the results of the DCCT and other studies (15,16) are applicable to this NIDDM subpopulation, these microvascular complications may be ameliorated by improved metabolic control. Long-term HbA_{1c} reductions of the magnitude seen in this study were associated with a reduction in the risk of progression of diabetic retinopathy of approximately one-third in the DCCT IDDM population (13). In addition, there is evidence, at least in certain Hispanic patients, that severity of microvascular disease predicts mortality from all causes, including death from macrovascular disease (17).

Miglitol's HbA_{1c} treatment effects in this study meet or surpass what has been seen in long-term miglitol trials in the U.S. NIDDM population as a whole (5) and are similar to

those produced by chronic treatment with any of the pharmacologic treatments used as monotherapy in the U.K. Prospective Diabetes Study (UKPDS) (18), as well as to those seen in trials of the α-glucosidase inhibitor acarbose (19,20). The difficulty experienced in the UKPDS of sustaining a long-term treatment effect of similar magnitude to the DCCT trial using monotherapy in NIDDM patients may imply that optimization of blood glucose control in NIDDM will necessitate the use of multiple pharmacologic agents in combination, each working additively through a different mechanism. α-glucosidase inhibitor treatment at a dose titrated by tolerance offers non–insulin-requiring U.S. Hispanic NIDDM patients the prospect of significantly improved glycemic control and of a reduced risk of long-term diabetic complications.

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