Endocrine, *vol. 13, no. 2, 201–206 October 2000* 0969–711X/00/13:201–206/$11.50

Orlistat

Selective Inhibition of Caloric Absorption Can Affect Long-Term Body Weight

Jonathan Hauptman

Hoffmann-La Roche Inc., Nutley, NJ

Orlistat is a novel, noncentrally acting antiobesity agent that selectively inhibits gastrointestinal lipase activity, thereby reducing the absorption of dietary fat by approximately one-third. In a series of 1- and 2-yr randomized, placebo-controlled trials of obese subjects, treatment with orlistat in combination with a mildly calorie-restricted diet consistently produced significantly greater mean weight loss than diet alone. More orlistat-treated subjects than placebo recipients achieved clinically meaningful weight reduction (≥5% or ≥10% of initial body weight) after 1 and 2 yr. Orlistat was also associated with a significant reduction in the regain of lost weight during long-term treatment. In addition, orlistat therapy resulted in significant improvements in several cardiovascular risk factors including serum total and low-density lipoprotein–cholesterol, serum insulin levels, systolic and diastolic blood pressure, and waist circumference. Furthermore, obese subjects with type 2 diabetes achieved a significantly greater decrease in body weight with orlistat compared with placebo, as well as significant improvements in HbA_{1c} and fasting glucose levels. Among subjects with impaired glucose tolerance, orlistat compared with placebo reduced the proportion who developed type 2 diabetes. Conversely, orlistat increased the proportion of subjects who achieved a normalization of glucose tolerance. Orlistat acts locally in the gastrointestinal tract and is only minimally absorbed. In long-term clinical trials, orlistat was well tolerated by both diabetic and nondiabetic subjects.

Key Words: Orlistat; antiobesity agents; fat-restricted diet; weight loss; coronary risk.

Introduction

The etiology of obesity is complex and involves the interplay of numerous environmental and genetic factors. However, obesity is essentially the consequence of a long-term positive energy balance in which energy intake exceeds energy expenditure.

Dietary intake and composition, together with physical activity, are the primary modifiable factors that influence energy balance. In particular, the excessive consumption of dietary fat may have a major contributory role in the development of obesity *(1–3)*. Dietary fat has a higher energy density than other macronutrients, providing 9 kcal/g (37 kJ/g) compared with just 4 kcal/g (17 kJ/g) with either protein or carbohydrate. Moreover, fat has only a weak effect on postprandial satiety. In studies of obese subjects, high-carbohydrate meals suppressed subsequent food intake to a greater extent than high-fat meals that were matched for energy density, volume, and sensory properties *(4)*. In another study, obese patients who ate from a range of either high-fat or high-carbohydrate foods voluntarily consumed twice as much energy from the high-fat items *(5)*. Several factors may play a role in the low satiating effect of fat, including stomach distension, nutrient absorption, hormonal release, and oxidation of nutrients.

Fat also tends to be very palatable, and studies have shown that both male and female obese individuals tend to report definite preferences for high-fat foods *(6)*. This, together with the high energy density and low satiating effect of fat, can result in the overeating or passive overconsumption of high-fat foods.

In addition, whereas the oxidation of both carbohydrate and protein is tightly correlated with intake, fat balance is less well controlled *(7)*. Fat oxidation, unlike the oxidation of either carbohydrate or protein, is correlated with energy intake rather than fat intake *(8,9)*. As a result, energy from fat leads to greater weight gain than calories from other macronutrients because they are less likely to be oxidized, and instead are readily stored as body fat. There is evidence to suggest that obese subjects have a reduced ability to oxidize fat in comparison with lean individuals. In one study, a 7-d high-carbohydrate diet resulted in a significant increase in carbohydrate oxidation in both obese and lean subjects. However, on a high-fat diet, fat oxidation increased among lean subjects but not obese subjects *(10)*. In another study, previously obese women with a genetic predisposition toward obesity were less able to increase fat oxidation in response to increased dietary fat content compared with never-obese control subjects *(11)*.

Received June 14, 2000; Accepted June 14, 2000.

Author to whom all correspondence and reprint requests should be addressed: Dr. Jonathan Hauptman, Hoffmann-La Roche Inc., 340 Kingsland Street, Nutley, NJ 07110-1199. E-mail: jonathan.hauptman@roche.com

The treatment of obesity involves the creation of a negative energy balance in order to reduce body fat stores. Several studies have shown that low-fat diets can promote weight loss in both lean and obese subjects, and a metaanalysis of 33 controlled studies of ad libitum low-fat dietary interventions reported that a 1% reduction in dietary fat produced a 0.22-kg weight loss *(3,12)*.

However, long-term weight reduction is difficult to maintain by dietary intervention alone, and most obese patients eventually regain much of their lost weight *(13,14)*. This may be partially attributed to compensatory physiologic processes that act to oppose weight loss and the maintenance of lower body weight. However, much of the failure associated with conventional dietary and behavioral modification is a direct result of the inability of many obese individuals to maintain long-term compliance with significant dietary and lifestyle changes.

The limited success of dietary and behavioral interventions in long-term weight control has meant that adjunctive pharmacotherapy that is both well tolerated and effective will become increasingly important in the management of obesity. One approach is the induction of weight loss by drug-mediated inhibition of fat absorption. Orlistat (Xenical®, Hoffmann-La Roche Inc.), a novel, noncentrally acting antiobesity agent, is a highly potent inhibitor of gastrointestinal (GI) lipases, enzymes that play a crucial role in the digestion of long-chain triglycerides. Orlistat produces a partial inhibition of triglyceride hydrolysis and a reduction in the subsequent absorption of free fatty acids and monoglycerides (Fig. 1) *(15)*.

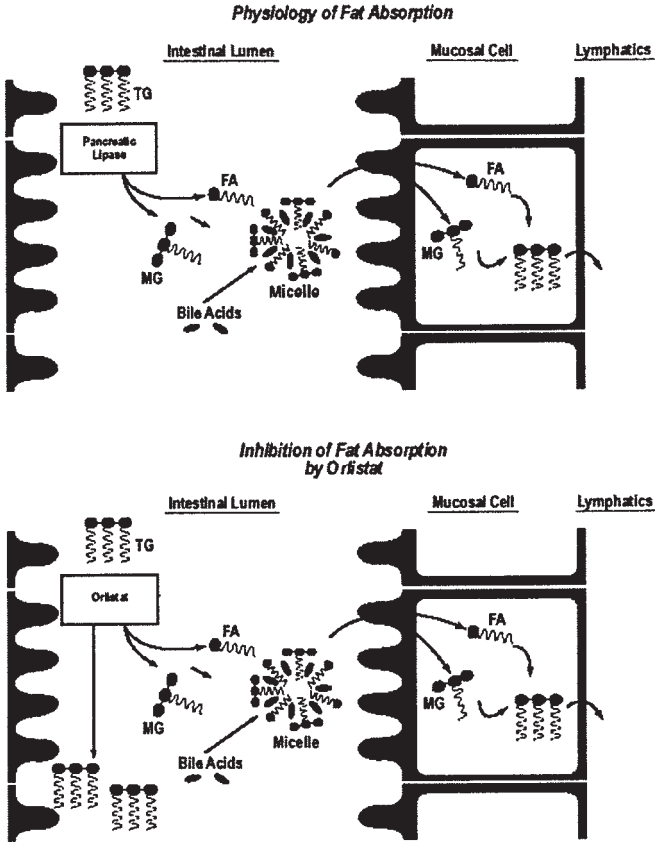

Fig. 1. Mode of action of orlistat. TG, triglyceride; MG, monoglyceride; FA, fatty acids.

The inhibitory effect of orlistat on dietary fat absorption has been evaluated using fecal fat excretion as a representative pharmacodynamic parameter. The inhibition of dietary fat absorption with orlistat is dose dependent, with the optimal therapeutic dosage being 120 mg administered three times daily with main meals *(16)*. This dosage consistently and reliably reduces the absorption of dietary fat by approximately one-third, resulting in a decrease in available calories after ingestion *(15)*.

Orlistat is highly selective and has no significant inhibitory effect on the hydrolysis and absorption of carbohydrates, proteins, and phospholipids. In addition, the absorption of orlistat from the GI tract is minimal, and therefore orlistat has virtually no potential for an inhibitory effect on systemic lipase activity *(17)*. Consequently, in contrast to some centrally acting appetite suppressants, adverse events owing to systemic drug absorption should be fewer with orlistat.

Weight Loss and Prevention of Weight Regain

In clinical trials, treatment with orlistat in combination with a mildly calorie-restricted diet has consistently produced significantly greater weight loss than diet alone in obese subjects. Unless otherwise stated, the results presented subsequently come from the intent-to-treat population, which includes data from all patients who received at least one dose of study medication and had at least one follow-up efficacy assessment. In a multicenter, 2-yr, randomized, placebo-controlled trial conducted in the United States by Davidson et al. *(18)*, 1187 obese men and women (body mass index (BMI) of 30–43 kg/m^2) were enrolled in a 1-mo single-blind, placebo lead-in period during which they were encouraged to follow a mildly hypocaloric diet. This diet was designed to provide a 600 kcal/d energy deficit with 30% of calories as fat. Subjects (n = 892) who completed this dietary lead-in period were randomly assigned (in a 3:1 ratio) to treatment with 120 mg of orlistat (n = 668) or placebo (n = 224) three times daily for 1 yr. Subjects continued to follow the hypocaloric diet during the first year of double-blind treatment. After 1 yr, subjects treated with orlistat had achieved significantly greater mean weight loss than placebo recipients (8.8 vs 5.8% of initial body weight; p <0.001). Moreover, a significantly higher proportion of orlistat-treated subjects achieved a clinically meaningful weight loss of ≥5% (65.7 vs 43.6%; p <0.01) or ≥10% (38.9 vs 24.8%; p <0.05). In the second year of the study, orlistat subjects who completed the first year were rerandomized to three times daily treatment with orlistat (n = 153), half-dose orlistat (60 mg) (n = 152), or placebo (n = 138), while subjects who received placebo during yr 1

continued to do so for a second year. In addition, all subjects were advised to follow a weight maintenance diet designed to promote stable body weight rather than continue with their hypocaloric weight loss diet. Of subjects who were treated with orlistat during the first year, those who were rerandomized to 120 mg of orlistat regained significantly less of their body weight during the second year compared with subjects rerandomized to placebo (35.2 vs 63.4% weight regain; $p < 0.001$). Treatment with 120 mg of orlistat for 2 yr resulted in mean weight loss of 7.6%, significantly greater than with 2 yr of placebo (4.5%; $p < 0.001$). In addition, twice as many orlistat-treated subjects maintained a weight reduction of ≥10% after 2 yr (34.1 vs 17.5%; $p < 0.05$).

The weight loss efficacy of orlistat has also been demonstrated in European trials that shared a design and methodology similar to that of the US study *(19,20)*. In a 2-yr study of 743 obese subjects (BMI of 28–47 kg/m^2), significantly greater mean weight loss was achieved with orlistat plus diet compared to diet alone after 1 yr (10.2 vs 6.1%; $p < 0.001$) (Fig. 2) *(19)*. More orlistat-treated subjects than placebo recipients achieved a weight loss of ≥5% (68.5 vs 49.2%), and twice as many subjects in the orlistat group as in the placebo group achieved a weight reduction of ≥10% (38.8 vs 17.7%). After 2 yr of treatment, subjects in the orlistat group achieved mean weight loss of 7.8%, compared with 4.6% in the placebo group. Twice as many orlistat-treated subjects as placebo recipients maintained a weight loss of ≥10% (33.8 vs 14.6%; $p < 0.05$). In another 2-yr European study, a significantly greater weight reduction was achieved with orlistat in conjunction with diet compared to diet alone after 1 yr (9.7 vs 6.6%; $p < 0.001$). This significantly greater weight loss with orlistat was sustained after 2 yr (7.6 vs 4.5%; $p < 0.001$) *(20)*.

As with the study by Davidson et al. *(18)*, participants in both of these European studies switched from a weight loss diet to a weight maintenance diet for the second year. As expected, some regain of lost weight occurred during yr 2. However, in both studies, weight regain was reduced by treatment with orlistat compared to placebo.

In each of these three 2-yr randomized, controlled trials of orlistat, obese subjects were generally recruited at specialist obesity clinics. However, in a further study, the effect of orlistat was investigated among subjects in a primary care setting *(21)*. A total of 796 obese subjects (BMI of 30–43 kg/m^2) entered a 1-mo dietary lead-in period before being randomized to 120 mg of orlistat, 60 mg of orlistat, or placebo three times daily. Subjects were prescribed a hypocaloric diet during the first year of treatment and were switched to a weight maintenance diet for the second year. Unlike previous studies of orlistat, subjects were counseled by health care staff who had no specialist training in diet or obesity management.

After 1 yr, subjects treated with 120 mg of orlistat had achieved significantly greater weight loss than placebo

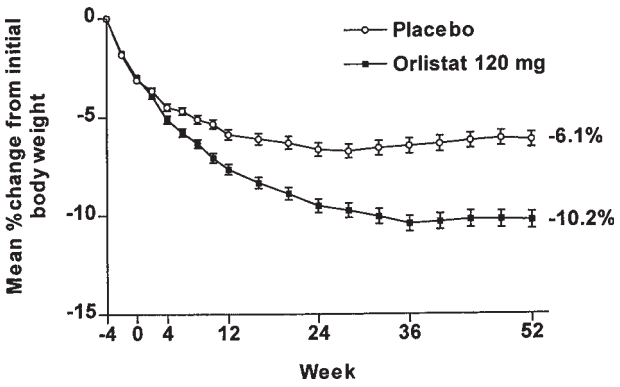

Fig. 2. Mean weight loss after 1 yr in obese patients randomized to double-blind treatment with 120 mg of orlistat ($n = 343$) or placebo ($n = 340$) plus a mildly hypocaloric diet. (Adapted from Sjöström et al. ref. *19*.)

recipients (7.9 vs 4.2%; $p < 0.0001$). Significantly greater weight loss with orlistat compared to placebo was sustained after 2 yr of treatment (5.0 vs 1.7%; $p < 0.0001$). In addition, almost three times as many subjects in the orlistat group as in the placebo group maintained a weight loss of ≥10% after 2 yr (18.6 vs 6.6%; $p < 0.001$). Mean weight reduction in this study, in both the orlistat and placebo groups, was slightly less than that achieved in other trials of orlistat *(18,19)*. However, the additional weight loss effect of orlistat compared with diet alone in this study was similar, if not greater, than reported in other studies and suggests that orlistat may be an important adjunct in the management of obesity in primary care.

The maintenance of lower body weight and the prevention of weight regain are essential components of successful long-term obesity management. In addition to the reduction in weight regain reported in 2-yr studies of orlistat, the effect of orlistat on weight regain has been specifically investigated in a large US multicenter study *(22)*. Obese subjects (BMI of 28–43 kg/m^2) were recruited at 17 clinical research centers and prescribed a hypocaloric diet (1000 kcal/d deficit) designed to produce a weight loss of 0.5–1.0 kg/wk for a 6-mo period. On completion, subjects who had lost ≥8% of their body weight were randomized to double-blind treatment with either placebo or 30, 60, or 120 mg of orlistat three times daily in combination with a weight maintenance diet for 1 yr. Of the 1313 subjects who entered the weight loss period, 729 achieved a weight reduction of ≥8% (mean weight loss of 10 kg) and entered the double-blind treatment period. After 1 yr, there was significantly less weight regain with 120 mg of orlistat compared to placebo (32.8 vs 58.7%; $p < 0.001$).

The effect of orlistat on body weight has also been demonstrated in a multicenter, US-based study of obese subjects with type 2 diabetes *(23)*. Weight loss is an important goal of therapy for obese type 2 diabetes patients. However, diabetic patients often have greater difficulty than nondiabetic subjects in achieving clinically meaningful weight

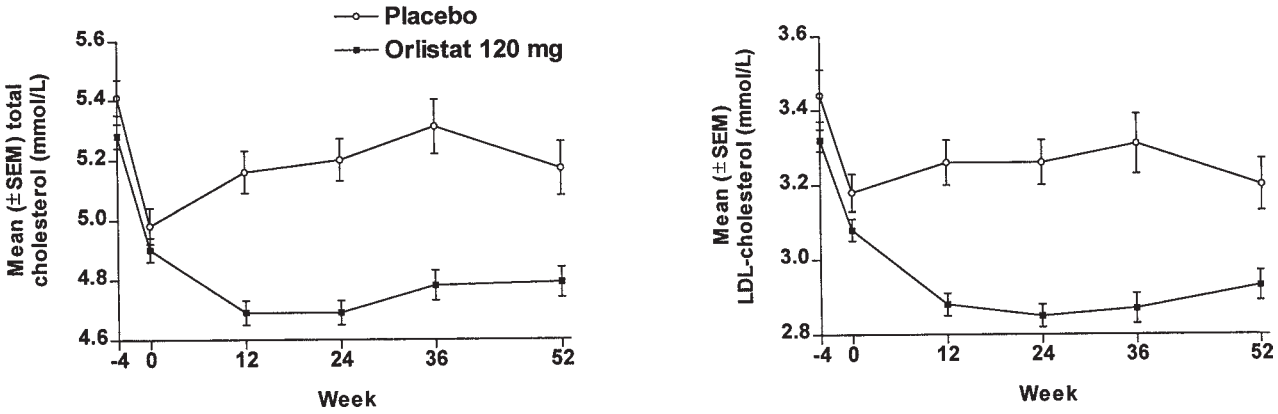

Fig. 3. Mean (±SEM) changes in serum total and LDL-cholesterol in obese patients randomized to double-blind treatment with 120 mg of orlistat or placebo plus a mildly hypocaloric diet. (Reproduced with permission from ref. *18*.)

reduction and maintaining lower body weight through dietary restriction or behavioral modification *(24–26)*. Weight loss may be especially difficult if patients are receiving treatment with diabetic medications that promote weight gain, such as insulin or sulfonylureas *(27,28)*.

A total of 391 subjects with type 2 diabetes controlled with oral sulfonylureas entered a 5-wk lead-in period during which they received placebo and a nutritionally balanced mildly hypocaloric diet (500 kcal/d deficit) *(23)*. On completion, subjects were randomized to either 120 mg of orlistat or placebo three times daily plus dietary intervention for 1 yr. Subjects treated with orlistat achieved significantly greater weight loss than placebo recipients (6.2 vs 4.3%; $p < 0.001$). Furthermore, twice as many patients receiving orlistat lost ≥5% of their initial body weight (49 vs 23%; $p < 0.001$). Similarly, more orlistat-treated patients than placebo recipients achieved a weight reduction of ≥10% (17.9 vs 8.8%; $p = 0.017$).

In addition to significantly greater weight loss, patients treated with orlistat also had a greater mean decrease in waist circumference in this study (–4.8 vs –2.0 cm; $p < 0.01$). Waist circumference is a marker of visceral abdominal obesity *(29)*. Excess visceral abdominal adipose tissue is associated with the insulin resistance syndrome, also known as the metabolic syndrome, and is an independent predictor of type 2 diabetes and coronary heart disease *(30–32)*. Significant reductions in waist circumference after treatment with orlistat were also reported in studies of obese nondiabetic subjects *(18,20)*.

Effects of Orlistat on Cardiovascular Risk Factors

Moderate weight loss of 5–10% is associated with improvements in several cardiovascular risk factors, including dyslipidemia, hypertension, hyperinsulinemia, glucose intolerance, and type 2 diabetes *(33,34)*. The effects of weight management with adjunctive orlistat therapy on these coronary risk factors have been assessed in several clinical trials.

Dyslipidemia

In the 2-yr study by Davidson et al. *(18)*, patients treated with orlistat achieved significantly greater reductions in serum total and low-density lipoprotein (LDL)-cholesterol than placebo recipients. During the 4-wk dietary lead-in period, total and LDL-cholesterol declined by approx 8%. However, after randomization, total and LDL-cholesterol concentrations increased in the placebo group despite further weight loss, but continued to decline in the orlistat group. After 1 yr, reductions in total and LDL-cholesterol were significantly greater with orlistat vs placebo ($p < 0.001$) (Fig. 3). The improvements in total and LDL-cholesterol achieved with orlistat were independent of the greater weight loss with orlistat compared to placebo. This additional lipid-lowering effect of orlistat is probably related to the partial inhibition of fat absorption from the GI tract. A similar independent lipid-lowering effect was reported in the European trials of orlistat *(19,20)* as well as in the study of overweight subjects with type 2 diabetes *(23)*.

Blood Pressure

Treatment with orlistat is also associated with improvements in systolic and diastolic blood pressure (BP). Numerous studies have reported that clinically significant reductions in BP are achieved with moderate weight loss and that a weight reduction of just 5 kg can significantly reduce BP in obese patients with or without hypertension *(35–37)*. In the Davidson et al. *(18)* study, systolic BP was reduced to a significantly greater extent with orlistat than placebo after 1 yr ($p = 0.002$). Diastolic BP also decreased more in the orlistat group than in the placebo group ($p = 0.009$). Sjöström et al. *(19)*, also reported significantly greater reductions in both systolic and diastolic BP after 1 yr of orlistat compared to placebo. The greater reductions in BP associated with orlistat treatment are consistent with the greater degree of weight loss experienced by the subjects.

The effect of orlistat on BP has been further assessed in a metaanalysis of five phase III clinical trials of orlistat

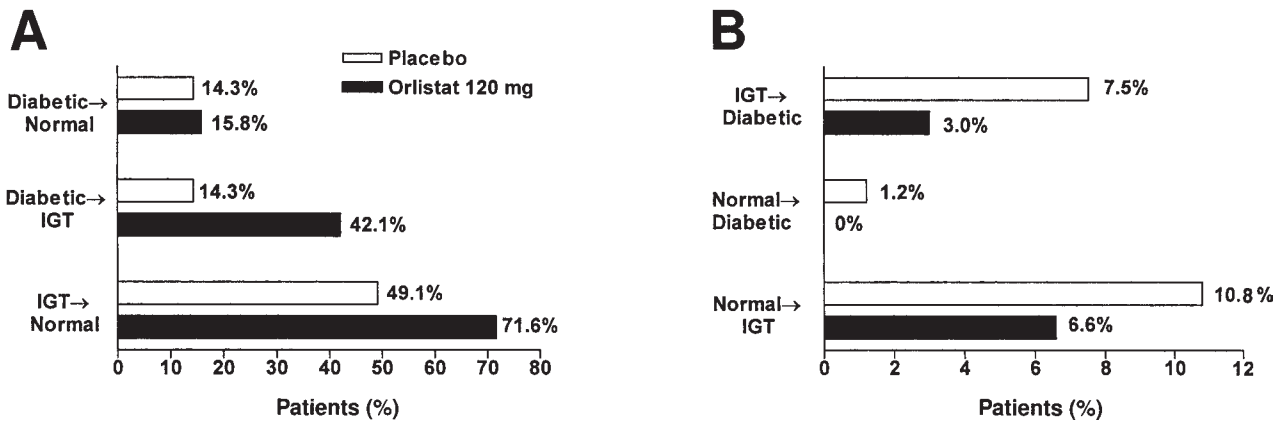

Fig. 4. Percentage of subjects with **(A)** improvement or **(B)** deterioration in oral glucose tolerance from randomization to end of treatment. The distribution of categorical status at the end point differed across treatments within the normal at baseline and impaired at baseline cohorts (p <0.05). IGT, impaired glucose tolerance. (Adapted from ref. *42*.)

(38). Obese subjects were randomized to orlistat (n = 1559) or placebo (n = 1116) in combination with diet for 1 yr. Among patients who achieved 5% weight loss (59% of orlistat-treated subjects vs 41% of placebo-treated subjects), mean systolic and diastolic BPs were reduced by 7.1 and 5.4 mmHg, respectively, with orlistat (vs 6.7 and 4.5 mmHg, respectively, with placebo). By comparison, reductions in systolic and diastolic BP were substantially smaller in subjects losing <5% of their body weight.

Insulin and Glucose Metabolism

There is considerable evidence to suggest that both hyperinsulinemia and hyperglycemia are independent risk factors for cardiovascular disease *(39–41)*. Treatment with orlistat is associated with improvements in insulin and glucose metabolism. In studies of nondiabetic obese subjects, orlistat in combination with diet resulted in significantly greater improvements in levels of fasting serum insulin and glucose after 1 and 2 yr than treatment by dietary intervention alone *(18,19)*. In addition, a metaanalysis of three randomized, placebo-controlled trials has shown that treatment with orlistat may have potential use in preventing or delaying the progression from impaired glucose tolerance to type 2 diabetes *(42)*. A total of 650 obese subjects were randomized to double-blind treatment with orlistat or placebo in combination with a mildly hypocaloric diet for 1 or 2 yr. Oral glucose tolerance tests were performed before and after treatment (average duration of follow-up of 587 d). Orlistat-treated subjects lost more weight than placebo-treated subjects (6.7 vs 3.8 kg; p <0.001). Among subjects with impaired glucose tolerance at baseline, fewer progressed to diabetic status in the orlistat group than in the placebo group (3.0 vs 7.5%). Conversely, more subjects with impaired glucose tolerance at baseline achieved normal glucose tolerance after orlistat treatment (71.6%) compared with placebo (49.1%) (Fig. 4). Treatment with orlistat was also associated with significantly greater reductions in the integrated glucose and insulin areas after oral glucose challenge.

Type 2 Diabetes

In a 1-yr study of obese patients with type 2 diabetes by Hollander et al. *(23)*, greater weight loss with orlistat compared to placebo was accompanied by a more marked improvement in glycemic control. Hemoglobin A_{1c} decreased by 0.28% after randomization to orlistat treatment whereas the placebo group increased by 0.18% (p <0.001). Fasting glucose decreased by 0.02 mmol/L following the use of orlistat whereas it increased by 0.54 mmol/L in the placebo group (p <0.001). In addition, patients treated with orlistat were able to reduce their average dose of sulfonylurea medication to a greater extent than placebo recipients (–23 vs –9%; p <0.05) and fewer orlistat-treated patients withdrew from the study as a result of poor glycemic control (2.5 vs 8.8% of patients).

Treatment with orlistat also produced greater improvements in several serum lipid parameters than placebo in patients with type 2 diabetes. Total cholesterol, LDL-cholesterol, LDL:high-density lipoprotein–cholesterol ratio, apolipoprotein-B (all p <0.001), and triglycerides (p <0.05) were all reduced to a significantly greater degree in the orlistat group vs the placebo group after 1 yr.

Safety of Orlistat

Because orlistat acts locally in the GI tract and is only minimally absorbed, it has not been shown to be associated with serious systemic adverse events such as those that have been reported with some centrally acting appetite suppressant drugs. Indeed, in clinical trials, orlistat has been shown to be well tolerated by both diabetic and nondiabetic obese subjects *(18,19,23)*. Orlistat was, however, associated with a higher incidence of certain GI events that relate to its partial inhibition of fat absorption, such as fatty/oily stools and fecal urgency. These GI consequences of orlistat tended to be of mild to moderate intensity, transient, and limited to one to two episodes per patient. Moreover, these effects mostly occurred within

the first 12 weeks of therapy, with half occurring within the first month. These findings, together with supportive anecdotal evidence, suggest that the pharmacologic effect of orlistat on fat absorption may encourage long-term compliance with a reduced-fat diet *(43)*.

The inhibition of dietary fat absorption by one-third with orlistat could, theoretically, have a potential impact on levels of fat-soluble vitamins and β–carotene. However, in 2-yr clinical trials, mean levels of vitamins A, D, and E and β-carotene remained within clinical reference ranges *(18,19)*. In the study by Davidson et al. *(18)*, treatment with orlistat compared to placebo was associated with a slightly higher incidence of two or more consecutive low values of vitamins A (2.5 vs 1.0% of subjects), D (5.8 vs 1.4%), and E (4.2 vs 0.5%) and β-carotene (4.5 vs 0.0%). Supplementation with once-daily multivitamins restored vitamins to within normal ranges in those individuals who experienced low levels.

Conclusion

Partial inhibition of dietary fat absorption with orlistat has been shown to be a well-tolerated and effective option as an adjunct to mild dietary modification in the long-term management of obesity. In clinical trials, orlistat in conjunction with dietary intervention has consistently and reliably been associated with significantly greater weight loss than achieved with diet alone in obese subjects with and without type 2 diabetes. Moreover, significant improvements in several obesity-related coronary risk factors, including hypercholesterolemia, hypertension, glucose intolerance, and insulin resistance, have all been reported with orlistat treatment.

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