Improvement of HbA_{1c} and Blood Glucose Stability in IDDM Patients Treated With Lispro Insulin Analog in External Pumps

VINCENT MELKI, MD
ERIC RENARD, MD
VÉRONIQUE LASSMANN-VAGUE, MD
SOPHIE BOIVIN, MD
BRUNO GUERCI, MD
HÉLÈNE HANAIRE-BROUTIN, MD
JACQUES BRINGER, MD
PAULINE BELICAR, MD
NATHALIE JEANDIDIER, MD
LAURENT MEYER, MD
PATRICK BLIN, PHD
BÉATRICE AUGENDRE-FERRANTE, MD
JEAN-PIERRE TAUBER, MD

OBJECTIVE — To compare the efficacy of the short-acting insulin analog lispro (LP) with that of regular insulin in IDDM patients treated with an external pump.

RESEARCH DESIGN AND METHODS — Thirty-nine IDDM patients (age, 39.4 ± 1.5 years; sex ratio, 22M/17W; BMI, 24.4 ± 0.4 kg/m^2; diabetes duration, 22.5 ± 1.6 years) who were treated by external pump for 5.1 ± 0.5 years were involved in an open-label, randomized, crossover multicenter study comparing two periods of 3 months of continuous subcutaneous insulin infusion with LP or with Actrapid HM, U-100 (ACT). Boluses were given 0–5 min (LP) or 20–30 min (ACT) before meals. Blood glucose (BG) was monitored before and after the three meals every day.

RESULTS — The decrease in HbA_{1c} was more pronounced with LP than with ACT (−0.62 ± 0.13 vs. −0.09 ± 0.15%, $P = 0.01$). BG levels were lower with LP (7.93 ± 0.15 vs. 8.61 ± 0.18 mmol/l, $P < 0.0001$), particularly postprandial BG levels (8.26 ± 0.19 vs. 9.90 ± 0.20 mmol/l, $P < 0.0001$). Standard deviations of all the BG values (3.44 ± 0.10 vs. 3.80 ± 0.10 mmol/l, $P = 0.0001$) and of postprandial BG values (3.58 ± 0.10 vs. 3.84 ± 0.10 mmol/l, $P < 0.02$) were lower with LP. The rate of hypoglycemic events defined by BG <3.0 mmol/l did not significantly differ between LP and ACT (7.03 ± 0.94 vs. 7.94 ± 0.88 per month, respectively), but the rate of occurrences of very low BG, defined as BG <2.0 mmol/l, were significantly reduced with LP (0.05 ± 0.05 vs. 0.47 ± 0.19 per month, $P < 0.05$). At the end of the study, all but two (95%) of the patients chose LP for the extension phase.

CONCLUSIONS — When used in external pumps, LP provides better glycemic control and stability than regular insulin and does not increase the frequency of hypoglycemic episodes.

From Service de Diabétologie (V.M., H.H.-B., J.-P.T.), Maladies Métaboliques et Nutrition, Hôpital de Rangueil, CHU Toulouse, Toulouse; Service des Maladies Endocriniennes (E.R., J.B.), Hôpital Lapeyronie, CHU Montpellier, Montpellier; Service de Diabétologie (V.L.-V., P.Be.), Hôpital de la Timone, CHU Marseille, Marseille; Service d'Endocrinologie (S.B., N.J.), Hôpital Civil, CHU Strasbourg, Strasbourg; Service de Médecine (B.G., L.M.), Hôpital Jeanne d'Arc, CHU Nancy, Toul; Eval (P.Bl.), Paris; and Laboratoire Lilly France (B.A.-F.), Saint-Cloud, France.

Address correspondence and reprint requests to Dr. Vincent Melki, Service de Diabétologie, Hôpital de Rangueil, CHU de Toulouse, 1 avenue Jean Poulhes, 31403 Toulouse Cedex 4, France.

Received for publication 23 September 1997 and accepted in revised form 24 February 1998.

P.Bl. is a paid consultant of Eval.

Abbreviations: ACT, Actrapid HM, U-100; ANOVA, analysis of variance; BG, blood glucose; CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; LP, lispro; MDI, multiple daily injection.

The Diabetes Control and Complications Trial (DCCT) has clearly demonstrated that intensive diabetes management with the goal of maintaining near euglycemia could reduce the risk of development and progression of long-term complications of IDDM (1–3). However, improvement of glycemic control is accompanied by an increase in the frequency of severe hypoglycemia. Therefore, the DCCT Research Group recommended that intensive therapy to achieve glycemic levels as close to the normal range as safely possible should be proposed for most IDDM patients.

Several studies have suggested that continuous subcutaneous insulin infusion (CSII) could reduce the rate of severe hypoglycemia compared with multiple daily injections (MDI) (4,5). Greater regularity and predictability in day-to-day absorption of insulin with CSII are probably involved in these results (6,7). However, subcutaneous administration of regular insulin, even with CSII, often fails to limit postprandial hyperglycemia because of delayed insulin absorption (8).

The development of a short-acting insulin analog was meant to solve these difficulties. When injected subcutaneously, lispro (LP) has a more rapid onset of action and a shorter duration compared with regular insulin (9). In MDI regimens, LP improves postprandial blood glucose (BG) levels and reduces the rate of hypoglycemia (10–13). To date, few studies have shown that LP could decrease HbA_{1c} levels (14–16). In a double-blind crossover trial comparing LP and regular insulin in CSII, Zinman et al. (17) demonstrated an improvement in glycemic control, assessed by the reduction of the HbA_{1c} levels, whereas the rate of hypoglycemia decreased with LP, although the decrease did not reach statistical significance when compared with regular insulin. However, because of the double-blind design of the trial, regular insulin was injected just before meals; therefore, its efficacy in controlling postprandial BG might have been blunted. Thus, to administer each insulin at the opti-

Table 1—*Patients' characteristics*

n	39
Sex (M/W)	22/17
Age (years)	39.4 ± 1.5
BMI (kg/m²)	24.4 ± 0.4
Duration of diabetes (years)	22.5 ± 1.6
Duration of CSII (years)	5.1 ± 0.5
HbA_{1c} (%)	7.84 ± 0.12
Daily insulin dose (IU/kg)	0.57 ± 0.02

Data are means ± SEM or *n*.

mum time before meals, we conducted a crossover study comparing the efficacy and safety of CSII treatment with LP and with regular insulin in an open-label design.

RESEARCH DESIGN AND METHODS

— The study protocol was approved by the Ethical Committee of Toulouse, and all patients gave written consent.

Patients

Thirty-nine IDDM patients between the ages of 18 and 60 years participated in the study. All were treated by CSII with regular insulin for at least 1 year before enrollment. Inclusion criteria at baseline were HbA_{1c} <8.5%, negative C-peptide response after intravenous injection of 1 mg glucagon, and anti-insulin antibodies <70%. None of the patients had untreated retinopathy, impaired renal function, gastric neuropathy, a BMI >30 kg/m², a daily insulin dose >2 IU/kg, a history of hypoglycemia unawareness, or any severe disease that could interfere with the study. The patients' characteristics are shown in Table 1.

Study design

The study was conducted in five French centers in a randomized crossover open-label design to compare LP (Humalog, U-100, Lilly France, Saint Cloud, France) with regular human insulin, i.e., Actrapid HM, U-100 (ACT) (Novo Nordisk, Boulogne-Billancourt, France), during CSII treatment with an external pump (MiniMed 506, Sylmar, CA). After a 4-week run-in period of treatment with ACT, the patients were randomly assigned to receive either LP or ACT for 3 months (first period) and then were switched to the alternate insulin for another 3 months (second period).

Patient instructions

The patients were instructed to inject the boluses 0–5 min before the meals with LP, and 20–30 min before the meals with ACT. The infusion site was changed every 2 days. Daily capillary BG measurements were performed before and 2 h after each meal, nightly once a week, and in case of hypoglycemic symptoms, using a One Touch II memory meter (Lifescan, Roissy, France). Adjustments of the insulin regimen were made by the patient based on the results of self-monitoring, and by the investigator at the 1-month study visit interval. The glycemic targets were 3.9–6.6 mmol/l before meals or during fasting periods, and 6.6–10.0 mmol/l 2 h after meals. The patients were instructed to record in a notebook all the episodes of hypoglycemia and any technical or metabolic incident such as ketonuria or severe hypoglycemia, as defined by the DCCT criteria.

Follow-up: data collection and biochemical determinations

The patients were seen monthly by the investigator. During each visit, insulin dosage and adverse events, such as those relative to pump treatment, were collected. The number of hypoglycemic events, defined by BG measurements <3.0 mmol/l, and of very low BG measurements, <2.0 mmol/l, were noted at each visit. The memory meters were downloaded on a computer (Glucofacts software, Bayer Diagnostics, Puteaux, France). At the end of each study period, blood samples were drawn for determination of HbA_{1c} and insulin antibodies. Blood pressure and weight were also recorded. At the end of the study, patients received a questionnaire focusing on their satisfaction with the two types of insulin.

Assay methods

HbA_{1c} was measured by high-performance liquid chromatography (reference range, 3.50–6.25%). For screening, insulin antibodies were determined by radioimmunoassay (Pasteur, Paris, France). During the follow-up, serum concentrations of human insulin–specific antibodies, insulin LP–specific antibodies, and cross-reacting antibodies were determined, using a liquid-phase radioassay developed by Lilly (18). All these biochemical determinations, except insulin antibodies for screening, were centralized.

Statistical analysis

Calculations were performed with SAS software (SAS Institute, Cary, NC). Results are given as means ± SE. All tests were two-tailed, and P values <0.05 were considered statistically significant.

The comparison of the groups for baseline characteristics was done using the χ^2 test for categorical variables (or Fisher's exact test when necessary), and one-way analysis of variance (ANOVA) for continuous variables.

Changes in continuous criteria (efficacy criteria, Diabetes Treatment Satisfaction Questionnaire [DTSQ], and quality-of-life questionnaire [QSD]) were studied by ANOVA applied for crossover study with period, treatment group, and interaction factors. In case of significant interaction or carryover effect, only the crossover first period was used in comparing treatments. Categorical criteria (adverse events and patient preference for insulin questionnaire) were compared by sign test between periods and between treatment groups.

RESULTS

— Thirty-eight patients completed the study. One subject dropped out during the first period of treatment for personal reasons and lack of compliance with the protocol.

Clinical results

We observed no significant difference in weight gain (0.04 ± 0.29 kg with LP vs. 0.48 ± 0.26 kg with ACT), systolic blood pressure variation (−5.1 ± 2.9 mmHg with LP vs. 2.8 ± 2.4 mmHg with ACT), or diastolic blood pressure variation (−3.9 ± 1.4 mmHg with LP vs. 0.1 ± 1.4 mmHg with ACT) between the two treatments.

HbA_{1c}

Analysis of HbA_{1c} results was performed only during the first period of treatment because of a carryover effect (Figs. 1 and 2). HbA_{1c} levels decreased from 7.74 ± 0.20 to 7.11 ± 0.15% with LP and from 7.97 ± 0.13 to 7.88 ± 0.16% with ACT during this period. The reduction in HbA_{1c} was significantly more pronounced with LP than with ACT (−0.62 ± 0.13 vs. −0.09 ± 0.15%, respectively, P = 0.01).

Daily BG measurements

Mean daily BG measurements, recorded during the last 30 days of each period, were significantly lower with LP compared with ACT (7.93 ± 0.15 vs. 8.61 ± 0.18 mmol/l, respectively, P < 0.0001) (Table 2). As expected, 2-h postprandial BG levels were dramatically improved with LP compared with ACT (8.26 ± 0.19 vs. 9.90 ± 0.20 mmol/l, respectively, P < 0.0001). In

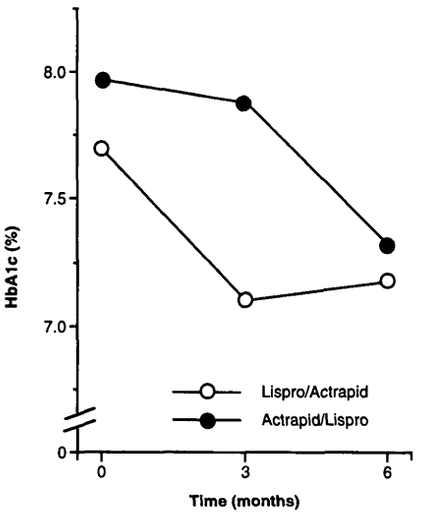

Figure 1—*HbA_{1c} levels at baseline and at the end of each 3-month period of treatment. Patients were randomly assigned to receive either LP then ACT or ACT then LP.*

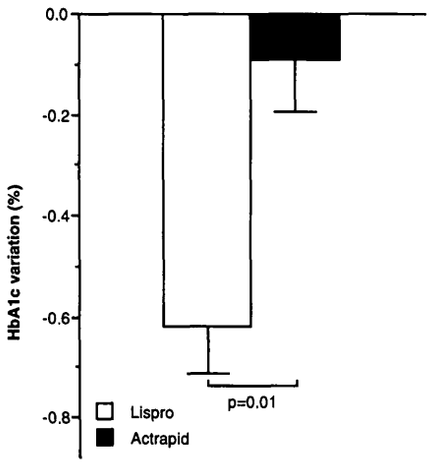

Figure 2—*HbA_{1c} variation from baseline to the end of the first 3-month period in patients treated with LP and ACT.*

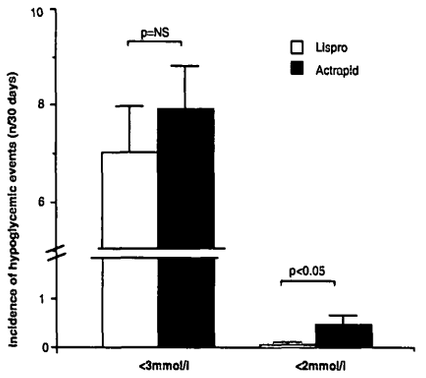

Figure 3—*Incidence of hypoglycemic events (BG <3.0 mmol/l and <2.0 mmol/l) during the last 30 days of the first 3-month treatment period in patients treated with LP and ACT.*

contrast, no difference in preprandial BG measurements could be shown between the two treatments.

BG stability was improved with LP, as assessed by the reduction of the mean standard deviation of BG values (3.44 ± 0.10 mmol/l with LP vs. 3.80 ± 0.10 mmol/l with ACT, $P = 0.0001$). Postprandial glycemic fluctuations were reduced with LP, as shown by the decrease of the standard deviation of postprandial BG values (3.58 ± 0.10 mmol/l with LP vs. 3.84 ± 0.10 mmol/l with ACT, $P < 0.02$). Conversely, the standard deviation of the preprandial BG values was only slightly lower with LP, and this difference did not reach statistical significance.

Insulin doses

At baseline, mean insulin dosage was 0.57 ± 0.02 IU · kg^{-1} · day^{-1} (Table 2). No difference in total insulin use (0.53 ± 0.02 IU · kg^{-1} · day^{-1} LP vs. 0.55 ± 0.02 IU · kg^{-1} · day^{-1} ACT, NS) or in basal insulin use (0.30 ± 0.01 IU · kg^{-1} · day^{-1} LP vs. 0.30 ± 0.01 IU · kg^{-1} · day^{-1} ACT, NS) was noted at the end of each treatment period. The daily bolus insulin dose was slightly but significantly lower with LP than with ACT (0.22 ± 0.01 IU/kg vs. 0.25 ± 0.01 IU/kg, respectively, $P < 0.005$).

Hypoglycemic events

To avoid any confusion due to a carryover effect, we restricted the analysis of hypoglycemic events to the last 30 days of the first treatment period (Fig. 3). Hypoglycemic events (BG <3.0 mmol/l) occurred at a rate of 7.03 ± 0.94 per month with LP and 7.94 ± 0.88 per month with ACT (NS). Nevertheless, very low BG measurements (<2.0 mmol/l) were significantly less frequent with LP than with ACT (0.05 ± 0.05 vs. 0.47 ± 0.19 per month, respectively, $P < 0.05$). Severe hypoglycemic episodes were reported 10 times during the study—3 times with LP and 7 times with ACT—in three and four patients, respectively. None of these episodes resulted in coma or seizures. The patients required external help to take sugar, but they never required glucagon or glucose injection.

Table 2—*Capillary BG measurements and daily insulin doses*

	LP	ACT	P
BG (mmol/l)			
Mean glycemia	7.93 ± 0.15	8.61 ± 0.18	<0.0001
Preprandial glycemia	7.70 ± 0.17	7.75 ± 0.21	NS
Postprandial glycemia	8.26 ± 0.19	9.90 ± 0.20	<0.0001
SD of BG values (mmol/l)			
Mean SD of BG values	3.44 ± 0.10	3.80 ± 0.10	0.0001
SD of preprandial BG values	3.24 ± 0.11	3.42 ± 0.12	NS
SD of postprandial BG values	3.58 ± 0.10	3.84 ± 0.10	<0.02
Daily insulin doses (IU/kg)			
Total	0.53 ± 0.02	0.55 ± 0.02	NS
Basal	0.30 ± 0.01	0.30 ± 0.01	NS
Bolus	0.22 ± 0.01	0.25 ± 0.01	0.004

Data are means ± SEM. Daily capillary BG measurements, standard deviations of blood glucose values, and daily insulin doses during the last 30 days of each treatment period are shown.

Technical incidents

Insulin precipitation in the catheter was reported five times: once with LP and four times with ACT. Other catheter obstructions, suspected because of an alarm or of unexplained hyperglycemia, occurred nine times with LP and nine times with ACT. There was no episode of ketoacidosis.

Antibodies

Changes in levels of specific antibodies (human insulin–specific and insulin LP–specific antibodies) were slight and did not differ between the two treatments. However, levels of cross-reacting antibodies showed a tendency to increase (2.40 ± 1.48%) during LP treatment and to decrease (−0.35 ± 1.04%) during ACT treatment ($P < 0.05$).

Patient satisfaction

At the conclusion of the study, the patients were asked which insulin they wanted for the continuation of their therapy. All but

Table 3—*Preference questionnaire*

Questions	Responses			P
	LP	ACT	No difference	
With which insulin do you feel better?	34 (89.4)	2 (5.3)	2 (5.3)	<0.0001
With which insulin are your daily activities easier?	32 (84.2)	2 (5.3)	4 (10.5)	<0.0001
Which insulin do you prefer?	35 (92.1)	2 (5.3)	1 (2.6)	<0.0001
Which insulin would you use in the future?	36 (94.7)	2 (5.3)	0 (0)	<0.0001
Which insulin gives you the most flexibility when you eat at home?*	33 (86.8)	2 (5.3)	1 (2.6)	<0.0001
Which insulin gives you the most flexibility when you eat outside?	32 (84.2)	3 (7.9)	3 (7.9)	<0.0001
During the study, with which insulin has your glycemia been the best balanced?	34 (89.4)	2 (5.3)	2 (5.3)	<0.0001

Data are *n* (%). *Two patients gave no answer.

two (95%) chose LP. This outcome was in agreement with the results of the questionnaire administered at the conclusion of the study, which explored the patients' preferences. The percentage of favorable responses for LP varied from 84 to 92% according to the questions (Table 3).

CONCLUSIONS — Most of the studies comparing insulin LP and regular insulin in an MDI regimen failed to demonstrate a significant difference in HbA_{1c} levels, despite a constant improvement in postprandial glycemic control with LP (10,12,13). The lower rate of hypoglycemic events partly explains these observations. A trend in preprandial BG rise is also probably involved (13) and may be due to the inability of basal insulins to achieve regular and sufficient insulin levels in order to obtain good preprandial glycemic control. Unlike regular insulin, the duration of action of which can exceed 8 h (8), LP does not exert any effect on the normalization of late postprandial and fasting glycemia, which must be controlled exclusively by the basal insulin. To optimize preprandial BG values and long-term metabolic control, basal insulin should be administered in at least two or more injections per day (15,16,19).

In this study, we report a reduction of 8% of the baseline value of HbA_{1c} with insulin LP (7.74 vs. 7.11%). The DCCT demonstrated that a 10% reduction in HbA_{1c} (e.g., 8 vs. 7.2%) is associated with a 43% lower risk of retinopathy progression in the intensive group (20). Therefore, this reduction in HbA_{1c}, although small, might be beneficial in reducing the risk of complications. In agreement with previous studies of MDI regimen, we observed a better postprandial glycemic control with LP in CSII treatment because of its pharmacokinetic properties (9). CSII using an external pump provides stable levels of insulinemia during fasting periods (7), particularly during the night. These findings represent one of the most relevant differences between MDI and CSII and may certainly have contributed to the absence of worsening in preprandial BG levels with LP, and thus to the improvement of HbA_{1c} levels.

Unlike MDI studies, our study did not demonstrate a significant reduction in the rate of hypoglycemic episodes with LP, except for very low BG measurements, <2.0 mmol/l. However, in this study, the improvement of HbA_{1c} with LP was not related to any increase in the frequency of hypoglycemic events, and the more profound and dangerous hypoglycemic events were fewer.

The standard deviation of glycemia reflects the fluctuations in BG levels. With LP, we found a significant reduction in the standard deviation of BG levels, which indicates an improvement in glycemic stability over the day. This finding is due mainly to a reduction in postprandial glycemic excursions but also to the decrease in low BG values, as previously described with LP in MDI regimens (12,19). Moreover, we observed a decrease in the standard deviation of the BG values collected during postprandial periods, which reflects a greater reproducibility of glycemic values after meals. These results can be related to the more regular absorption of LP, assessed by the reduced within-patient variability of the LP pharmacokinetic profile (21). Such an improvement in diabetes stability, associated with a significant decrease in HbA_{1c} and in frequency of hypoglycemic events, was previously reported in patients treated by continuous intraperitoneal insulin infusion with an implantable pump (22), which allows a more rapid onset and a shorter duration of action of the insulin boluses because of the portal route of insulin absorption.

The occurrence of technical incidents was similar in the two groups of treatment. All of these problems were solved by the patients themselves, none of whom required hospitalization. It is important that no case of ketoacidosis was reported, particularly in association with LP treatment, during which an interruption in insulin infusion might result in a more rapid onset of ketonuria (23,24). All the patients had a large experience of pump therapy, were used to checking BG six times a day and ketonuria when necessary, had received an intensive education, and were able to face any technical or metabolic incident. This point is important with regard to the safety of pump therapy, particularly when LP is used.

Our results confirmed those reported by Zinman et al. (17). In a similar crossover study comparing LP and regular insulin in CSII, they reported a reduction in HbA_{1c} levels and postprandial hyperglycemia that occurred during LP treatment without any increase in the rate of hypoglycemia. Nevertheless, because of the double-blind design of the study, the insulin boluses were injected immediately before meals, regardless of which insulin was used. Therefore, the optimum time of injection was used for LP, but not for regular insulin, which should be injected at least 20 min before meals to fully exert its action on postprandial glycemia. This difference increased the discrepancies in metabolic efficacy of the two insulins in a way that was favorable to LP. Thus, we chose to conduct our study in an open-label design so that we could administer each insulin at the optimum time before meals and give both insulins the best

conditions of efficacy. Recently, another open-label study comparing LP and regular insulin in CSII was conducted in Germany. The boluses were injected at the appropriate time before meals. The authors reported that LP was associated with slightly better HbA_{1c} levels, a significant reduction in postprandial BG, and no difference in the rate of hypoglycemia (25).

Because of a carryover effect, the comparison of HbA_{1c} levels and of hypoglycemia incidence had to be performed during only the first 3-month period of treatment, leading to a reduced power of statistical analysis. This factor may have contributed to the failure to demonstrate a significant reduction in the rate of hypoglycemia (BG <3.0 mmol/l) in patients treated with LP. The reduction in HbA_{1c} levels obtained with the analog was similar in the two groups of patients, LP being given during either the first or the second period. HbA_{1c} levels remained almost unchanged in the patients treated with ACT during the first period. In those who received ACT during the second period, HbA_{1c} increased only slightly, from 7.10 to 7.18%, suggesting that this period of three months was not long enough to totally reverse the remaining beneficial effects of LP that occurred during the first period. The hypoglycemic episodes occurred at a lower rate in the patients who received LP during the second period than in those treated with the analog during the first period. This difference might be due to the progressive enhancement of the investigators' experience throughout the study, which allowed them to improve their management of LP in CSII and to provide early advice about hypoglycemia prevention to the patients treated by LP during the second period.

Our study indicates that subcutaneous infusion of the short-acting insulin analog LP by external pumps improves glycemic control and BG stability without increasing the risk of hypoglycemic events. Moreover, the ability to inject boluses immediately before meals obviously provides a practical benefit for the patients. To be efficient and safe, CSII requires intensive education of patients as well as frequent monitoring of BG and ketone bodies, particularly with the use of LP, given its pharmacokinetic profile. Under these conditions, our results lead us to consider LP as the insulin of choice for CSII in IDDM patients.

Acknowledgments— This study was supported by Lilly France.

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