SWITCH FROM INSULIN THERAPY TO INTENSIVE COMBINATION THERAPY WITH PIOGLITAZONE AND OTHER ORAL HYPOGLYCEMIC AGENTS IN PATIENTS WITH TYPE 2 DIABETES

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Abstract

Aim: Insulin therapy is considered the final option for patients with progressive type 2 diabetes. This study investigated, whether reconverting patients from insulin therapy to oral medicine using thiazolidinedione pioglitazone is possible without further deterioration of glycemic control.

Methods: One hundred sixty subjects (112 male and 48 female) aged 61.4 ± 13.8 years with an mean insulin dose of 28.3 ± 18.7 U/day, mainly using preprandial bolus dose of rapid-acting or ultra-rapid-acting insulin preparations, a duration of insulin therapy of 3.1 ± 1.0 years and an average hemoglobin A1c (A1c) of 9.9 ± 1.8% were switched from insulin therapy to combination therapy with pioglitazone and other oral hypoglycemic agents (biguanide, a-glucosidase inhibitor, and glinide).

Results: During the observation period (3.2 ± 1.3 months), 113 patients (70.6%) treated with insulin injections (24.8 ± 14.3 U/day), could be successfully switched from insulin therapy to pioglitazone-based oral combination therapy. Their mean A1c significant decreased from 9.9 ± 2.0 to 6.2 ± 0.5%, and all patients could achieve A1c < 7.0%. Although the remaining 47 patients (29.4%) could not be successfully switched, their A1c significant decreased from 10.1 ± 1.47 to 7.4 ± 0.8% and their mean insulin dose significantly decreased from 36.7 ± 24.6 to 6.8 ± 10.1 U/day. The success rate of switching from insulin to oral agents was significantly higher in the patients treated with non-insulin secretagogues plus glinide, than in the patients treated with non-insulin secretagogues alone.

Conclusion: Pioglitazone-based oral combination therapy can efficiently and safely substitute for insulin therapy in patients with type 2 diabetes, treated with mainly preprandial bolus insulin injections.

Key words: thiazolidinedione, pioglitazone, mitiglinide, insulin therapy, therapy switch

INTRODUCTION

In Japan, sulfonylureas (SU) are often used as first-line drugs for the treatment of type 2 diabetes mellitus, probably based on the wide-spread view that reduced insulin secretion is a primary factor in this disease in Japanese patients. Unnecessary use of SU for prolonged periods can cause further exhaustion of pancreatic β-cells, leading to further reduction in insulin secretion, and secondary failure of treatment may result in such cases. At present, many patients with type 2 diabetes mellitus for whom insulin therapy has been introduced may be viewed as cases of secondary failure of SU therapy.[1)]

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Amelioration of excessive insulin resistance (a primary pathogenesis of type 2 diabetes) and reduction of excessive insulin secretory requirement can lead to alleviation of pancreatic β-cell exhaustion and recovery of insulin secretory capacity.[2)] This seems to apply well to cases of type 2 diabetes with poor blood glucose control despite insulin therapy.[3)]

ADOPT (A Diabetes Outcome Progression Trial) has provided interesting results.[4)] In newly diagnosed type 2 diabetic patients treated with SU, after an initial decline, A1c rose continuously due to progressive loss of β-cell function. In contrast, TZDs caused an initial reduction in A1c that was sustained over the 5-year duration of the study due to preservation of β-cell function. The ACT NOW (Actos Now for Prevention of Diabetes) revealed a 81% reduction in conversion of impaired glucose tolerance to type 2 diabetes with pioglitazone.[5)] In addition to its insulin sensitizing effect, pioglitazone yielded preservation of β-cell function.[2)]

The DPP (Diabetes Prevention Program) study showed

Table 1　Baseline characteristics of the patients and intervention using oral hypoglycemic agents

gender (Male/Female)	112/48
Age (years)	61.4 ± 13.8
Weight (kg)	66.2 ± 14.2
BMI (kg/m^2)	25.1 ± 4.4
Insulin therapy duration (years)	3.1 ± 1.0
A1c (%)	9.9 ± 1.8
A1c < 7.0%	4.4% (7/160)

BMI: body mass index, A1c: hemoglobin A1c

a: non-insulin secretagogue,

b: insulin secretagogue

Insulin preparations	n	dose (min - max) [U/day]
Rapid-acting analogue	156	26.7 ± 16.3 (3 - 150)
Regular	3	44.7 ± 65.2 (6 - 120)
Long-acting analogue	11	14.3 ± 12.2 (4 - 48)
Intermediate-acting (NPH)	6	15.0 ± 6.07 (72 - 24)
Daily total dosage	160	28.3 ± 18.7 (8 - 150)
Oral hypoglycemic agents	**n**	**dose (min - max) [mg/day]**
TZD (Pioglitazone)[a]	160	35.3 ± 12.2 (7.5 - 45)
Biguanide (Buformin)[a]	124	144.6 ± 17.6 (30 - 150)
alpha-GI (Voglibose)[a]	41	0.56 ± 0.21 (0.2 - 0.9)
Glinide (Mitiglinide)[b]	119	51.5 ± 14.2 (10 - 60)

that metformin (a biguanide) reduced the risk of diabetes by 31% in subjects with impaired glucose tolerance, while the STOP-NIDDM trial confirmed the efficacy of acarbose (an α-GI) in decreasing the risk of diabetes by 36% in a similar high-risk population.[6)7)]

This study investigated whether withdrawal from insulin therapy is possible with intensive intervention with a combination of oral agents, i.e., pioglitazone combined as needed with voglibose (an α-GI), buformin (a biguanide), and mitiglinide (a glinide), without deterioration of glycemic control in patients with type 2 diabetes treated with insulin therapy.

Of these drugs, mitiglinide is a rapid-acting insulin secretagogue used for amelioration of postprandial hyperglycemia through reproduction of physiological postprandial additional insulin secretion, and has been highly appraised for lack of promotion of pancreatic β-cell exhaustion and hypoglycemia because it does not stimulate excessive secretion of insulin, unlike SU.[8)] The author previously reported that the use of mitiglinide in combination with non-insulin secretagogues allowed successful switching from SU therapy in patients with type 2 diabetes, without causing hypoglycemia while allowing further improvement in blood glucose control.[9)] In the present study, mitiglinide was used to substitute or complement for the effects of preprandial bolus doses of rapid-acting insulin preparation.

MATERIAL AND METHODS

Insulin therapy was introduced for 495 type 2 diabetic patients with inadequate glycemic control (A1c level of 8.0 to 11.5%), in spite of treatment with maximal dose of SU at Saijo Central Hospital between April 2005 and February 2009. One hundred ninety-six patients had amelioration in their glycemic control with mainly preprandial bolus dose of rapid-acting or ultra-rapid-acting insulin preparations. Among 196 patients, 160 patients had deterioration in their glycemic control gradually in spite of bolus insulin therapy as mentioned above. In these 160 patients whose basal insulin secretory capacity might be reserved mostly (only 17 patients [11%] treated with basal dose of long-acting insulin preparations), we deliberately attempted withdrawal from insulin therapy with the use of combined oral hypoglycemic agents, i.e., treatment with pioglitazone as a base drug combined as needed with buformin, voglibose, and mitiglinide between March 2009 and April 2010.

In each case, we attempted to reduce the insulin dose level gradually and withdraw the patient from insulin therapy within 6 months, by evaluatiing the results of self-monitoring blood glucose, and A1c level at each office visit, according to our original insulin algorithm. (i.e., insulin therapy withdrawal could be decided, when preprandial bolus insulin dose level ≤ 20 U/day and A1c < 7.0% were achieved in each case.)

Of the oral agents used for intervention, pioglitazone was administered as a base agent for all patients at dose levels between 7.5 and 45 mg/day. Buformin (30-150 mg/day), voglibose (0.2-0.9 mg/day) and mitiglinide (10-60 mg/day) were additionally used as needed.

This study was approved by the Institutional Review Board of the Saijo Central Hospital, and all patients gave informed consent. Most of the patients strongly desired to discontinue insulin self-injections and receive treatment with oral agents alone.

Results are expressed as the mean ± SD. A1c was expressed in National Glycohemoglobin Standardization Program (NGSP) units.[9)] The paired t-test was used for analysis of intra-group differences in mean values, and the independent t-test was used for analysis of inter-group differences in mean values. The chi-square test or McNemar test was employed for testing of differences in percentages.

RESULTS

Table 1 shows in detail of intervention using oral agents and the background variables of the patients. The duration of insulin therapy before the start of study was relatively short (3.1 ± 1.0 years). The number of patients

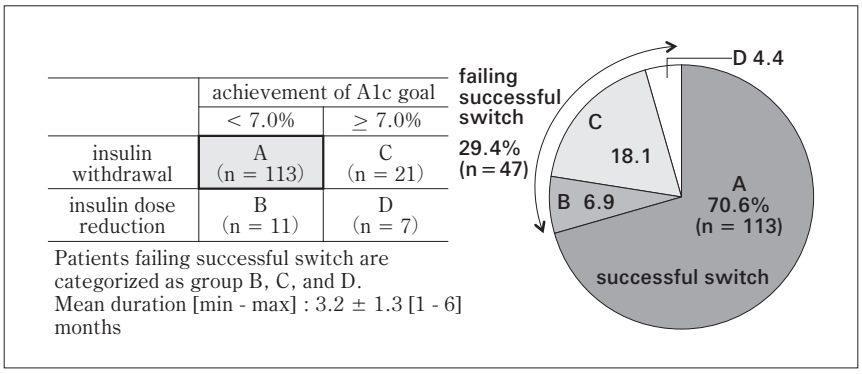

Fig. 1 Success rate of switch from insulin to oral agents

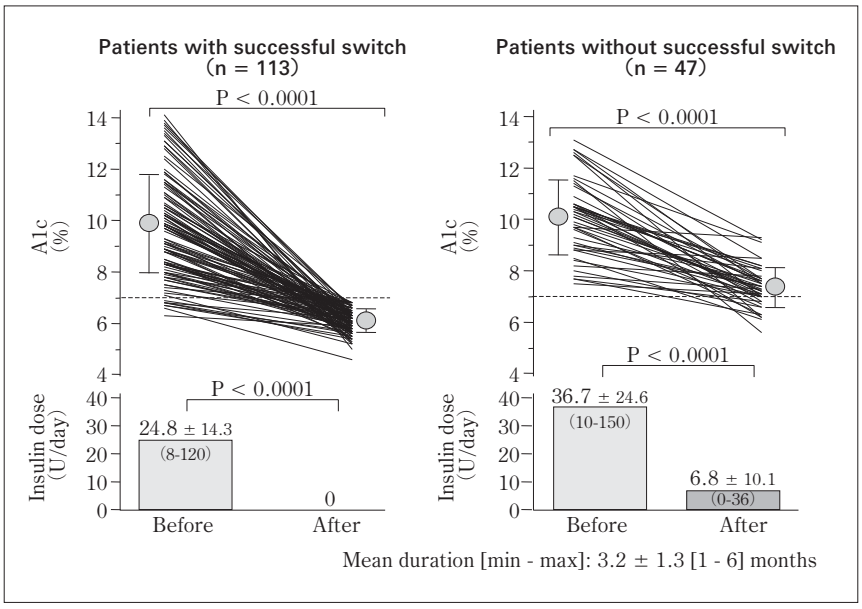

Fig. 2 Changes in HbA1c and insulin dose level before and after intervention according to the success of the switch from insulin to oral agents

receiving long-acting soluble type or intermediate type of insulin (n = 17) was smaller than the number of those receiving rapid-acting insulin (n = 159). Mean BMI was 25.1 ± 4.4 kg/m^2, and about half of all patients were obese (BMI over 25 kg/m^2). Thus, basal insulin secretion had been preserved relatively well in the patients studied, and the majority of the patients had been receiving bolus insulin to compensate for inadequate additional postprandial secretion.

Fig. 1 shows the success rate of switching from insulin to oral agents after the start of intervention in all patients. Switching from insulin therapy was achieved by 113 (70.6%) of the 160 patients by 3.2 ± 1.3 months after the start of intervention using oral agents. Among the remaining 47 patients (29.4%), 21 patients could be switched without achievement of A1c goal (< 7.0%), 11 patients could achieve A1c goal without switch, and 7 patients could not achieve A1c goal and not be switched.

Changes in A1c were analyzed separately for the patients with successful insulin switch and the patients without successful insulin switch (**Fig. 2**). A1c was found to have markedly improved in successful switch group (from 9.9 ± 2.0% to 6.2 ± 0.4%). Properly, all 113 patients could achieve A1c goal (< 7.0%), accompanied by insulin withdrawal. Although remaining 47 patients could not be successfully switched, their mean A1c significantly decreased from 10.1 ± 1.5 to 7.4 ± 0.8 % and their mean insulin dose significantly decreased from 36.7 ± 24.6 to 6.8 ± 10.1 U/day. Deterioration of blood glucose control was not observed in any of these patients.

Baseline characteristics were compared between patients with successful switch and patients without successful switch (**Table 2**). There were no statistical differences in gender (male/female ratio), age, BMI, A1c, and duration of insulin therapy between groups. But, total insulin dose was significantly lower in patients with successful switch than those without successful switch (0.37 ± 0.16 U/kg/day vs 0.56 ± 0.38 U/kg/day), and the percentage of patients using basal insulin preparations was also significantly lower in patients with successful

Table 2　Baseline characteristics of the patients according to the success of the switch from insulin to oral agents

	Patients with successful switch (n = 113)	Patients without successful switch (n = 47)	P value
Gender (Male/Female)	81 [71.7%] / 32 [28.3%]	31 [66.0%] / 16 [34.0%]	0.5959
Age (years)	62.2 ± 13.8	59.3 ± 13.9	0.2361
BMI (kg/m^2)	25.1 ± 4.4	25.3 ± 4.5	0.7158
A1c (%)	9.9 ± 2.0	10.1 ± 1.5	0.4100
Duration of insulin therapy (years)	3.09 ± 0.10	3.09 ± 1.02	0.9845
Total insulin dose (U/kg/day)	0.37 ± 0.16	056 ± 0.38	< 0.0001
Basal insulin prepaerations	5 [4.2%]	12 [25.5%]	< 0.001

BMI: body mass index, A1c: hemoglobin A1c

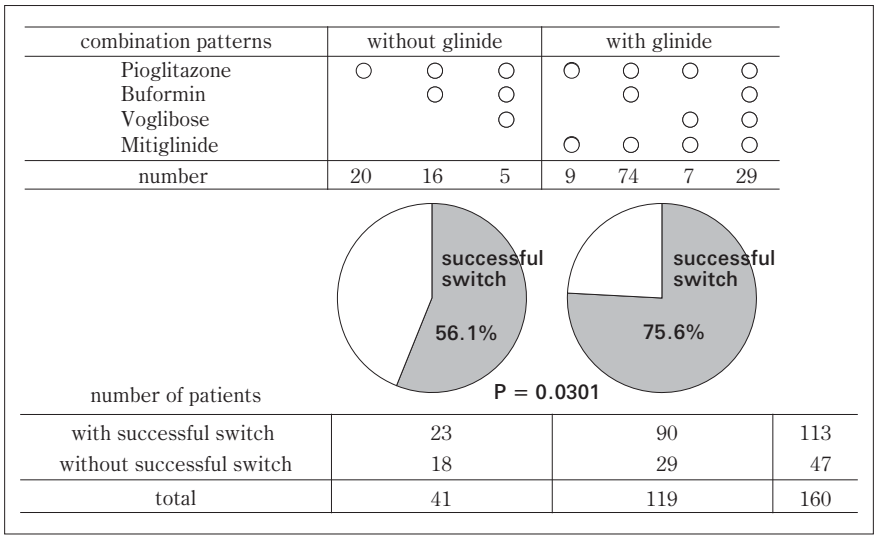

Fig. 3　Success rate of switch from insulin therapy according to the combination patterns of oral hypoglycemic agents

switch (4.2% vs 23.4%).

When success rate of switching from insulin therapy were compared between the non-insulin secretagogue group and the group with mitiglinide addition, success rate was significantly higher in the group with mitiglinide addition than in the non-insulin secretagogue group (**Fig. 3**). Duration of insulin therapy was significantly longer in the group with mitiglinide addition (3.2 ± 1.0 years vs 2.8 ± 1.1 years; $p < 0.05$). BMI was significantly lower in the group with mitiglinide addition (24.5 ± 3.9 kg/m^2 vs 26.9 ± 5.4 kg/m^2; $p < 0.01$). Moreover, patients with non-insulin secretagogues plus mitiginide were significantly older than patients with non-insulin secretagogues alone (63.4 ± 12.7 years vs 55.4 ± 15.3 years; $p < 0.01$).

BMI was significantly increased from 25.1 ± 4.4 kg/m^2 to 26.4 ± 5.1 kg/m^2 in the group of all patients. None of the patients withdrew from the study, although six female patients developed mild peripheral edema. No severe adverse event (including hypoglycemic symptoms) was noted in any patients during intervention, indicating good tolerability.

DISCUSSION

Among type 2 diabetic patients had amelioration in their glycemic control with mainly preprandial bolus dose of rapid-acting/ultra-rapid-acting insulin preparations due to secondary failure of SU therapy at Saijo Central Hospital, patients who had deterioration in their glycemic control gradually in spite of bolus insulin therapy as mentioned above, were enrolled in this study. Thus, it was thought that basal insulin secretory capacity in these patients might be reserved mostly (only 17 patients [11%] treated with basal dose of long-acting insulin preparations). This study was deliberately conducted whether withdrawal from insulin therapy is possible with intensive intervention with pioglitazone-based oral combination therapy, without further deterioration of glycemic control in type 2 diabetic patients could be well characterized by insulin secretory capacity. Consequently, switching from insulin therapy was achieved by 113 (70.6%) of the 160 patients after the

start of intervention. When baseline characteristics of the patients with or without successful switch were analyzed, it was observed that total insulin dose and the percentage of patients using basal insulin preparations were significantly lower in patients with successful switch (**Table 2**). These results indicate that pioglitazone-based oral combination therapy may become an efficient substitutive option for type 2 diabetic patients treated with mainly bolus insulin preparations, whose basal insulin secretory capacity was mostly reserved.

Few published studies have deal with withdrawal from insulin therapy by means of intervention with pioglitazone-based oral combination therapy in patients with type 2 diabetes. Okamoto et al. attempted intervention with pioglitazone (26.4 ± 12.4 mg/day), voglibose (0.84 ± 0.22 mg/day), and glimepiride (2.3 ± 1.2 mg/day) in 36 Japanese patients with type 2 diabetes with a duration of insulin therapy of 6.4 ± 8.5 years, insulin dose level of 27.2 ± 12.4 U/day, fasting plasma C-peptide level of 1.95 ± 0.75 ng/mL, and A1c of 7.2 ± 1.3%. They reported that switch from insulin therapy was successful in 30 of the 36 patients, with A1c maintained at 6.3% at 4 months after switching.[11] They additionally reported that pre-intervention insulin dose level was significantly lower for the 30 patients successfully switched from insulin therapy than for the 6 patients in whom switching failed, and that no change was noted in body weight after intervention from the pre-intervention level. In the present study, body weight increased by 3.4 ± 5.7 kg after intervention, probably because the pioglitazone dose level was high (35.3 ± 12.2 mg/day) and insulin strongly suppressed lipolysis following amelioration of insulin resistance.

The PIO switch study, conducted in Germany, was designed to attempt intervention with pioglitazone combined as needed with glimepiride in type 2 diabetic patients with BMI 30.9 ± 5.2 kg/m^2 receiving insulin therapy.[12] Switch from insulin therapy was possible in 75 (77%) of the 98 patients, with A1c kept on the order of 6% at 6 months later. The pre-intervention insulin dose level was significantly lower in the successful switching group than in the failed switching group (0.31 ± 0.2 vs 0.50 ± 0.4 U/kg/day, $p = 0.004$). Moreover, the glucagon challenge test was performed before and after intervention, and plasma C-peptide/pro-insulin ratio was evaluated as an indicator of insulin secretory capacity. This ratio decreased markedly (by 10.1%) in the failed switching group, while the successful switching group exhibited a 5.2% increase in this ratio, with significant improvement. It appeared that amelioration of insulin resistance reduced the excessive load on insulin secretion, resulting in alleviation of exhaustion of pancreatic β-cells. Furthermore, mean A1c level in the successful switching group was slightly decreased, accompanied by significant elevation of adiponectin and significant reduction of high-sensitivity CRP. These findings suggest that switching insulin to pioglitazone-based treatment may yield advantages in terms of suppression of progression of atherosclerosis.

In the present study, 119 of the 160 patients additionally received mitiglinide (**Fig. 3**). Mitiglinide stimulates insulin secretion mildly but very rapidly, and is used as a means of reproducing physiological postprandial additional insulin secretion. The results of the present study indicate that in cases in which insulin resistance has been reduced by pioglitazone, mitiglinide may be an adequate substitute for a preprandial bolus dose of rapid-acting or ultra-rapid-acting insulin preparations.

Yoshihara et al. reported a study of 30 patients with type 2 diabetes who were hospitalized to maintain glycemic control with long-acting soluble insulin glargine and ultra-rapid-acting insulin aspart. In that study, which was designed to evaluate the diurnal profile of plasma glucose level following switching from insulin aspart to mitiglinide (60 mg/day), good glycemic control was maintained in 15 of 30 cases after switching.[13] They additionally reported that responders (n = 15) had a significantly higher body weight and significantly lower aspart dose level than nonresponders (n = 15) (69.1 ± 13.3 vs 57.6 ± 11.6 kg, 0.27 ± 0.13 vs 0.42 ± 0.14 U/day/kg). Since 69.1 x 0.27 = 18.7, it appears that mitiglinide dose of 60 mg/day is equivalent to a 19 U aspart dose. In the present study, addition of mitiglinide resulted in a significant increase in the percentage of patients with successful switching from insulin (**Fig. 3**). This finding suggests that mitiglinide can adequately reproduce postprandial additional insulin secretion.

In the present study, it was suggested that insulin resistance persisted during insulin therapy, that pancreatic β-cell function can partially resume with pioglitazone (and buformin)-induced amelioration of insulin resistance,[4)14)] and that the insufficient additional postprandial insulin secretion can be adequately compensated for mitiglinide,[13] resulting in successful switching from mainly bolus insulin therapy.

Notably, withdrawal from insulin therapy was successful in a considerably high percentage of patients (70.6%, 113 of 160 patients) with amelioration of glycemic control. These results indicate that pioglitazone-based oral combination therapy may become an efficient substitutive option for type 2 diabetic patients treated with mainly bolus insulin preparations, whose basal insulin secretory capacity was mostly reserved.

In the future, we plan to follow these patients to ensure that they maintain good glycemic control without return to insulin therapy.

CONFLICT OF INTEREST

There are no conflicts of interest.

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