Successful switch from insulin therapy to treatment with pioglitazone in type 2 diabetes patients with residual β-cell function: results from the PioSwitch Study

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Aim: Insulin treatment is considered to be the final option for patients with progressive type 2 diabetes. This study investigated, whether reconverting type 2 patients from insulin treatment to oral treatment using pioglitazone is possible without deterioration of blood glucose control.

Methods: The PioSwitch study was a prospective, open label, proof of concept study. Thiazolidinedione-naïve patients with residual β-cell function were switched from an existing insulin therapy to treatment with pioglitazone and glimepiride for 6 months. Efficacy was assessed by laboratory parameters and scores for evaluation of metabolic control, β-cell function, insulin resistance and cardiovascular risk.

Results: In total, 98 patients [66 men, 32 women, age (mean ± s.d.): 59 ± 9 years; disease duration: 5.6 ± 3.6 years; Hemoglobin A1c (HbA1c): 6.9 ± 0.8%; body mass index (BMI): 33.9 ± 5.2 kg/m2, initial daily insulin therapy dose: 0.36 ± 0.3 U/kg body weight] out of 117 screened patients were treated. During the observation period, 23 patients were prematurely terminated because of an increase in HbA1c from baseline > 0.5% or other reasons. In 75 patients (76%), no deterioration of glucose metabolism occurred and additional improvements were seen in the majority of the observation parameters [baseline vs. endpoint; HbA1c: 6.79 ± 0.74%/6.66 ± 0.69% (p < 0.05), glucose: 6.4 ± 1.5/5.2 ± 1.4 mmol/l (p < 0.001), adiponectin: 7 ± 3 mg/l/17 ± 8 mg/l (p < 0.001), C-peptide: 987 ± 493/1756 ± 789 (p < 0.001), sensitivity index derived from the intravenous glucose tolerance test (SI(ivGTT)): 1.21 ± 0.85/1.49 ± 0.95 (p < 0.05), hsCRP: 3.3 ± 2.4/2.6 ± 2.4 mg/l (p < 0.01), macrophage chemo-attractant protein 1 (MCP1): 487 ± 246/382 ± 295 ng/l (p < 0.05)], BMI increased from 33.8 ± 5.1 to 34.4 ± 5.3 kg/m2 (p < 0.001).

Conclusions: The switch from insulin therapy resulting in a moderately HbA1c level, to oral treatment with pioglitazone was successful in a majority of patients with sufficient residual β-cell function. It allows a simple and less expensive therapy with a better cardiovascular risk marker profile.

Keywords: insulin therapy, pioglitazone, therapy switch

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Introduction

The management of type 2 diabetes starts with education, diet, physical activity and the attempt to reduce body weight in obese patients. When these measures fail to achieve adequate blood glucose control, oral antidiabetic agents or insulin are usually introduced. Today, numerous drugs and drug combinations are used in the treatment, and insulin therapy is generally considered to be the last treatment option, when oral therapy fails to provide stable glycaemic control [1,2]. Several current treatment guidelines and many disease management programmes based on cheaper drugs [3] do not consider the different possible pathophysiological...
phenotypes of the disease, and in consequence many patients are switched to insulin therapy, for example, without ever being treated with an effective insulin resistance therapy.

Type 2 diabetes mellitus, however, is characterized by a β-cell dysfunction resulting in deterioration of secretion timing, quantity and quality and also by insulin resistance. The disease is associated with numerous cardiovascular risk factors such as endothelial dysfunction, activation of the coagulation cascade, increased blood pressure and deterioration of lipid metabolism [4]. Insulin resistance can be defined as an impaired response to the physiological effects of insulin, including those on glucose, lipid and protein metabolism and also on vascular endothelial function [5]. In recent years, multiple epidemiological and interventional studies documented an independent association between insulin resistance and sub clinical or clinical coronary heart disease (CHD), and many patients have insulin resistance for years to decades before diagnosis of type 2 diabetes [6,7]. However, the CHD risk has not been substantially changed during the past decades despite the fact that the Steno Diabetes Center in Denmark, STENO2 study was able to demonstrate improvements if all deteriorated conditions were normalized in parallel [8,9].

One pharmacological approach in the treatment of type 2 diabetes, the stimulation of peroxisome proliferator-activated receptor gamma concentrates on the improvement of insulin sensitivity which provides beneficial effects on glucose and lipid metabolism [10,11]. In addition, previous studies gave further support that at least pioglitazone might evolve additional vasoprotective effects, eventually leading to reduction of cardiovascular mortality [12,13].

In general practice, most patients switched to an insulin treatment regimen are rarely reconverted to an oral treatment regimen. A rationale for such a procedure appears to be missing and it has never been proven to be successful by means of well-designed clinical trials. This study investigates, whether it is possible to convert type 2 diabetic patients with sufficient residual β-cell function from an insulin treatment to an oral therapy regimen without deterioration of metabolic control, when focusing on effective insulin resistance treatment with pioglitazone. This therapeutic approach strikingly demands for a sufficient residual β-cell function, which was an essential inclusion criterion for this study. Co-medication with the β-cell secretagogue glimepiride was allowed at the discretion of the investigator and according to the patients individual requirements, because pioglitazone requires 4–6 weeks of uptake before fully exerting its hypoglycaemic effects [14].

Material and Methods

Study Design

The PIOSwitch Study was a prospective, single arm, open label, multicentre proof of concept trial. The hypothesis of the study was that switching type 2 diabetic patients previously treated with insulin (with or without metformin) to pioglitazone (with or without glimepiride) does not result in an impairment of metabolic control (hemoglobin A1c (HbA1c)) after a treatment period of 6 months. The study was approved by the responsible ethics committee and followed the recommendations of the Declaration of Helsinki. Informed consent of all patients was obtained in writing. To be eligible for the study, the patients had to fulfil the following inclusion criteria: type 2 diabetes, HbA1c < 7.5% with any kind of insulin therapy for 1 year excluding combinations with oral drugs. Exclusion criteria included type 1 diabetes, fatal disease, heart failure and significant kidney or liver disease. After enrolment and at endpoint, an i.v. glucagon test was performed to assess residual β-cell function (see below) and eligible patients received 30 mg of pioglitazone with the opportunity of an up-titration to 45 mg/day by the investigator according to the patient’s individual demands as indicated by increased fasting blood glucose values. To ensure optimal glucose control, co-medication with glimepiride in a range of 13 mg/day was allowed, but not mandated. Blood samples were stored frozen at 80 °C at a central laboratory immediately after blood draw until laboratory testing. The primary efficacy variable was the proportion of patients where the increase of HbA1C after 6 months of treatment compared to the baseline HbA1C value [i.e. the difference of HbA1C after 6 months (visit 7) minus baseline HbA1C (screening visit V1)] was not more than 0.5%.

Glucagon Test

After collection of a baseline blood sample, 1 mg glucagon was given intravenously and 6 min later another blood sample was taken for determination of C-peptide and intact proinsulin. At baseline, a stimulated C-peptide level of ≥0.6 nmol/l was used as an indicator for identifying patients with sufficient insulin secretion capacity [15].

Observational Parameters

Next to HbA1c, the following efficacy parameters were investigated: The homeostatic model assessment (HOMA) score [16] and the intravenous glucose
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Data Analysis

Data were obtained from the case record forms by double data entry and subsequent crosschecks. Replacement of data was not allowed. Where appropriate, the last observation carried forward (LOCF) approach was applied prior to analysis. Statistical analysis was performed using standard descriptive statistics and appropriate parametrical and non-parametrical tests. Exploratory two-sided 95% confidence intervals (Pearson-Clopper) were provided for the primary objective and for the total incidence of adverse events and SAEs as well as for the proportion of patients with severe hypoglycaemic episodes. Secondary efficacy parameters were analysed with the per protocol data set. All calculations were made with the SAS software package (version 8.2) [SAS Institute, Cary, NC]. p Values below 0.05 are considered statistically significant. For Minimal Model analysis, the SAAM 1.2 software package (SAAM Institute, Seattle, WA, USA) was used.

Results

In total, 98 patients out of 117 screened patients were treated. Screening failures were related to the residual β-cell function requiring a postglucagon C-peptide value > 0.6 nmol/l. The intend-to-treat (ITT) study cohort consisted of 66 men (66.3%) and 32 women (32.7%). Most of the patients were of Caucasian origin [94/98 (95.9%) patients]. The mean age was 59 ± 9 years (range: 35–74 years), mean body mass index (BMI) was 33.9 ± 5.2 kg/m² and the mean diabetes duration was 5.6 ± 3.6 years. 9/98 patients (9.2%) received additional metformin therapy. While 75 patients completed the trial, 23 patients discontinued prematurely because of various reasons (SAEs or adverse events: six patients; lost to follow-up: one patient; consent withdrawn because of lack of efficacy: seven patients; multiple other reasons: nine patients). It is noteworthy that prior to study entry the study completers required significant lower doses of insulin (0.31 ± 0.2 U/kg/day) in comparison to the patients with early study termination (0.5 ± 0.4 U/kg/day; p = 0.004). The study drugs were well tolerated. During the observation period, six SAEs affecting 5/98 (5.1%) patients were reported. All SAEs were considered to be not related to study treatment. No clinical significant alteration of laboratory safety parameters occurred. Only one single severe hypoglycaemic episode was reported from the entire study population. As far as no major protocol violations occurred and by application of the LOCF approach, 98 patients belong to the ITT analysis set and 75 patients were treated for the entire 6 months (completers). Table 1 summarizes the results of this study. The data are given as baseline values and measurements at endpoint for both analysis groups. Patients with early termination agreed to participate into an i.v. glucagon test but no further measures regarding secondary objectives could be obtained. At endpoint 15 study completers were on pioglitazone monotherapy (20%), while 60 were on a pioglitzone/glimepiride combination [glimepiride doses 3 mg: 23 (30.7%), 2 mg: 6 (8.0%), 1.5 mg: 4 (5.3%), 1 mg: 15 (20%), and 0.5 mg: 12 (16%)]. In the ITT group, the majority of investigated parameters did not change considerably but remained stable after therapy switch. All observed changes reflect improvements of the patient’s conditions. The only exception was a significant body weight gain. Among the metabolic markers, adiponectin increased significantly. Insulin resistance improved...
Table 1 Summary of the results in regard of the investigated parameters and scores

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ITT population (n = 98)</th>
<th>Study completor (n = 75)</th>
<th>Premature termination (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Endpoint</td>
<td>Baseline</td>
</tr>
<tr>
<td>Daily insulin therapy (U/kg)</td>
<td>0.36 ± 0.3</td>
<td>0.31 ± 0.2</td>
<td>0.50 ± 0.4</td>
</tr>
<tr>
<td>Metformin co-medication [number (%)]</td>
<td>9 (9.2%)</td>
<td>7 (9.3%)</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.8</td>
<td>34.1</td>
<td>34.1</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.87 ± 0.78</td>
<td>6.79 ± 0.74</td>
<td>7.13 ± 0.84</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>6.5 ± 1.5</td>
<td>6.4 ± 1.5</td>
<td>6.9 ± 1.5</td>
</tr>
<tr>
<td>Sensitivity index (ivGTT)</td>
<td>1.26 ± 0.86</td>
<td>1.21 ± 0.86</td>
<td>1.46 ± 1.19</td>
</tr>
<tr>
<td>HOMAIR (mU/l)</td>
<td>7.6 ± 7.9</td>
<td>7.6 ± 7.9</td>
<td>9.2 ± 7.3</td>
</tr>
<tr>
<td>Irisi score</td>
<td>70 ± 17</td>
<td>70 ± 17</td>
<td>75 ± 17</td>
</tr>
<tr>
<td>PROCAM</td>
<td>13.3 ± 8.5</td>
<td>13.3 ± 8.6</td>
<td>11.6 ± 5.5</td>
</tr>
<tr>
<td>Framingham</td>
<td>17.3 ± 9.3</td>
<td>17.5 ± 9.0</td>
<td>15.4 ± 4.9</td>
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<tr>
<td>UKPDS</td>
<td>16.6 ± 8.4</td>
<td>16.6 ± 8.4</td>
<td>16.0 ± 8.3</td>
</tr>
<tr>
<td>HOMA%B (U/mmol)</td>
<td>123 ± 162</td>
<td>122 ± 162</td>
<td>102 ± 53</td>
</tr>
<tr>
<td>C-peptide (pmol/l)</td>
<td>944 ± 472</td>
<td>967 ± 493</td>
<td>969 ± 418</td>
</tr>
<tr>
<td>Intact proinsulin (pmol/l)</td>
<td>18 ± 14</td>
<td>17 ± 12</td>
<td>22 ± 19</td>
</tr>
<tr>
<td>Adiponectin (mg/l)</td>
<td>6 ± 3</td>
<td>7 ± 3</td>
<td>3 ± 4</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.9 ± 1.1</td>
<td>4.9 ± 1.1</td>
<td>4.9 ± 1.1</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>2.8 ± 0.9</td>
<td>2.8 ± 0.9</td>
<td>2.7 ± 0.9</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.3 ± 0.3</td>
<td>1.3 ± 0.3</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.8 ± 0.8</td>
<td>1.8 ± 0.8</td>
<td>2.1 ± 1.0</td>
</tr>
<tr>
<td>hsCRP (mg/l)</td>
<td>3.2 ± 2.4</td>
<td>3.3 ± 2.4</td>
<td>4.4 ± 4.7</td>
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<tr>
<td>MCP1 (pg/ml)</td>
<td>407 ± 245</td>
<td>487 ± 246</td>
<td>414 ± 112</td>
</tr>
<tr>
<td>MMP9 (ng/ml)</td>
<td>767 ± 434</td>
<td>766 ± 437</td>
<td>827 ± 380</td>
</tr>
<tr>
<td>sCD40L (ng/ml)</td>
<td>4.3 ± 2.3</td>
<td>4.3 ± 2.3</td>
<td>4.6 ± 2.9</td>
</tr>
</tbody>
</table>

BMI = body mass index; ITT = intent-to-treat analysis; HbA1c = Haemoglobin A1c; HDL = High density lipoprotein cholesterol; HOMA = Homeostatic model assessment; HsCRP = High sensitivity C-related protein; ivGTT = Intravenous glucose tolerance test; LDL = Low density lipoprotein cholesterol; MCP = Macrophage chemo-attractant protein; MMP = Matrix metallo-proteinase; PROCAM = PROspective CArdiovas-
ular Münster heart Study; UKPDS = United Kingdom Prevention of Diabetes complications Study.

Data are given for baseline and endpoint for the different analysis population values. Statistical significance was calculated using two-sided t-test (n.d.: value not given, as analysis could not be done for the entire patient population). Asterisks represent statistical significance baseline vs. endpoint.

*p < 0.05; **p < 0.01; ***p < 0.001.

when assessed with the HOMAIR Score and the sensitivity index as calculated by means of the Minimal model analysis, but no change was observed in the IRISII score. The scores and the markers of cardiovascular risk did not change considerably except for a decrease in MCP1. The picture was similar but slightly more pronounced, however, for those 75 patients who completed the study successfully per protocol, that is, without a significant increase in HbA1c during the observation period. The per cent changes of the observation parameters for the study completers are shown in figure 1. The C-peptide and intact proinsulin levels during the i.v. glucagon test of the completers and early termination group at baseline and endpoint are provided in figure 2. Patients who did not respond well to the switch (premature termination group) showed no increase in the secretion of correctly processed β-cell secretion product, while responders to the switch had a qualitatively improved secretion at endpoint. The quality of the β-cell secretion product as assessed by calculating the C-peptide/intact proinsulin ratio was improved in the completer group (+5.2%), while it was further deteriorated in the patients who failed to complete the entire study protocol (10.1%, p < 0.01 vs. completers).

Discussion

Functional insulin deficiency, either because of β-cell secretion failure or cellular insulin resistance, is the major cause for diabetes. However, it is a general consideration that treatment of type 2 diabetes with insulin is the final therapeutic step and indicates the ultimate progression of the disease into its final stage. In consequence, no information is available from controlled clinical trials investigating a switch from insulin therapy to treatment with oral antidiabetic drugs. On the other hand, it is tempting to speculate that patients with sufficient residual β-cell function might have benefits from an oral anti-diabetic therapy focussing on an effective treatment of insulin resistance after stabilization by temporary insulin...
Based on the inclusion criteria, we screened 117 patients and only 19 patients were rejected for insufficient β-cell function after the glucagon test. This finding indicates that a significant number of insulin-treated type 2 patients may still have substantial β-cell functionality. A successful switch from insulin back to oral therapy should be indicated by an equal or improved metabolic situation accompanied by a decrease in insulin resistance, a diminished CHD risk marker profile and a better quality of life by omitting the insulin application procedure and frequent blood glucose testing requirements. It is well known that pioglitazone has shown similar results in a multitude of clinical trials with orally treated patients [14,22], and may therefore be a drug with a good probability of success for such a procedure. It can be expected that the likelihood for a successful switch may increase, if a thiazolidinedione was never regularly applied to a patient prior to insulin initiation. Our pilot study aimed to investigate this switch under controlled clinical conditions. As endogenous insulin is required for successful pioglitazone action [14], we only included patients with residual β-cell function as

**Fig. 1** Per cent change in risk markers from baseline to endpoint in the study completer group (n = 75). Asterisks represent statistical significance baseline vs. endpoint: *p < 0.05; **p < 0.01; ***p < 0.001.

**Fig. 2** C-peptide and proinsulin stimulation by i.v. glucagon at baseline and endpoint and the per cent change in the quality of the secretion product (C-peptide/intact proinsulin ratio) in patients who terminated the study prematurely and in study completers.
assessed using accepted risk scores (Framingham Score, [12,29,31,33]. The cardiovascular risk was additionally inflammatory effects of pioglitazone as shown previously significant, displaying the glucose-independent anti-
cally significant, the MCP1 and hsCRP reductions were
hsCRP, MMP9 and MCP1 concentrations decreased in
here, sCD40L values remained nearly constant, but
As reported here, sCD40L values remained nearly constant, but
hsCRP, MMP9 and MCP1 concentrations decreased in
our study. While the decrease in MMP9 was not statistically
significant, the MCP1 and hsCRP reductions were
significant, displaying the glucose-independent anti-
inflammatory effects of pioglitazone as shown previously
[12,29,31,33]. The cardiovascular risk was additionally assessed using accepted risk scores (Framingham Score, UKPDS Score and PROCAM Score). No significant varia-
tion in cardiovascular risk scores was observed in this study, irrespective of the score used. This suggests that the switch from insulin to glitazone did in any case not elevate the patient's risk for cardiovascular events, when assessed by these different risk engines and other conventional risk markers. It needs to be considered, however, that data on surrogate markers can be misleading as their value is not entirely confirmed by outcome studies.

Elevated fasting intact proinsulin has been demonstrated to be a highly specific marker for β-cell dysfunction and insulin resistance [34]. In early disease stages, glibizide monotherapy led to an increase in fasting intact proinsulin levels indicating an increase in β-cell stress, while thiazolidinediones when given alone or in addition to a sulphonylurea drug or metformin have shown to reduce intact proinsulin levels independently from the glucose lowering effects [35]. In this study, the β-cell protecting effects of pioglitazone were counter-balanced by the increased pressure on the β-cell subsequent to the lack of external insulin support. This may be the reason why no decrease in intact proinsulin concentrations was observed in our trial. The observed decrease in HOMAB, a supposed measure of β-cell function is driven by the definition of this parameter that involves fasting insulin secretion as an important contributor to the score value. Oedema was not a major cause for dropouts. Seven per cent of the patients presented with lack of efficacy, which may well be attributed to non-response to the study drug as this percentage is comparable to the prevalence of non-responders reported in other clinical trials [14]. A major difference between study completers and patients who failed a successful switch is indicated by the increase in correctly processed C-peptide before and after the i.v. glucagon challenge in the study completer group. This increase represents the capability of the β-cell to regain an improved qualitative secretion profile in these patients, while no such improvement was seen in patients with early termination, which may have been one potential reason of deterioration of glucose control. This observation is further supported by the fact that study completers required significant lower doses of insulin prior to study start compared to patients with early termination. In our opinion these findings indicate that β-cell dysfunction may be reversible when treated early enough in the course of the disease. Body weight and body mass index raised by study treatment, but waist to hip ratio was stable. It is well known that pioglitazone has effects on body weight [14,22]. Fluid retention is considered one of the causes for this observation. In addition, the increase of insulin sensitivity by pioglitazone treatment may allow insulin to exert its fat tissue building properties more
aggressively in a situation where glycaemic control is improved with the consequence of a reduced renal excretion of glucose in the postprandial stage. However, this unfavourable situation can be avoided if the pioglitazone treatment starts in concert with expert diet advice, which was shown recently in an observational trial [36]. A weakness of our study is the lack of a control group. However, baseline values can be used in this type of switch studies, especially as insulin therapy is considered to be the best treatment option for the investigated patient population and the patients were already well controlled. Conclusions for the secondary objectives, however, may have to be drawn carefully and only in the context of corresponding findings from other controlled clinical trials. In addition, only a limited number of patients were on insulin + metformin therapy in this study. We therefore suggest to be sensitive when translating our results to this patient population prior to the availability from further data of such cohort. When applying the results from this proof of concept study to daily therapy, it is important to realize that a residual β-cell function was a prerequisite for eligibility in the trial and that the switch from insulin to oral therapy was harshly and instantly made by us at study entry. In daily therapy, the switch may be more elegantly initiated by simply adding pioglitazone to the existing insulin treatment. Good responders may clinically become apparent over time by a drastic reduction in insulin dose, which may ultimately result in a total discontinuation of insulin therapy. We selected the described immediate procedure only to proof our concept that a treatment solely using sulphonylurea drugs and metformin prior to insulin initiation does not effectively address insulin resistance and leads to insulin treatment in patients who might well be also effectively controlled by treatment with pioglitazone. In Germany, mean patient insulin treatment costs (generic products including blood glucose test strips) are calculated to be in the range from US$ 1500–1700 per year (assumptions: conventional insulin therapy, a daily dose of 80 IU and seven blood glucose measurements/week). A successful switch would reduce these costs to approximately $ 900 year (pioglitazone alone).

In summary, this crude pilot study illustrates that the switch from an insulin therapy to treatment with pioglitazone was performed without major disadvantages in a majority of patients with sufficient residual β-cell function. The results of this study may be taken into account in future treatment decisions, as this alternative oral therapy is more convenient and cheaper than insulin therapy (including blood glucose measurement) and may even result in a lower cardiovascular risk.

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