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Long-term effects on lipids and lipoproteins of pioglitazone versus gliclazide addition to metformin and pioglitazone versus metformin addition to sulphonylurea in the treatment of type 2 diabetes

Received: 27 January 2005 / Accepted: 11 August 2005 / Published online: 10 November 2005
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Abstract *Aims/hypothesis:* The aim of this study was to determine the long-term effects of pioglitazone add-on to metformin or sulphonylurea on plasma lipids and lipoproteins. *Materials and methods:* The effects of pioglitazone were studied in two clinical trials in patients with inadequately controlled type 2 diabetes ($\text{HbA}_{1c} \geq 7.5$ and $\leq 11\%$). In the first trial, patients currently receiving metformin were randomised to pioglitazone (15–45 mg/day, $n=317$) or gliclazide (80–320 mg/day, $n=313$) add-on therapy. In the second study, pioglitazone (15–45 mg/day, $n=319$) or metformin (850–2,550 mg/day, $n=320$) was added to sulphonylurea therapy. Patients were force-titrated to the maximum tolerated dose of add-on therapy, which was maintained to the 2-year endpoint. *Results:* There were no statistically significant differences between the groups with respect to HbA_{1c} reduction from baseline to week 104. Whether added to metformin or sulphonylurea, pioglitazone caused highly significant greater decreases in triglycerides and increases in HDL cholesterol from baseline to week 104 than treatments with gliclazide or metformin add-on therapies ($p \leq 0.001$). The triglyceride reductions noted with pioglitazone were maintained over time, with decreases of 16–18% at 1 year and 17–23% at 2 years. In the pioglitazone groups, the improvement in HDL cholesterol at 1 year was maintained, with 21–22% augmentations at 2 years ($p < 0.001$ between-group differ-

ence). Small but statistically significant greater reductions in LDL cholesterol were observed with gliclazide vs pioglitazone add-on to metformin and metformin vs pioglitazone add-on to sulphonylurea ($p < 0.001$ for between-group difference). In the pioglitazone groups, mean LDL cholesterol at 2 years was similar to mean baseline LDL cholesterol. *Conclusions/interpretation:* After 2 years, highly significant decreases in triglycerides and increases in HDL cholesterol that were sustained over time or even improved were observed when pioglitazone was added to metformin or sulphonylurea therapy. These effects of pioglitazone on lipids may be potentially beneficial in reducing cardiovascular risk in type 2 diabetes.

Keywords Lipids · Lipoproteins · Pioglitazone · Gliclazide · Add-on therapy · Metformin · Sulphonylurea · Type 2 diabetes

Abbreviations AIP: atherogenic index of plasma · ITT: intention to treat

Introduction

Patients with type 2 diabetes show specific lipid abnormalities, such as hypertriglyceridaemia, low HDL cholesterol and the presence of small, dense LDL particles that are likely to promote atherosclerosis and to explain the residual cardiovascular risk observed in patients with type 2 diabetes treated with potent LDL cholesterol-reducing statins [1–3]. Pioglitazone, a thiazolidinedione that activates peroxisome proliferator-activated receptor- γ , has been shown in short-term studies to improve glycaemic control and increase HDL cholesterol, while decreasing the levels of triglycerides [4–7]. We analysed the long-term effects on plasma lipid and lipoprotein concentrations of pioglitazone when combined with metformin or sulphonylurea in two long-term (2-year), randomised, double-blind, double-dummy clinical trials in patients aged 35–75 years who had inadequately controlled type 2 diabetes ($\text{HbA}_{1c} \geq 7.5$ or $\leq 11\%$).

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Subjects and methods

In the first trial, patients currently receiving metformin were randomised to add-on therapy with pioglitazone (15 mg/day titrated to a maximum of 45 mg/day, $n=317$) or gliclazide (80 mg/day titrated to a maximum of 320 mg/day, $n=313$). In the second study, pioglitazone (15–45 mg/day, $n=319$) or metformin (850–2,550 mg/day, $n=320$) was added to sulphonylurea therapy. During the first 12–16 weeks, patients were force-titrated to the maximum tolerated dose of add-on therapy, which was maintained for the remainder of the 2-year studies. No change in metformin dose from the pre-study level was permitted in the first study. In the second study, if patients had actual symptomatic hypoglycaemia during titration the dose of

existing sulphonylurea could be reduced (one-step reduction), but the dose could not be changed after titration. Changes from baseline to week 104 were assessed in all patients using a last observation carried forward approach. The difference between treatment groups in the change at week 104 was compared using an analysis of covariance model with the factor treatment and baseline value as covariate on the intention-to-treat (ITT) population. The ITT population included all patients who received at least one dose of study medication after randomisation and for whom at least one post-baseline HbA_{1c} value was available. A p value less than 0.05 was considered significant. Details of methods and baseline data have been described previously [6, 7]. All data discussed here are based on the ITT population, unless otherwise specified.

Table 1 Analysis of change from baseline to last visit in lipid and lipoprotein parameters in the two studies (ITT population)

Variable	Add-on to metformin		Add-on to sulphonylurea	
	Pioglitazone	Gliclazide	Pioglitazone	Metformin
Triglycerides (mmol/l)				
Baseline±SD	2.90±1.94	2.78±1.89	2.47±1.69	2.38±1.72
Change at week 52±SEM	−0.60±0.06	−0.25±0.06	−0.42±0.06	−0.28±0.06
Change at week 104±SEM	−0.74±0.07	−0.20±0.07	−0.50±0.06	−0.26±0.06
Change at week 104 (log-transformed data)	−23%	−7%	−17%	−9%
Ratio of geometric means at week 104 (log-transformed data) (95% CI)	0.83 (0.78, 0.88); <i>p</i> <0.001		0.90 (0.85, 0.96); <i>p</i> =0.001	
HDL cholesterol (mmol/l)				
Baseline±SD	1.10±0.25	1.09±0.23	1.09±0.24	1.11±0.27
Change at week 52±SEM	0.18±0.01	0.01±0.01	0.16±0.01	0.09±0.01
Change at week 104±SEM	0.25±0.01	0.08±0.01	0.23±0.01	0.16±0.01
Change at week 104 (log-transformed data)	22%	7%	21%	15%
Ratio of geometric means at week 104 (log-transformed data) (95% CI)	1.14 (1.11–1.17); <i>p</i> <0.001		1.06 (1.03–1.08); <i>p</i> <0.001	
LDL cholesterol (mmol/l)				
Baseline±SD	3.34±0.98	3.28±0.93	3.57±0.86	3.58±0.92
Change at week 52±SEM	0.27±0.04	−0.11±0.04	0.08±0.04	−0.16±0.04
Change at week 104±SEM	0.07±0.04	−0.20±0.04	−0.13±0.05	−0.37±0.05
Change at week 104 (log-transformed data)	2%	−6%	−5%	−11%
Ratio of geometric means at week 104 (log-transformed data) (95% CI)	1.08 (1.04–1.12); <i>p</i> <0.001		1.07 (1.03–1.11); <i>p</i> <0.001	
Total cholesterol: HDL cholesterol ratio				
Baseline±SD	5.36±1.46	5.33±1.52	5.45±1.47	5.38±1.53
Change at week 52±SEM	−0.54±0.05	−0.20±0.05	−0.55±0.05	−0.55±0.05
Change at week 104±SEM	−0.90±0.05	−0.53±0.05	−0.99±0.06	−0.92±0.06
Change at week 104 (log-transformed data)	17%	10%	−19%	−17%
Ratio of geometric means at week 104 (log-transformed data) (95% CI)	0.92 (0.89–0.95); <i>p</i> <0.001		0.98 (0.95–1.01); <i>p</i> =0.282	
AIP				
Baseline±SD	0.83±0.69	0.78±0.71	0.67±0.71	0.63±0.69
Change at week 52±SEM	−0.36±0.03	−0.07±0.03	−0.31±0.09	−0.17±0.09
Change at week 104±SEM	−0.46±0.03	−0.14±0.03	−0.38±0.03	−0.23±0.03
Change at week 104	−55%	−18%	−57%	−36%
Change from baseline to week 104 (adjusted ITT data) (95% CI); <i>p</i> value	−0.32 (−0.39 to −0.25); <i>p</i> <0.001		−0.16 (−0.23 to −0.08); <i>p</i> <0.001	

AIP atherogenic index of plasma, ITT intention-to-treat

Results

Despite differences in patterns in effect over time there were no statistically significant differences between groups in mean HbA_{1c} reduction from baseline to week 104. When pioglitazone and gliclazide were added to metformin, the decrease in HbA_{1c} from baseline to week 104 was 0.89% with pioglitazone add-on therapy and 0.77% with gliclazide add-on (adjusted mean difference, -0.12 ; 95% CI $-0.31, 0.07$; $p=0.200$). Reductions in mean HbA_{1c} from baseline to week 104 were 1.03% with addition of pioglitazone to sulphonylurea and 1.16% with addition of met-

formin to sulphonylurea (adjusted mean difference, 0.13 ; 95% CI $-0.06, 0.31$; $p=0.173$).

The triglyceride reductions noted with pioglitazone were maintained over time, with decreases of 16–18% from baseline at 1 year and 17–23% at 2 years. When pioglitazone was added to metformin, the change from weeks 52 to 104 was statistically significant ($p=0.0125$). Whether added to metformin or sulphonylurea, pioglitazone caused highly significantly greater reductions in triglyceride levels at weeks 52 and 104 than gliclazide added to metformin ($p<0.01$ for the between-group comparison) or metformin added to sulphonylurea (between-group comparison, $p<$

Fig. 1 Time course of change from baseline to last value (last observation carried forward) for (a) triglycerides, (b) HDL cholesterol and (c) LDL cholesterol. Closed circles pioglitazone add-on to metformin; open squares gliclazide add-on to metformin; open circles pioglitazone add-on to sulphonylurea; closed triangles metformin add-on to sulphonylurea

0.001). Pioglitazone and metformin as add-on therapies resulted in sustained reductions in triglycerides to week 104, whereas reductions from baseline when gliclazide was added to metformin had begun to return to baseline levels. This deterioration of plasma triglycerides over time in patients with type 2 diabetes treated with gliclazide has been reported previously [8].

In the pioglitazone groups, the improvement in HDL cholesterol at 1 year was maintained to week 104, with 21 and 22% augmentations vs baseline at 2 years. Increases in HDL cholesterol levels from baseline to weeks 52 and 104 were significantly greater for pioglitazone add-on therapy than for gliclazide add-on to metformin and for metformin add-on to sulphonylurea ($p < 0.001$) (Table 1; Fig. 1a). Changes in all four treatment groups were sustained over the 104 weeks (Table 1); however, the differences between treatment groups remained statistically significant ($p < 0.001$).

Small but statistically significantly greater reductions in LDL cholesterol were observed at both time points with gliclazide vs pioglitazone add-on to metformin and metformin vs pioglitazone add-on to sulphonylurea (between-group difference, $p < 0.001$). In the pioglitazone groups in both studies, the slight increases observed in mean LDL cholesterol at week 52 had returned to baseline levels.

At week 104, the reduction in the mean total cholesterol: HDL cholesterol ratio was significantly greater for pioglitazone than for gliclazide add-on to metformin (between-group difference, $p < 0.001$) and similar for pioglitazone and metformin addition to sulphonylurea (between-group difference, $p = 0.390$) (Table 1).

Small, dense LDL particles may be more atherogenic than large, more buoyant ones [3]. However, we did not measure this directly. It has been suggested that the atherogenic index of plasma (AIP) may be of potential importance as a surrogate for the presence of LDL [9]. This might reflect a decrease in macrovascular complications in patients with type 2 diabetes. In this study, the AIP decreased from baseline to week 104 in all four treatment groups. When added to either metformin or sulphonylurea therapy, pioglitazone caused significantly greater decreases in the AIP than were seen with metformin or gliclazide add-on therapies (between-group differences, $p < 0.001$). Since there appears to be an inverse correlation between AIP and LDL particle size, we believe that pioglitazone treatment may cause a favourable change in LDL cholesterol from small, dense to large, more buoyant LDL particles. Such a reduction in the number of small dense LDL particles has been reported previously with pioglitazone [10, 11].

Mean fasting levels of non-esterified fatty acids were decreased at week 104 by 0.11 mmol/l in the pioglitazone plus metformin group vs 0.04 mmol/l in the gliclazide plus metformin group (between-group difference, $p = 0.046$) and by 0.08 mmol/l in the pioglitazone plus sulphonylurea group vs 0.03 mmol/l in the metformin plus sulphonylurea group (between-group difference, $p = 0.053$).

Discussion

These analyses from two large, long-term (2-year) studies demonstrate the clinical effect on glycaemic control and lipid and lipoprotein parameters of add-on therapy with pioglitazone compared with gliclazide and metformin add-on therapies. We have shown that pioglitazone add-on to existing metformin or sulphonylurea therapy provided highly significant decreases in triglycerides and increases in HDL cholesterol that were sustained over time. Since HbA_{1c} was reduced in all the patient groups from both trials, we believe that the reduction in plasma triglycerides and the increase in HDL cholesterol observed in the pioglitazone-treated patients are related to the drug itself and not to beneficial effects on lipids due to improvement of glucose control.

Statins are recommended for the primary and secondary prevention of cardiovascular disease in patients with diabetes. They are highly effective in reducing LDL cholesterol and the risk of cardiovascular disease; however, there is a residual cardiovascular disease risk in patients on statins. There is an association between cardiovascular morbidity and mortality in patients with type 2 diabetes and the presence of high triglyceride levels and low HDL cholesterol levels. The recent guidelines from the American Diabetes Association recognise the importance of increasing HDL cholesterol levels and suggest that this should be the second priority for the treatment of dyslipidaemia in patients with type 2 diabetes [12]. In the studies reported here, long-term pioglitazone add-on therapy resulted in significantly greater increases in HDL cholesterol compared with gliclazide or metformin add-on therapies at week 104. Not only was the improvement in HDL cholesterol sustained, but there were also further improvements seen from weeks 52 to 104. The increases observed at week 104 with pioglitazone add-on therapy are consistent between studies (21 and 22%).

Although pioglitazone add-on therapies caused small increases in LDL cholesterol that were significantly different from the decreases observed with gliclazide and metformin add-on therapies at week 52, there was a decrease in LDL cholesterol in the pioglitazone groups from weeks 52 to 104 and levels returned to approximately baseline concentrations by the end of the 2-year period. The differences in LDL cholesterol levels cannot be explained by a bias due to statin treatment, which was comparable within studies.

The combination of insulin sensitisers with statins should result in potentially important complementary effects on the lipid profiles of patients with type 2 diabetes. More importantly, long-term outcome studies, for example the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), which will assess the impact of pioglitazone treatment on the incidence of macrovascular comorbidity and total mortality in over 5,000 high-risk patients with type 2 diabetes, should help to establish

whether the benefits of pioglitazone in terms of modulating the dyslipidaemia associated with type 2 diabetes will translate into reduced cardiovascular risk over the longer term [13].

Duality of interest This work was supported by Takeda Europe R&D Centre and Eli Lilly and Company, USA. BV has received honoraria from Takeda for speaking engagements.

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