Long-term glycaemic effects of pioglitazone in triple oral therapy: Results from PROactive

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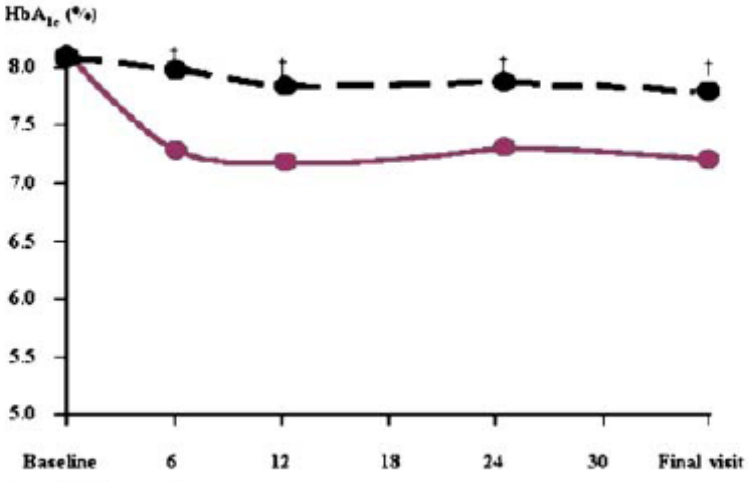
Background and Aims: Type 2 diabetes is a progressive disease and its treatment eventually requires multiple-agent therapy, including insulin. PROactive was a cardiovascular outcome study, which examined the effects of pioglitazone on patients whose type 2 diabetes had been diagnosed on average 9.5 years before study entry. Little data exists on the benefits of using triple oral therapy (metformin +sulfonylurea+thiazolidinedione) in those patients failing dual oral treatment. This subanalysis evaluates the longterm glycaemic effects of pioglitazone add-on therapy in patients with type 2 diabetes and macrovascular disease who entered on metformin plus sulfonylurea.

Materials and Methods: PROactive randomised patients to either pioglitazone or placebo, in addition to other glucose-lowering and cardiovascular medication, which was adjusted as necessary to treat to IDF target. Pioglitazone doses were force-titrated from 15 mg to 45 mg. Mean follow-up was 34.5 months. In total, 1314 patients entered the study on metformin plus sulfonylurea. Within this cohort, mean baseline HbA_{1c} values were similar between groups (pioglitazone: 8.16%; placebo: 8.14%).

Results: Significantly greater reductions in HbA_{1c} were seen with pioglitazone (j0.9%) compared with placebo (j0.4%, $P<0.0001$). The significant improvement in HbA_{1c} with pioglitazone versus placebo was shown with the following changes in associated glucose-lowering medication: more pioglitazone patients had either metformin or sulfonylurea dropped from their regimen (16%) and fewer had insulin added to their regimen (16%) than did placebo patients (8% and 31%, respectively). The metformin dose increased by 19 mg with pioglitazone versus 228 mg with placebo ($P<0.0001$). Sulfonylurea doses decreased or were unchanged in the pioglitazone group (j1.4 mg for glibenclamide versus j0.2 mg for placebo, $P=0.013$;j33 mg for gliclazide versus j23 mg for placebo, $P=0.270$; 0 mg for glimepiride versus+0.6 mg for placebo, $P=0.009$). Oedema occurred in 29% of patients in the pioglitazone group versus 17% in the placebo group ($P<0.0001$) and hypoglycaemia occurred in 27% in the pioglitazone group versus 20% in the placebo group ($P=0.0013$). There was a weight increase of 4.1 kg in the pioglitazone group and a decrease of 0.7 kg in the placebo group ($P<0.0001$).

Conclusion: Little data exist on the benefits of triple oral therapy in patients with type 2 diabetes. Adding pioglitazone to a dual oral therapy regimen (metformin+sulfonylurea), thus resulting in a triple oral regimen, resulted in a sustained improvement in glycaemic control and a reduced need for insulin, with a good overall safety profile.

Changes in glycaemic control (as measured by HbA_{1c}) over time with pioglitazone (solid lines) or placebo (dashed lines) in patients receiving metformin plus sulfonylurea



†p<0.0001 *versus* placebo