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Metformin-Based Oral Antidiabetic Therapy Proved Effective in Hyperglycaemia Associated With Pasireotide in Patients With Acromegaly

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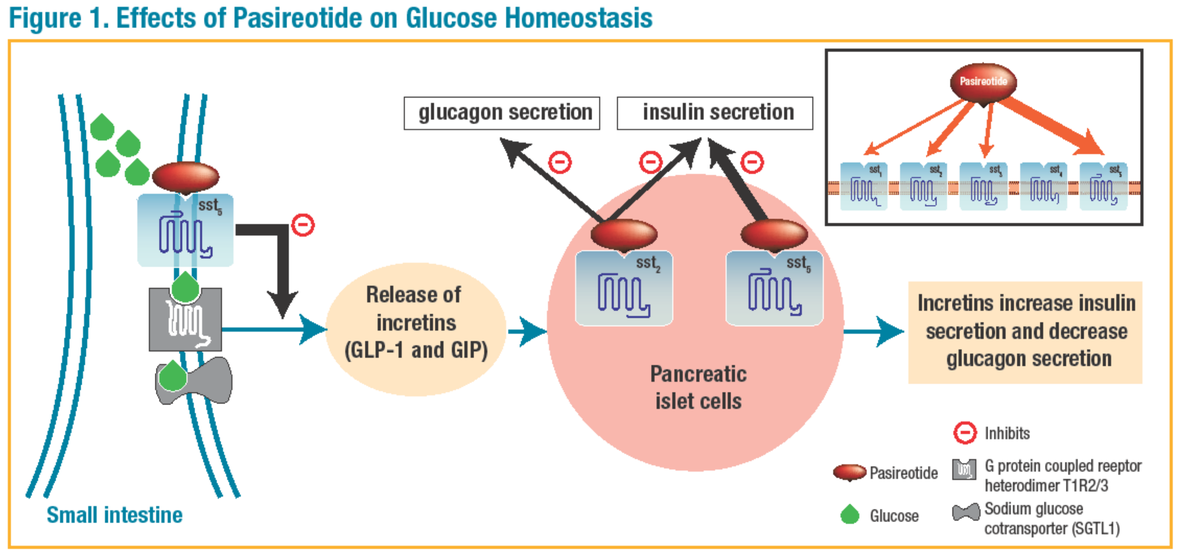
INTRODUCTION

- Pasireotide is approved for the treatment of acromegaly by both FDA and EMA.[1,2]
- In a 12-month phase III C2305 study, pasireotide LAR, a next-generation somatostatin analogue (SSA), demonstrated superior efficacy over octreotide LAR in patients with medically naïve acromegaly.[3]
- Pasireotide is a multireceptor-targeted SSA, which exerts its action by targeting sst_2 and sst_5 on growth hormone (GH)-secreting pituitary adenomas.[3,4] Differential binding affinity of pasireotide is shown in **Figure 1** (top right box).
- Somatostatin receptors also play important roles in blood glucose regulation[5] by inhibiting the secretion of glucagon (sst_2) and insulin (sst_2 and sst_5) (**Figure 1**).
- In the C2305 study, the safety profile of pasireotide LAR was similar to that of octreotide LAR, except for a higher degree and frequency of hyperglycaemia.[3] The effects of pasireotide on glucose homeostasis are consistent with the higher binding affinity of pasireotide for sst_5 than sst_2 (**Figure 1**).

Figure 1. Effects of Pasireotide on Glucose Homeostasis



GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; sst, somatostatin receptor subtype.

- In healthy volunteers, pasireotide causes a marked reduction in insulin secretion but a smaller reduction in glucagon secretion.[6]
  - Insulin sensitivity is not affected by pasireotide.[6]
- Pasireotide also inhibits secretion of the incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which induce the secretion of insulin (**Figure 1**).[6]
- Metformin increases GLP-1 levels and improves insulin sensitivity, countering the effects of pasireotide and GH/IGF-1 excess, respectively. As such metformin may represent a good treatment option in patients with acromegaly experiencing pasireotide-associated hyperglycaemia.[7]
- The present post hoc analysis of the large, phase III randomised C2305 study was carried out to better understand the effects of antidiabetic agents on pasireotide-associated hyperglycaemia during the study.

METHODS

Study Design - C2305

- Patients aged ≥ 18 years with active, medically naïve acromegaly were enrolled in the double-blind, multicentre study and were randomised to receive either pasireotide LAR 40 mg/28 days (n = 176) or octreotide LAR 20 mg/28 days (n = 182) for 12 months.
- At months 3 and 7, up-titration to pasireotide LAR 60 mg or octreotide LAR 30 mg was permitted if mean GH was ≥ 2.5 µg/L and/or insulin-like growth factor 1 (IGF-1) > upper limit of normal. Dose decreases to pasireotide LAR 20 mg or octreotide LAR 10 mg were allowed for tolerability issues.[3]

Post Hoc Analysis Population

- Each patient who initiated treatment with antidiabetic medication (ADM) in the pasireotide LAR group during the 12-month core phase was assigned to one of 3 groups (metformin alone, metformin + oral antidiabetic (OAD) or insulin ± OAD) based on the ADM received.
- Patients who received prior antidiabetic treatment were excluded, to avoid bias from previous antidiabetic treatment.

Assessment of Fasting Plasma Glucose and Glycosylated Haemoglobin Levels

- Blood samples for fasting plasma glucose (FPG) and glycosylated haemoglobin (HbA_{1c}) assessments were taken after an overnight fast, prior to the administration of study drug, at baseline, and monthly thereafter.

RESULTS

Antidiabetic Medications

- Fifty-seven patients in the pasireotide LAR group initiated antidiabetic medication at any time during the 12-month study.
- There were three antidiabetic treatment groups (each containing ≥ 10 patients) defined as shown in **Table 1**; of the 57 patients who initiated ADM, 4 (sulfonylurea, n = 3; other, n = 1) were excluded from the analysis, as they do not belong to any of the antidiabetic treatment groups defined.
- Metformin was the most commonly initiated antidiabetic agent during the 12-month study.

Table 1. Number of Pasireotide LAR Patients in Each Antidiabetic Treatment Group

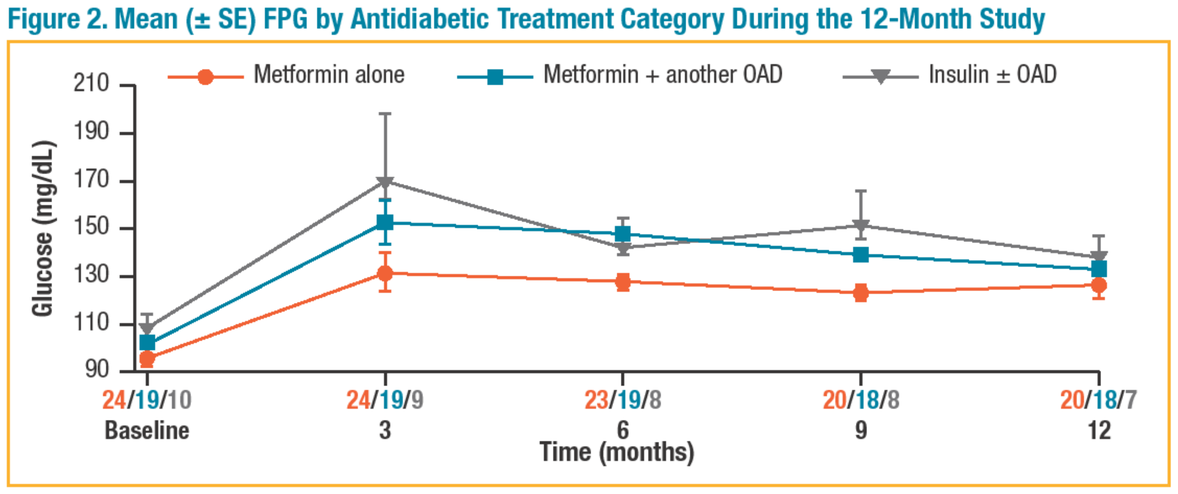
Treatment Group	Definition Based on Antidiabetic Medication Received	Number of Patients
Metformin alone	≥ 1 dose of metformin with no other OAD or insulin	24
Metformin + another OAD	≥ 1 dose of metformin and ≥ 1 dose of another OAD, either alone or in combination	19
Insulin ± OAD	≥ 1 dose of insulin with or without an OAD	10

OAD, oral antidiabetic drugs.

FPG Levels

- At baseline, mean ± SD FPG was lowest in the metformin alone group (94.7 ± 13.0 mg/dL) and highest in the insulin ± OAD group (106.7 ± 19.7 mg/dL); mean FPG was 99.7 ± 12.8 mg/dL in the metformin + another OAD group.
- After initiation of pasireotide LAR, mean FPG increased up to month 3 but decreased and stabilised thereafter in all groups (**Figure 2**).
- At month 3, the difference in mean FPG values between the 3 antidiabetic treatment groups was most apparent (**Figure 2**).
  - Mean ± SD FPG values at month 3 for metformin alone, metformin + another OAD, insulin ± OAD were 131.0 ± 37.18 mg/dL, 153.2 ± 41.60 mg/dL, and 170.0 ± 88.61 mg/dL, respectively.

Figure 2. Mean (± SE) FPG by Antidiabetic Treatment Category During the 12-Month Study

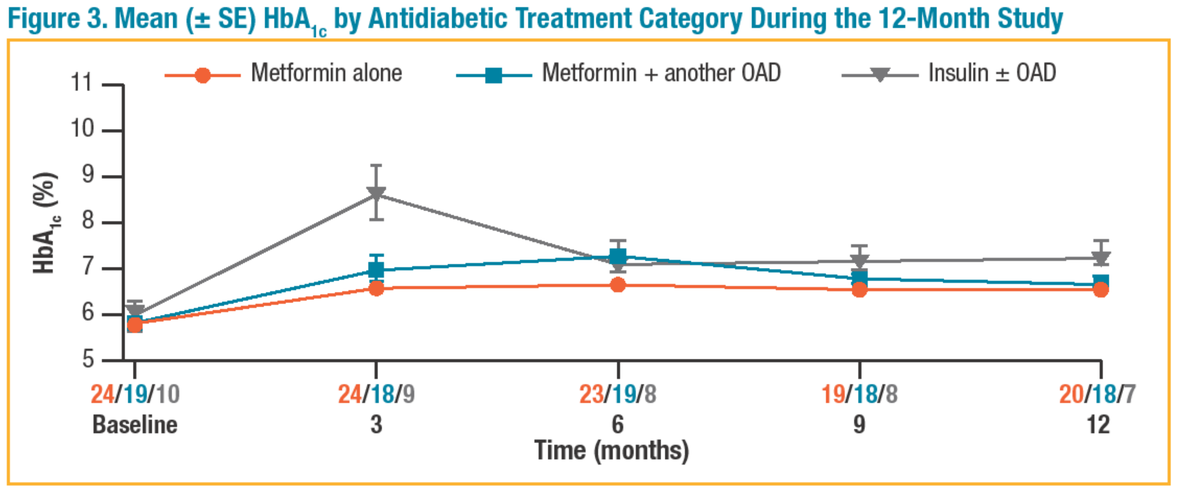


FPG, fasting plasma glucose; OAD, oral antidiabetic drugs; SE, standard error.

HbA_{1c} Levels

- Baseline mean ± SD HbA_{1c} was similar between the metformin alone (5.8 ± 0.4%), metformin + another OAD (5.8 ± 0.4%), and insulin ± OAD (6.1 ± 0.5%) groups.
- HbA_{1c} increased after initiation of pasireotide LAR, with the largest difference in mean values between treatment groups observed at month 3; thereafter, HbA_{1c} values stabilised until month 12 (**Figure 3**).
- Mean HbA_{1c} levels at month 12 were 6.6%, 6.7%, and 7.2% in the metformin alone, metformin + another OAD, and insulin ± OAD groups, respectively.

Figure 3. Mean (± SE) HbA_{1c} by Antidiabetic Treatment Category During the 12-Month Study



HbA_{1c}, glycosylated haemoglobin; OAD, oral antidiabetic drugs; SE, standard error.

CONCLUSIONS

- **In patients treated with metformin monotherapy or in combination with OADs, mean HbA_{1c} levels at month 12 met the recommended American Diabetes Association and European Association for the Study of Diabetes goal of < 7%.**
  - **Therefore, in this subset of patients, metformin-based OAD therapy was effective in controlling hyperglycaemia associated with pasireotide.**
- **Metformin may represent a good treatment option in patients with acromegaly experiencing pasireotide-associated hyperglycaemia.**
  - **Metformin increases GLP-1 levels and improves insulin sensitivity, countering the effects of pasireotide and GH/IGF-1 excess, respectively.[7]**

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Pituitary clinical

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