Sitagliptin in Type 2 Diabetes Mellitus: Efficacy After Five Years of Therapy

BACKGROUND:
- Type 2 diabetes is a progressive disease, often requiring patients to be on multiple therapies to achieve and maintain adequate glycemic control. Several combinations are effective in reducing HbA1c however, the effects on long-term results are different for the various treatments.

OBJECTIVE:
- Assess if the addition of a DPP-4 inhibitor, Sitagliptin, is a good alternative as an add-on to monotherapy therapy to maintain adequate glycemic control after five years of treatment.

METHODS:
- **Design**: Observational, prospective (concurrent) cohort design, non-randomized, unblinded.
- **Duration**: 60 months.
- **Inclusion criteria**: Type 2 diabetics over 18 years old of either sex, according to the ESC (European Society of Cardiology) and EASD (European Association for the Study of Diabetes) Guidelines Criteria; Poor glycemic control on current therapy, expressed as A1c > 8.0%; Overweight expressed as BMI > 25 but BMI < 30 kg/m².
- **Exclusion criteria**: History of ketoacidosis or unstable/rapidly progressive diabetic retinopathy, nephropathy, or neuropathy; Impaired hepatic function (plasma aminotransferase and/or GTT level > 3x the ULN for age and sex); Impaired renal function (SCR > ULN for age and sex); Severe anemia; Serious CVD (NYHA class I-IV CHF or history of MI/stroke); Cerebrovascular conditions within 6 mo. prior to study enrollment; Previous history of cancer or pathological fractures.
- **Primary outcome measure**: positive effects of study medications were based on glycemic control which was evaluated by assessing hemoglobin A1c, fasting plasma glucose, post-prandial glucose, fasting plasma insulin and body mass index at baseline and every 6 months.
- **Secondary outcome measures**: included Tolerability assessments & they focused on: Hypoglycemia, Developing bladder cancer, Developing femoral fracture, Developing pancreatitis or Developing pancreatic cancer.

- **Sitagliptin Group (Cases)**: 624 patients not well controlled with current therapy including:
  - Taking Metformin = 216 patients
  - Taking Sulfonylureas = 206 patients
  - Taking Pioglitazone = 202 patients

- **Comparison Group (Control)**: 620 patients matched for age, sex and diabetes duration and were treated with the following one of the following combinations:
  - Metformin + Sulfonylureas
  - Metformin + Pioglitazone
  - Sulfonylureas + Pioglitazone

- **Drug Dose**: Sitagliptin 100 mg/day added to the uncontrolled monotherapy regimen in the Cases.

Data handling method was not mentioned in the study.

RESULTS:
- Authors did not report how many patients completed the study.
- **Primary outcome measure**:
  - **Results in Sitagliptin + Metformin group when compared to Sulfonylurea + Metformin**:
    - A1c: Higher A1c after 6 mo.; No significant difference from mo. 7-41; Lower after 42 mo. (P < 0.05); Lower from 54 mo. until end of study (P < 0.01)
    - FPG: Higher at 6 and 18 mo. (P < 0.05)
    - FPG & PPG: Similar reduction compared to Sulfonylurea + Metformin
    - FPI: Lower from 42 mo. until end of study (P < 0.05)
    - BMI: Lower weight from 24 mo. until end of study (P < 0.05)
  - **Results in Sitagliptin + Pioglitazone group when compared to Metformin + Pioglitazone**:
    - A1c: Lower after 6 mo. and from 42 mo. until end of study (P < 0.05)
    - FPG: Lower at 12 mo. and from 36 mo. until end of study (P < 0.05)
    - PPG: Lower after 12 mo. and from 48 mo. until end of study (P < 0.05)
FPI & BMI: No significant difference between groups

- **Results in Sitagliptin + Sulfonylurea group when compared to Pioglitazone + Sulfonylurea:**
  - A1c: Lower from 36 mo. until end of study (P < 0.05)
  - FPG: Lower after 12 and 18 mo. and lower from 42 mo. until end of study
  - PPG: Lower at 24 mo. (P < 0.05) and until end of study (P < 0.01)
  - FPI: No significant difference between groups
  - BMI: Lower weight after 18 mo. and until end of study (P < 0.05)

- Researchers noted a significant increase in BW from 42 mo. until the end of the study in the Pioglitazone + Sulfonylurea group (P < 0.05)

- **Secondary outcome measures:**
  - No major incidence of pancreatitis or pancreatic cancer observed with Sitagliptin; Major incidences of N/V/D and abdominal pain with Metformin (P < 0.05); Higher incidence of hypoglycemia with Sulfonylureas compared to Sitagliptin (P < 0.05)

- **Author’s conclusion:** Changes in HbA1c suggest better effects on glycemic control and BMI over the long-term with Sitagliptin compared to other treatments. Other parameters evaluated in the study, including FPG, PPG and FPI levels, confirmed the trends observed for the value of HbA1c.

**STRENGTHS:**
- Design: Appropriate use of Observational design for a 5 year study and to examine if certain exposures might affect a later outcome. Prospective Cohort design used is better than the retrospective cohort design because it’s less subject to bias and inaccuracies
- HbA1c is the gold standard diagnostic tool for diabetes assessment and management and HPLC serves as the reference standard for which other assays are compared

**LIMITATIONS:**
- Doses were not mentioned for any medications, with exception to Sitagliptin
- Researchers did not state the number of patients in each control group, may have been skewed
- Unblinded study which increases risk of bias being introduced
- Possibility of selection bias because patients were not randomized
- Compliance was not assessed, thus compliance bias is a possibility
- CI’s not mentioned
- Power and sample size to reach the power was not mentioned; unknown Type II error risk
- Exclusion Criteria: should have included drugs that interact with Sitagliptin, patients intolerant or allergic to Sitagliptin, and assessment of CrCl which is necessary for dosing Sitagliptin properly
- Exercise and diet were encouraged but not assessed or accounted for in results

**CONCLUSION:**
- Although Sitagliptin looked efficacious after 5 years when compared to other treatments, the weaknesses would make me apprehensive to use it in everyone. When compared to Sulfonylureas as a class, the long-term safety in regards to the beta cell exhaustion makes Sitagliptin more reasonable although I can’t directly compare other adverse effects between the two drugs.
  - When added to Metformin, the results on glycemic control were attractive in this study and Janumet is a new Sitagliptin + Metformin combination available that is almost the same price as Sitagliptin alone. With this in mind, I think it’s a reasonable option
  - Future research is needed to evaluate effects of individual sulfonylureas instead of looking at them as a class and Sitagliptin’s long-term effects on diabetes complications such as neuropathy, nephropathy and retinopathy.


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