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/m^2
- **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**:
    - <u>Results in Sitagliptin + Metformin group when compared to Sulfonylurea + Metformin</u>:
        - 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 ($P < 0.05$)
    - <u>Results in Sitagliptin + Pioglitazone group when compared to Metformin + Pioglitazone</u>:
        - 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.

Reference: Derosa G, D'Angelo A, Maffioli P. Sitagliptin in type 2 diabetes mellitus: Efficacy after five years of therapy. Pharmacol Res. 2015;100:127-34.

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