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A1c Reduction and Weight Loss in a Veteran Population Using GLP-1-RAs

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A1c Reduction and Weight Loss in a Veteran Population Using GLP-1-RAs

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Abstract

Background: Diabetes mellitus is a metabolic disorder defined by high blood glucose. Glucagon-like peptide-1 receptor agonists (GLP-1-RAs) are a newer class of medications that offer potential 2 to 3 kg weight loss and a 1% to 1.5% decrease in A1c. At the Indianapolis Veterans Affairs Medical Center (VAMC), GLP-1-RAs are non-formulary.

Objectives: Primary outcomes included mean change in weight, body mass index (BMI) and A1c in VAMC patients. Secondary outcomes included the comparison to published values, analysis of insulin needs, and analysis of GLP-1-RA discontinuation reasons.

Methods: Indianapolis VAMC patients ages 18-80 with type 2 diabetes who started a GLP-1-RA from January 1, 2010 to July 1, 2016 were identified. The following data points were gathered at monthly intervals before spreading out to biannual: specific GLP-1-RA and dose; weight; BMI; A1c; other diabetes medications; insulin requirements; and any reason for discontinuation. This report is an analysis of the baseline, 24 week, and 48 week data.

Results: With a mean age of 62.2 years and a 90.2% male population, the cohort decreased their weight from baseline by 2.5 kg at 24 weeks of use and 3.6 kg at 48 weeks. A1c decreased by 1.3% in the first 24 weeks and was maintained at 48 weeks. Insulin use decreased during the study. Seven percent of patients discontinued GLP-1-RAs due to GI intolerance.

Conclusion: GLP-1-RAs have a similar effect on weight and A1c in the veteran population compared to previous study populations. Based on this and further research, GLP-1-RA use may be expanded in the future.

Key Points - Background

- In the general population, insulin can lead to 2 to 3 kg of weight gain for every 1% decrease in A1c, while glucagon-like peptide-1 receptor agonists (GLP-1-RAs) have been shown to decrease weight 2 to 3 kg and A1c 1% to 1.5%.
- Since GLP-1-RAs affect gastrointestinal (GI) motility, a common reason for GLP-1-RA discontinuation is GI intolerance.

Key Points – Findings

- Veterans receiving care at the Indianapolis VA Medical Center have seen a mean decrease in A1c of 1.3% at 24 weeks of use and this decrease is maintained at 48 weeks. Mean weight loss from baseline equated to 2.5 kg and 3.6 kg at 24 and 48 weeks, respectively.
- The decrease in weight and A1c is not statistically different from reported literature values. Therefore, the veteran population likely responds similarly to the patient populations in other studies.
- The need for insulin decreased over time and correlated in a statistically significant manner to the decrease in body mass index.

Background

Diabetes mellitus is a metabolic disorder that results in high blood glucose levels, also known as hyperglycemia.[1,2] Hemoglobin A1c (A1c) is a biomarker that can provide an overview of a patient's blood glucose control over the past three months.[2] An individual without diabetes should have an A1c of less than 5.7%, while a typical goal for those with diabetes is between 6.5% to 7% if they are relatively healthy otherwise.[1,2] Risk factors for type 2 diabetes include increasing age, male gender, history of gestational diabetes, family history, cardiovascular disease, hypertension, A1c between 5.6% and 6.5%, sedentary lifestyle, and overweight (body mass index [BMI] 25-29.9 kg/m^2) or obese (BMI $\geq$ 30 kg/m^2) status.[1,2] For patients who are overweight or obese, physical activity for 150 minutes per week and sustained weight loss of 7% or greater can help prevent the development of diabetes and help improve glycemic control, insulin sensitivity and cardiovascular risk factors.[3] Greater than 75% of patients that receive care within the Veteran Affairs (VA) healthcare system are either overweight or obese,[4] and 25% have diabetes.[5] Lifestyle management, which includes physical activity, nutrition therapy, and diabetes self-management education, is the first step in the treatment of diabetes mellitus, and it should be continued throughout pharmacotherapy.[1,2]

Drug therapy recommendations for the treatment of diabetes vary between organizations. While there are several classes of oral hypoglycemic agents, glucagon-like peptide-1 receptor agonists (GLP-1-RAs) are a newer class of injection-based medications that offer potential weight loss along with improved blood glucose control. On average, GLP-1-RAs can lead to A1c reductions of 1% to 1.5% within 26 to 52 weeks.[2,6] A meta-analysis of 25 randomized controlled trials involving GLP-1-RAs

showed an average weight reduction of 3.2 kg in those without diabetes and an average of 2.8 kg in those with diabetes.[7] The decrease in weight with GLP-1-RA use is a positive difference from some other diabetes medications, as sulfonylureas, thiazolidinediones, and insulin often promote weight gain while they improve blood glucose control.[8] For every 1% decrease in A1c, patients using insulin gain 2 to 3 kg on average.[9] Five GLP-1-RAs are approved for use in the United States: albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide.[10] The 2017 American Diabetes Association guidelines place GLP-1-RAs as a second-line option after metformin for initial monotherapy treatment.[2] In contrast, the 2015 American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines state GLP-1-RAs are appropriate first-line monotherapy agents.[1] Metformin, SGLT-2 inhibitors, DPP-4 inhibitors, and alpha glucosidase inhibitors are also first-line agents in these guidelines.[1] For patients with symptomatic hyperglycemia or for those who do not reach treatment targets on other agents, both practice guidelines recommend starting insulin and/or GLP-1-RAs.[1,2]

There are three main potential barriers to adherence with GLP-1-RAs: side effects, cost, and ease of administration. Due to changes in gastrointestinal (GI) motility, a common side effect is GI intolerance.[8] Over time, GI side effects such as nausea, vomiting, and diarrhea may diminish, but some patients discontinue GLP-1-RA therapy due these GI symptoms.[8] While nausea may lead to decrease in appetite and choleric intake, the weight loss seen with GLP-1-RAs is not caused by nausea alone.[11] Nonetheless, the nausea experienced during GLP-1-RA treatment remains a valid concern due to a large incidence rate. In one particular study, 42.6% of patients using GLP-1-RAs reported nausea and 9.6% reported vomiting.[12] Comparatively, patients using

insulin reported rates of 3.1% of nausea and vomiting.[12] GI side effects of GLP-1-RAs led to 7% of the patients withdrawing from this particular study.[12] One potential solution to help decrease GI adverse effects is to use lower doses of GLP-1-RAs and basal insulin together, and studies have shown benefit and success with physically combining the injections together (insulin degludec and liraglutide, as well as insulin glargine and lixisenatide).[8]

In part due to the high cost of GLP-1-RAs, these medications are not on formulary at the Richard L. Roudebush VA Medical Center (VAMC) in Indianapolis, IN, but can be attained through a lengthy authorization process. Two initial Medication Use Evaluations suggested that Roudebush VAMC patients have seen a decrease in weight, A1c, and, Total Daily Dose (TDD) of insulin over the course of six months. The purpose of this study is to investigate the effect of GLP-1-RAs over a longer study period. Results from this study will help guide therapy at the Indianapolis VAMC in the future.

Research Method

This research study was a retrospective cohort electronic medical record review conducted at the Richard L. Roudebush VAMC in Indianapolis, Indiana. It was approved by the Butler University Institutional Review Board (IRB) and the Indiana University IRB as a quality improvement project. The Computerized Patient Record System and Decentralized Hospital Computer Program generated a list of 90 patients who have been prescribed a GLP-1-RA at any point from January 1, 2010 to July 1, 2016. Patients without at least two weights and two A1c readings were not analyzed. Patients who discontinued a GLP-1-RA within the first month were not included for intense analysis but were included in the analysis of GLP-1-RA discontinuation reasons.

Baseline was defined as the patient's most recent measurements and medication doses immediately before the initiation of a GLP-1-RA, with weight and A1c data included if measured within the three months prior to GLP-1-RA use. From the GLP-1-RA initiation date, an Excel® spreadsheet was programmed to give projected dates at 0, 1, 2, 3, 6, 9, 12, 16, 20, 24, 30, 36, 42, and 48 months. One month was defined as four weeks. Information was gathered for each time period if it was taken within the halfway points between the previous and following projected dates. This report is a focused review of the baseline, 6 month, and 12 month data to align with 26 week and 52 week trial data.

The following information was gathered: specific GLP-1-RA and dose, patient weight, BMI, A1c, other diabetes medications, enrollment in the comprehensive VA MOVE program, and long-acting and short-acting insulin requirements if applicable. Any diabetes medication adjustments made during the addition of the GLP-1-RA were noted. The presence or absence of sliding scale insulin was documented. The reason for GLP-1-RA discontinuation was also recorded if indicated in the electronic medical record. A cost analysis was also performed using VAMC purchasing costs.

Primary Outcomes:

The primary outcome of this focused study within the larger data gathering efforts included the mean change in weight, BMI, and A1c in VAMC patients at 24 weeks (6 months) and 48 weeks (12 months) of GLP-1-RA use. Patients were analyzed as the entire cohort as well as two separate cohorts based on insulin use.

Secondary Outcomes:

Secondary outcomes included the comparison of mean change in weight and A1c to published values, analysis of trends in insulin requirements, and analysis of trends in GLP-1-RA discontinuation.

Inclusion and Exclusion Criteria:

Patients 18 to 80 years old with a diagnosis of type 2 diabetes mellitus were included if they started the GLP-1-RA at the Indianapolis VAMC. Those on two separate GLP-1-RAs for two distinct time periods were included, while those who made a direct switch were only included for the first GLP-1-RA to prevent a potentially confounding effect. Patients were excluded from the study if they were diagnosed with type 1 diabetes, did not follow up after baseline, and/or did not have at least one baseline and one follow up A1c and weight measurement.

Data Analysis

Each patient was assigned a unique random study number. Daily doses of short-acting and long-acting insulin were added together to calculate the TDD. Cohort means were determined for each time period. Individual change in weight, BMI, and A1c from baseline were assessed before being averaged together for a cohort mean. This was done to minimize the pull of outliers and to better capture the individual patient response. All final statistical analyses were conducted using Microsoft Excel 2016 and Statistical Package for Social Sciences (SPSS) version 24 software**.** One sample t-tests were performed to compare changes in A1c and weight to published values of 2 to 3 kg weight loss and 1% to 1.5% reduction in A1c. Spearman's rho correlation coefficient was calculated for BMI and TDD.

Results

Demographics: The electronic health records contained 90 patients who were prescribed a GLP-1-RA during the study period. Of this group, 19 patients were excluded due to insufficient A1c and weight data and 10 patients discontinued GLP-1-RA use within 1 month. The final analysis included 61 patients who were tracked until GLP-1-RA discontinuation or until October 31, 2016, whichever came first. At baseline, the cohort of 61 patients had a mean age of 62.2 years (range 39 to 78 years) and was a 90.2% male population. Exenatide was given to 6.6% of patients and once-daily liraglutide was given to 93.4%. Of the four patients that used exenatide, one used the once-weekly formulation (Bydureon-AstraZeneca) while three used the once-daily formulation (Byetta-AstraZeneca). To help manage side effects upon initiation, 51% of GLP-1-RA doses were titrated up within the first 14 days. The percentage of male patients and liraglutide use remained steady through the study.

Change in Diabetes Medications: Before starting GLP-1-RAs in patients using insulin, the total daily dose (TDD) of insulin was preemptively decreased 12.4 units to a baseline measurement of 168.9 units. The mean TDD of insulin decreased over the study to 166.5 units at 24 weeks and 161.4 units at 48 weeks. As a cohort, the mean number of oral hypoglycemic agents used per person decreased from 1.34 agents at baseline to 1.12 agents at 48 weeks. Metformin use decreased minimally from 77.0% to 75.8%. Sulfonylurea and DPP-4 inhibitors use decreased by a larger degree from 21.3% to 15.2% and from 26.2% to 12.1%, respectively. Insulin use decreased from 78.7% to 71.9%, with one patient discontinuing insulin use completely by the 48-week mark.

Change in Weight, BMI, and A1c: In the first 24 weeks of use, 58 patients decreased their weight on average by 2.5 kg, BMI by 0.90 kg/m^2, and A1c by 1.3%. At

48 weeks of use, 33 patients decreased their weight on average by 3.6 kg, BMI by 1.30 kg/m^2, and A1c by 1.3% from baseline. The GLP-1-RA dose was titrated up before or during the 24 week and 48 week appointments for 59% and 9.4% of patients, respectively. As a trend, the BMI and A1c of patients using insulin decreased through both 24 weeks and 48 weeks, while patients not using insulin saw both an increase in BMI and A1c from 24 weeks to 48 weeks (Table 1). This increase in BMI and A1c seems to be based on the small number of patients in the non-insulin cohort (n=8), as they previously responded better than the entire study cohort to GLP-1-RA treatment (Table 2). The non-insulin cohort had lower BMI and A1c values at each of the three time periods, except the mean BMI was 0.1 kg/m^2 greater at 24 weeks.

Statistical Analysis: The one sample t-tests showed that this study's results were not statistically different from published values. Spearman's rho correlation coefficient was calculated at 1.000 for the relationship between BMI and TDD of insulin.

Discontinuation Analysis: Of the 71 patients who met criteria for discontinuation analysis, GLP-1-RAs were discontinued most often due to GI intolerance (7%), followed by combined prescriber and patient decisions (4%) and by miscellaneous factors (4%). All five of the patients who discontinued GLP-1-RAs due to GI intolerance stopped within the first month of use. The majority (72%) of patients continued GLP-1-RA use through the study. Miscellaneous factors include one incidence of pancreatitis, one patient refusal due to cancer in study animals, and one patient's dislike of needles. Other reasons for discontinuation included provider change, bariatric surgery, moving locations, and death. Zero patients discontinued GLP-1-RAs due to cost.

Discussion

GLP-1-RAs are not on the Indianapolis VAMC formulary in part due to cost. At the time of this study, liraglutide was the preferred agent. Cost data from March 28, 2017, indicated that liraglutide cost the VAMC $409.02 for a box of three pens, which is a 30-day supply at the maximum 1.8 mg daily dose. Comparatively, long-acting insulin glargine cost $47.45 for a box of five pens and short-acting insulin aspart cost $27.25 for a box of five pens. Even when these costs are doubled to account for Indianapolis VAMC patients using about two boxes a month of each type of insulin (16 to 17 days per box), insulin is still more cost effective to acquire over GLP-1-RAs. While a cost utility analysis was not performed for this study, patients did see A1c and weight reductions similar to published values. This was independent of insulin use status. Therefore, despite a higher acquisition cost, GLP-1-RAs may be a cost-effective option when accounting for other healthcare costs related to diabetes.[13]

Strengths of this study include real-life use of GLP-1-RAs within the spectrum of VA healthcare in Indiana. Future directions for GLP-1-RA research at the Indianapolis VAMC include the further investigation of factors that may predict success or failure with GLP-1-RAs, any differences seen with once-daily or once-weekly GLP-1-RAs, any changes in response for GLP-1-RA use beyond one year, and a long-term cost-utility analysis.

Limitations

Limitations of this study include less than one year of quality data, as the use of GLP-1-RAs at the Indianapolis VAMC has only recently increased. The starting population of patients not already on insulin was also small (n=13; 21.3%) due to the VA

formulary status of insulin. This factor, along with no comparator group to insulin-only patients without GLP-1-RAs, limits the ability to determine the direct effect of GLP-1-RAs. Because this investigation took place within a larger data collection effort, some weight and A1c data was missing at the 24 week or 48 week marks.

Conclusions

GLP-1-RAs can lower A1c, weight, and BMI in the veteran population regardless of insulin use status. In this small scope study, veterans experienced a similar A1c and weight decrease compared to published data and there was a decreased insulin need and BMI over the course of GLP-1-RA use.

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Table 1: Change in Weight and Hemoglobin A1c
Cohort Means are averages of all available weights and A1c. Mean Individual Differences are averages of individual response compared to baseline. Weight is listed in kilograms. BMI = Body Mass Index (kg/m^2). A1c = hemoglobin A1c (%). SD = Standard Deviation. EC = Entire Cohort. IP = Insulin Patients. NP = Non-insulin Patients.

	Cohort Mean [SD]	Mean Individual Differences [SD]	Ranges of Individual Change
Weight			
Baseline			
EC	126.7 [23.1]	-	-
IP	127.0 [22.2]	-	-
NP	125.2 [26.4]	-	-
24 weeks			
EC	124.2 [23.8]	(-) 2.5 [5.2]	(-) 15.3 to (+) 10.3
IP	124.1 [23.5]	(-) 2.0 [5.0]	(-) 14.9 to (+) 10.3
NP	125.0 [24.6]	(-) 4.8 [5.5]	(-) 15.3 to (+) 4.0
48 weeks			
EC	127.5 [23.0]	(-) 3.6 [5.2]	(-) 14.2 to (+) 3.9
IP	125.4 [21.8]	(-) 3.0 [5.0]	(-) 12.8 to (+) 3.9
NP	133.8 [25.1]	(-) 4.9 [5.7]	(-) 14.2 to (+) 1.7
BMI			
Baseline			
EC	40.5 [7.7]	-	-

IP	41.0 [7.5]	-	-
NP	38.2 [7.8]	-	-
24 weeks			
EC	39.5 [7.4]	(-) 0.7 [1.7]	(-) 5.1 to (+) 4.1
IP	39.9 [7.4]	(-) 0.7 [1.7]	(-) 5.1 to (+) 4.1
NP	38.3 [7.1]	(-) 0.9 [1.9]	(-) 3.6 to (+) 3.7
48 weeks			
EC	39.2 [6.5]	(-) 1.3 [1.6]	(-) 4.7 to (+) 1.1
IP	38.6 [6.2]	(-) 1.2 [1.6]	(-) 4.7 to (+) 1.1
NP	40.8 [7.0]	(-) 1.6 [1.7]	(-) 4.0 to (+) 0.5
A1c			
Baseline			
EC	9.1 [1.4]	-	-
IP	9.1 [1.3]	-	-
NP	8.9 [1.8]	-	-
24 weeks			
EC	7.7 [1.2]	(-) 1.3 [1.3]	(-) 6.7 to (+) 0.7
IP	7.9 [1.1]	(-) 1.3 [1.4]	(-) 6.7 to (+) 0.7
NP	6.5 [0.6]	(-) 1.5 [1.1]	(-) 3.6 to (-) 0.1
48 weeks			
EC	7.6 [1.0]	(-) 1.3 [1.2]	(-) 3.6 to (+) 2.1
IP	7.8 [1.1]	(-) 1.2 [1.2]	(-) 2.9 to (+) 2.1
NP	7.1 [0.6]	(-) 1.7 [1.2]	(-) 3.6 to (-) 0.3

Table 2: Sub-analysis of remaining patients not using insulin at 48 weeks who resulted in higher group mean A1c and BMI at 48 weeks compared to the entire cohort.

The 8 of the 13 original non-insulin patients who remained at 48 weeks had better A1c and BMI values in three of the four preceding data points. The fourth value, BMI at 24 weeks, is a difference of 0.1 kg/m^2. This comparison suggests that increase in A1c and BMI may be due a small number of non-insulin patients rather than a more "unhealthy" cohort remaining.

* signifies values from the eight remaining patients at 48 weeks not on insulin.

	A1c* **(# of patients)**	**Cohort A1c (# of patients)**	**BMI* (# of patients)**	**Cohort BMI (# of patients)**
Baseline	8.4 (8)	9.1 (61)	40.1 (8)	40.5 (61)
24 weeks	6.3 (4)	7.7 (38)	39.7 (7)	39.6 (41)
48 weeks	7.1 (4)	7.6 (19)	40.8 (6)	39.2 (24)