REVIEW ARTICLE

Albiglutide, a Once-Weekly GLP-1RA, for the Treatment of Type 2 Diabetes

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Abstract

Choosing an agent for initial or add-on therapy in type 2 diabetes can be overwhelming for clinicians due to the numerous agents available. Patient specific characteristics, such as the presence of obesity or renal complications, further complicate treatment choices. In clinical studies, albiglutide has been compared to placebo, oral diabetes medications, as well as other injectable agents. The most common adverse effects associated with albiglutide are gastrointestinal in nature, an adverse effect which often subsides with continued use. Serious adverse effects, as with all GLP-1RAs, warrant cautious use of albiglutide in certain patient populations. In addition to its proven safety and efficacy profile, albiglutide may afford patients the added benefits of potential weight loss and improved adherence.

Keywords: albiglutide, diabetes, GLP-1RA, treatment

1. Introduction

More than 30 million Americans have diabetes, with 1.5 million new diagnoses occurring annually.[1,2] In 2012, it was estimated that the total healthcare cost for those with diabetes in the United States was $245 billion.[1] Type 2 diabetes (T2DM) is the most prevalent form of diabetes, accounting for 90-95% of cases. Although there are many causes of T2DM, obesity and lack of physical activity significantly increase one's risk of developing the disease.[2]

Pharmacological treatment recommendations in patients with T2DM differ between the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE). The ADA recommends initial treatment with metformin; however, the AACE/ACE recommends initial monotherapy with any of the following medication classes: metformin, glucagon-like peptide-1 receptor agonists (GLP-1RAs), dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium-glucose cotransporter 2 inhibitors (SGLT-2i), sulfonylureas/glinides (SU/GLN), thiazolidinediones (TZD), or alpha-glucosidase inhibitors (AGI).[3,4] Drugs which affect the incretin system, such as the GLP-1RAs, are gaining favor in the treatment algorithm for T2DM due to their ability to improve

glycemic control while causing weight loss. The purpose of this article is to review the GLP-1RA, albiglutide, including clinical evidence regarding its use in combination with other agents in treating T2DM.

2. Albiglutide Summary

Albiglutide works as an agonist of the GLP-1 receptor. GLP-1RAs suppress glucagon release and mimic the glucoregulatory effects of GLP-1. This leads to enhanced glucose-dependent insulin secretion, with resultant weight loss, decreased hypoglycemic events, and improvements in fasting and postprandial glucose (PPG) levels.[3,5,6] Albiglutide is indicated as an adjunct to diet and exercise in the management of T2DM.[6] Albiglutide may be used as monotherapy or in combination with metformin, SUs, TZDs, or basal insulin.[7]

Albiglutide is available as a weekly 30 mg or 50 mg single-dose pen for subcutaneous injection. Patients should be initiated on 30 mg, and the dose may be titrated to 50 mg if glycemic response is inadequate. Prior to use, the medication must be reconstituted. Before administration, one must wait 15 to 30 minutes for the 30 mg pen and 50 mg pen, respectively.[6] The medication must be administered within eight hours of reconstitution. As this is a once weekly medication, it should be given on the same day every week and can be given without regards to meals. If a dose is missed, it should be taken as soon as possible. If it has been more than three days, patients should skip that dose, and resume with their next scheduled weekly dose.[6]

There is no dosage adjustment required in patients with renal or hepatic impairment. However, caution should be used when initiating or adjusting albiglutide doses in patients with renal impairment as there have been post marketing reports of acute renal failure or worsening of chronic renal failure.[6] Albiglutide, like other GLP-1RAs, is contraindicated in patients with a personal or family history of medullary thyroid carcinoma, in patients with multiple endocrine neoplasia syndrome type 2, or anyone with a prior serious hypersensitivity reaction to albiglutide.[6] Patients at risk for thyroid c-cell tumors and acute pancreatitis should use albiglutide with caution. Albiglutide should only be prescribed in patients where the benefits of therapy outweigh the potential risks.[6] Other limitations include the lack of studies in patients with pancreatitis, severe gastrointestinal (GI) disease such as gastroparesis, or those on prandial insulins. In addition, albiglutide is not indicated for the treatment of type 1 diabetes or diabetic ketoacidosis.

When used in conjunction with SUs or insulin, the risk of hypoglycemia may be increased; therefore, patients may require a dose adjustment when albiglutide is initiated. No other drug interactions were identified during clinical trials; however, due to its effect on gastric emptying, there is the potential impact on absorption of oral medications.[6]

3. Significant Albiglutide Trials

The safety and efficacy of albiglutide has been examined in eight randomized, multicenter studies, Harmony 1 through 8.[8-16] Patients enrolled in all studies were over 18 years of age, with an average baseline hemoglobin A1c (A1c) from 8.1 to 8.5%, and a duration of T2DM of 4 to 9 years. The primary endpoint was change in baseline A1c (See Table 1). Other glycemic parameters were assessed in addition to safety endpoints. The trials are discussed in more detail below.

Table 1: Summary of Harmony Trials

Trial Name	Duration of Trial (weeks)	Population Size (n)	Active comparators	Change in HbA1c from Baseline	Change in Fasting Plasma Glucose from Baseline	Change in Weight from Baseline
Harmony-1[8]	52	310	ALB 30mg once weekly vs PBO	-0.75 % [95% CI, -0.95, -0.56]	-29.5 mg/dL [95% CI, -39, -20]	-0.2 kg [95% CI, -1.2, 0.8]
Harmony-2[9]	52	309	ALB 30mg once weekly vs PBO ALB 50mg once weekly vs PBO	-0.84 % [95% CI, -1.11, -0.58] -1.04 % [95% CI, -1.31, -0.77]	-34 mg/dL [95% CI, -46, -22] -43 mg/dL [95% CI, -55, -31]	-0.3 kg [95% CI, -0.9, 1.5] -0.2 kg [95% CI, -1.4, 1.0]
Harmony-3[10]	104	1049	ALB 30mg once weekly vs PBO ALB 30mg weekly vs SIT100mg daily ALB 30mg weekly vs. GLI 2-4mg daily	-0.91 % [95% CI, -1.16, -0.65] -0.35 % [95% CI, -0.53, -0.17] -0.27 % [95% CI, -0.45, -0.09]	-28 mg/dL [95% CI, -39, -16] -16 mg/dL [95% CI, -24, -8] -10 mg/dL [95% CI, -18, -2]	-0.2 kg [95% CI, -1.14, 0.73] -0.4 kg [95% CI, -1.01, 0.31] -2.4 kg [95% CI, -3.03, -1.71]
Harmony-4[11]	52	779	ALB 30mg (up to 50mg) weekly vs GLAR 10Units daily (option to titrate up)	0.11 % [95% CI, -0.04, 0.27]	ALB: -15.7 mg/dL GLAR: -37.1 mg/dL (P<0.001)	ALB: -1.1 kg GLAR: +1.6 kg (P<0.0001)
Harmony-5[12]	52	685	ALB 30mg (up to 50mg) weekly vs PBO ALB 30mg (up to 50mg) vs PIO 30mg (up to 45mg) daily	-0.87 % [95% CI, -1.07, -0.68] 0.25 % [95% CI, 0.1, -0.4]	ALB: -12 mg/dL PIO: -31 mg/dL PBO: 12 mg/dL (P<0.0001)	ALB: -0.4 kg PBO: -0.4 kg ALB vs PIO: -4.9 kg (P<0.0001)
Harmony-6[13,14]	26, 52	586	ALB 30mg once weekly vs LIS (wk 26) ALB 30mg once weekly vs LIS (wk 52)	-0.16 % [95% CI, -0.32, 0] -0.17 % [95% CI, -0.35, 0.02]	-4.9 [95% CI,-13.2, 3.3] -11.2 [95% CI, -21.2, -1.2]	-1.54 kg [95% CI, -2.09, -1] -2.61 kg [95% CI, -3.61, -1.62]
Harmony-7[15]	32	812	ALB (up to) 50mg weekly vs LIRAG (up to) 1.8mg daily	-0.21 % [95% CI, 0.08, 0.34]	ALB: -22.1 mg/dL LIRAG: -30.4 mg/dL (P=0.50)	ALB: -0.64 kg LIRAG: -2.9 kg
Harmony-8[16]	26	507	ALB (up to) 50mg weekly vs SIT	-0.32 % [95% CI, -0.49, -0.15]	ALB: -25.6 mg/dL SIT: -3.9 mg/dL (P<0.0001)	ALB: -0.8 kg SIT: -0.2 kg (P<0.0281)

Abbreviations: ALB: albiglutide, PBO: placebo, CI: confidence interval, HbA1c: glycated hemoglobin, SIT: sitagliptin, GLI: glimepiride, GLAR: glargine, PIO: pioglitazone, LIS: lispro, LIRAG: liraglutide

3.1 Compared with Placebo

Albiglutide has been compared to placebo in patients taking other antidiabetic agents as well as those who were drug naïve.[8,9] Harmony 1 evaluated the safety and efficacy of subcutaneous albiglutide in a three-year, randomized, double-blind, placebo-controlled study.[8] Patients were randomized to albiglutide 30mg once weekly (n=155), or matching placebo (n=155), in addition to their baseline regimen of pioglitazone with or without metformin. At week 52, change in baseline A1c was significantly decreased with albiglutide (-0.75%, p<0.0001) and more patients achieved an A1c goal of < 7.0% (44.3% vs 14.8%). The rapid decline in fasting plasma glucose (FPG) noted in week four was maintained up to week 52. GI adverse effects were reported in 31.3% of patients in the albiglutide arm compared with 29.8% in the placebo arm.

Harmony 2 differed from Harmony 1, with an intent to study albiglutide in drug naïve patients.[9] This randomized, placebo-controlled study evaluated the safety and efficacy of subcutaneous albiglutide given as either 30mg once weekly (n=102), 30mg titrated to 50mg once weekly (n=102), or placebo (n=105). Patients noted to have persistent hyperglycemia were administered metformin, SUs, sitagliptin and/or insulin in addition to albiglutide (defined as hyperglycemic rescue). The primary endpoint included change in A1c from baseline at week 52; secondary endpoints included change in FPG, time to hyperglycemic rescue, body weight change and percentage of patients reaching their A1c goal. Change in A1c was significant for both the 30 and 50mg treatments groups (-0.84%, -1.04%, respectively; p<0.001). Time to hyperglycemia rescue was statistically significant favoring both albiglutide groups (p<0.0001). Weight loss was not different within the three groups. GI events were commonly reported with albiglutide, however, similarly observed within the three groups (31.7% and 30.3% with albiglutide 30 and 50 mg, respectively; 26.7% with placebo).

In both aforementioned trials, the safety profiles were comparable with GI events reported most commonly, aligning with the known profile of GLP-1 agonists. Efficacy was maintained at one year in Harmony 1 and 2; with a dose response relationship observed in the latter trial.

3.2 Compared with Oral Agents

The efficacy of albiglutide compared with various oral agents was investigated in Harmony 3 and 5.[10,12] In both trials, baseline metformin was continued and albiglutide was titrated from 30 mg to 50 mg once weekly, based on predefined hyperglycemia criteria. In Harmony 3, Ahren and colleagues randomized patients with T2DM to albiglutide 30 mg once weekly, sitagliptin 100 mg once daily, glimepiride 2 mg once daily, or placebo.[10] After two years, albiglutide produced superior reductions in A1c compared with sitagliptin (-0.35%; p=0.0001), glimepiride (-0.27%; p=0.0033), and placebo (-0.91%; p<0.0001). Weight loss was noted with albiglutide (-1.21 kg), sitagliptin (-0.86 kg), and placebo (-1.00 kg); weight gain was observed with glimepiride (+1.17 kg). Harmony 5 was a three-year study comparing the efficacy and safety of albiglutide with pioglitazone in addition to baseline metformin and glimepiride.[12] The A1c treatment difference from baseline between albiglutide and pioglitazone was

0.25%, which did not meet the specified margin of 0.30%. Non-inferiority to pioglitazone was not established. As expected with this class, weight gain was noted with pioglitazone (+4.4 kg) while albiglutide patients experienced weight loss (-0.4 kg).

The Harmony 8 trial was uniquely designed to study albiglutide in patients with T2DM and renal impairment (estimated glomerular filtration rate [eGFR] 15-89 mL/min/1.73m^2).[16] Once-weekly albiglutide (30 mg titrated to 50 mg weekly) was superior to sitaglitpin (25 to 100mg depending on glycemic levels) in this randomized, double-blind, 52-week study. Patients were inadequately controlled on diet and exercise and/or oral therapy consisting of metformin, a TZD, a SU, or combination of these. Duration of diabetes, body mass index (BMI) and A1c was similar between the groups at baseline. The A1c reduction for albiglutide was significantly greater at week 26 compared to sitagliptin (-0.83% vs. -0.52%; p=0.003) with similar results observed across the three eGFR groups (mild [$\geq$60 to $\leq$89], moderate [$\geq$ 30 to $\leq$ 59], severe [$\geq$ 15 to $\leq$ 29 mL/min/1.73m^2]). Decreases in FPG and weight were also noted. GI complaints were more commonly observed in the albiglutide arm. Harmony 8 demonstrated once-weekly albiglutide was safe and effective in patients with varying degrees of renal impairment. Many antidiabetic agents require dose reductions or may not be used at all in patients with renal dysfunction, therefore, it important that options are explored in this patient population.

3.3 Compared with Injectable Agents

Albiglutide was shown to be non-inferior to insulin glargine and insulin lispro in Harmony 4 and Harmony 6.[11,13,14] Patients with T2DM treated with metformin ($\pm$SU) were randomly assigned to receive albiglutide 30 mg once weekly (n=516) or insulin glargine 10 units once daily (n=263).[11] Albiglutide could be titrated to 50 mg once weekly and insulin glargine to a target A1c < 7%, if needed (median dose of insulin glargine 30 units). The A1c goal of less than 7% occurred at similar rates between the groups. The reduction in A1c from baseline was also similar between insulin glargine and albiglutide, indicating noninferiority of albiglutide to insulin glargine, based on pre-specified non-inferiority margins. The reduction in FPG was significant in favor of insulin glargine compared to albiglutide (-37.1mg/dl and -15.7 mg/dl, respectively). Body weight increased in the insulin glargine group and decreased in the albiglutide arm. Hypoglycemia was significantly higher in the insulin arm.

Harmony 6 compared albiglutide to three-times daily prandial insulin lispro in patients inadequately controlled on insulin glargine alone or in combination with metformin and/or a TZD.[13,14] No between group difference was observed in A1c lowering and FPG at 26 weeks; non-inferiority was achieved. Similar to the above trial, body weight decreased from baseline in the albiglutide group and increased in the insulin lispro group at week 26 and 52. GI events occurred more frequently in the albiglutide group and were more commonly noted during the first 26 weeks. Most hypoglycemic events occurred during the first 26 weeks, and were more frequently observed in the insulin lispro arm. Pancreatitis was not reported. Medullary thyroid cancer required one patient to discontinue the study after one dose of albiglutide was received.

A head-to-head trial comparing albiglutide to liraglutide resulted in a greater A1c and FPG reduction with liraglutide.[15] The Harmony 7 trial was a randomized, open-label, non-inferiority study assessing these two GLP-1RAs in patients with T2DM inadequately controlled on oral antidiabetic

drugs. Both albiglutide (up to 50mg/weekly) and liraglutide (up to 1.8mg/weekly) were titrated during the 32 week trial. The A1c reduction was slightly greater with liraglutide compared with albiglutide (-0.99% and -0.78%, respectively; p=0.0846). Albiglutide failed to meet noninferiority to liraglutide. Weight loss was significantly greater with liraglutide (-2.19 kg and -0.64 kg, respectively, p<0.0001). GI events were common in both groups, but occurred more frequently in the liraglutide group than the albiglutide group (49.0% and 35.9%, respectively; p=0.001). No significant differences between groups were observed in treatment satisfaction.

3.4 Summary of Clinical Trials

Eight phase III clinical trials (Harmony 1 through 8) assessed the efficacy, safety and tolerability of once-weekly albiglutide in more than 5000 patients. Albiglutide was evaluated as monotherapy and in combination with both oral and injectable anti-diabetic agents. Albiglutide decreased A1c by 0.55-0.9% from baseline. Superiority of albiglutide was achieved when compared to placebo, sitagliptin, and glimepiride. Albiglutide was found to be noninferior to insulin lispro and insulin glargine and failed to achieve noninferiority when compared with liraglutide and pioglitazone. Weight loss was modest and gastrointestinal side effects were observed, although at a lower rate when compared with liraglutide. Albiglutide was associated with low rates of hypoglycemia.

4. Adverse Effects

Common adverse effects associated with albiglutide use include upper respiratory tract infection, diarrhea, nausea, injection site reaction, cough, back pain, arthralgia, sinusitis, and influenza.[6] Adverse effects considered to be more serious in nature are highlighted below.

4.1 Cardiovascular

In 2008, the FDA issued recommendations for industry requiring evaluation of cardiovascular risk in new medications used to treat T2DM. This requirement stemmed, in part, from discussions during a meeting of the Endocrinologic and Metabolic Drugs Advisory Committee regarding the need for increased attention to cardiovascular risk during drug development.[17] Few studies have been conducted examining the cardiovascular effect of albiglutide. One study aimed to determine if the use of albiglutide, up to 30mg weekly in non-diabetic patients with reduced ejection fraction would improve myocardial metabolic abnormalities.[18] In this study, patients were randomized to receive albiglutide 3.75mg, 15mg, or 30mg weekly, or placebo for 12 weeks. While the results of this study showed albiglutide does not improve myocardial metabolic abnormalities, it was determined that albiglutide at a dose of up to 30mg weekly is safe for use in patients with heart failure. In a study of 85 healthy subjects, the effect of albiglutide on heart rate was evaluated.[19] Subjects received albiglutide 30mg (up to 50mg) weekly or placebo for six weeks. Results of this study showed albiglutide raised heart rate by 3 bpm and 6 to 8 bpm for the 30mg and 50mg doses, respectively. Other trials examining the effect of GLP-1RAs on heart rate have demonstrated no increase in risk of cardiovascular disease despite an increase in heart rate. HARMONY Outcomes, a cardiovascular outcomes trial involving albiglutide, is currently ongoing with results expected in 2019.[20] The results of this study will further elucidate the cardiovascular risks, if any, of albiglutide.

4.2 *Pancreatitis*

Due to a potential increased risk of acute pancreatitis, albiglutide is being monitored via an FDA REMS (Risk Evaluation and Mitigation Strategy) program.[21] The fact

sheet, which can be found at http://www.tanzeumrems.com/assets/pdf/REMS_Factsheet.pdf, offers guidance to health care providers regarding steps to take in the event patients experience symptoms consistent with pancreatitis. The overall incidence of pancreatitis in all 8 HARMONY trials was reported as only 0.3%.[22] However, a recent meta-analysis examining all GLP-1RAs found a statistically significant increase in the risk of pancreatitis with albiglutide.[23] The mechanism by which GLP-1RAs increase the risk of pancreatitis is unknown; however, it is suspected that chronic over-stimulation of GLP-1 receptors may be a likely cause.[23]

4.3 Thyroid C-cell Tumors

The package insert for albiglutide includes a black box warning regarding the potential for thyroid c-cell tumors.[6] Animal data has shown other GLP-1RAs are associated with thyroid c-cell tumors; however, an association with albiglutide has not been substantiated . Whether this increased risk translates to humans is also unknown. To ensure safe use of albiglutide, the REMS program also includes information regarding the risk of these cancers.[21] A recent systematic review examining whether longer acting GLP-1RAs, like albiglutide, are associated with an increased risk of tumors showed there is no increased risk of tumor development in any tissue regardless of agent.[24]

5. Comparison to Other GLP-1RAs

Few head to head studies exist comparing GLP-1RAs to one another. Currently there are six GLP-1RAs on the market (see Table 2). GLP-1RAs are categorized according to their duration of activity into short acting and long acting agents. The short acting agents, twice-daily exenatide and lixisenatide, are thought to work primarily by delaying gastric emptying thereby reducing PPG excursions. Albiglutide, dulaglutide, once-weekly exenatide, and liraglutide, the long acting agents, work primarily by stimulating insulin release from the pancreas providing a more continuous effect on blood glucose levels. Both the short and long acting agents additionally suppress glucagon secretion and appetite.[25]

Table 2: Currently Available GLP1-RAs

Brand Name	Generic Name	Duration of Action	Dose
Byetta®	Exenatide	Short acting	5 to 10 mcg twice daily
Adlyxin®	Lixisenatide	Short acting	20 mcg once daily
Tanzeum®	Albiglutide	Long acting	30 to 50 mg once weekly
Victoza®	Liraglutide	Long acting	1.2 to 1.8 mg once daily
Trulicity®	Dulaglutide	Long acting	0.75 to 1.5 mg once weekly
Bydureon®	Exenatide	Long acting	2 mg once weekly

Compared to placebo, all GLP-1RAs reduce A1c and FPG, albeit to varying degrees. Reductions in A1c range from 1.21% with dulaglutide to 0.55% with lixisenatide. FPG levels decreases range from 35 mg/dL with dulaglutide to 13 mg/dL with lixisenatide.[26] Weight loss is also significantly reduced by all GLP-1RAs when compared to placebo with the greatest reduction (1.96 kg) seen with liraglutide. With the exception of lixisenatide and albiglutide, all other GLP-1RAs significantly reduce systolic blood pressure (BP).[26] Heart rate is significantly increased with all GLP-1RAs except lixisenatide with the greatest increase seen with liraglutide. Despite an increase in heart rate, there appears to be no increased risk of cardiovascular disease. The long acting agents produce significant improvements in lipid levels compared to placebo.[26] Additionally, all GLP-1RAs increase the risk of hypoglycemia and nausea. Rates were similar between albiglutide and placebo. The risk of vomiting and diarrhea was significantly greater with all GLP-1RAs except lixisenatide.[26]

Comparisons among the GLP-1RAs are more limited; however, the following trends exist within this class of agents. With the exception of albiglutide, the long acting agents produce significant improvements in A1c and FPG over twice-daily exenatide and lixisenatide.[26,27] This is thought to be due to the fact that the short acting agents primarily affect PPG levels while the long acting agents affect both PPG and FPG levels.[27] Within the long acting agents, liraglutide and dulaglutide appear to be more efficacious in lowering A1c and FPG.[27] All GLP-1RAs cause weight loss to varying degrees with liraglutide and exenatide being the most efficacious.[27] Within the GLP-1RA class, the risk of hypoglycemia was similar between agents. GI adverse effects are commonly reported with GLP-1RAs and appear to be dose related for all agents.[28] The risk of nausea is greater with twice-daily exenatide and lixisenatide compared to albiglutide and once-weekly exenatide. This difference is thought to be due to the fluctuation in GLP-1 plasma levels with the shorter acting agents.[27] Nausea subsides in most patients with repeated dosing of all GLP-1RAs. Diarrhea risk is no different between the short and long-acting GLP-1RAs.[26] Injection site reactions may be more common with the longer acting agents, specifically exenatide once weekly.[29]

6. Conclusion

Albiglutide is a once weekly GLP-1RA indicated for the treatment of T2DM. The ADA and AACE/ACE recommend GLP-1RAs early in the treatment algorithm due to their efficacy and safety profiles. Data from the Harmony trials demonstrate albiglutide is non-inferior to basal and prandial insulins with the added benefit of weight loss. Compared to the other GLP-1RAs, albiglutide may cause less GI adverse effects at the cost of being slightly less efficacious. Caution should be exercised when using GLP-1RAs in patients with kidney dysfunction; however, results from Harmony 8 indicate albiglutide may be appropriate in this population. Albiglutide is a safe, efficacious and well tolerated treatment option for patients desiring once-weekly treatment for T2DM.

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