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Liraglutide for Obesity: Do the Benefits Outweigh the Risks?

By: Maya Wai, Pharm.D.

Introduction: Obesity affects over one-third of adults in the United States and is associated with heart disease, stroke, and type 2 diabetes. However, pharmacologic management of obesity remains challenging. The Food and Drug Administration (FDA) recently approved liraglutide under the brand name Saxenda® as a once-daily 3 mg subcutaneous injection for the treatment of obesity in those with a BMI ≥ 30 kg/m² or ≥ 27 kg/m² with ≥ 1 weight-related comorbidity, such as hypertension or dyslipidemia.^{1,2}

What is Liraglutide?: Liraglutide is a long-acting analog of human glucagon-like peptide-1 (GLP-1), an incretin hormone, which is released in response to food intake.² It has been shown to decrease hunger and increase feelings of satiety after eating, which can regulate appetite and food intake. Its dual role in blood glucose and appetite regulation may benefit obese patients with

type 2 diabetes.¹ Liraglutide has also been FDA-approved for the treatment of type 2 diabetes mellitus under the brand name Victoza®, with an initial dose of 0.6 mg once daily subcutaneously, titrated to a maximum dose of 1.8 mg daily.³

Safety Concerns with Liraglutide: When liraglutide was initially FDA-approved in 2010 as a treatment for diabetes, animal studies demonstrated a dose-dependent and treatment duration-dependent risk of medullary thyroid cancer. Additionally, an increased incidence of acute pancreatitis (including necrotizing pancreatitis) was associated with liraglutide use in clinical trials. These risks prompted the FDA to require a black box warning and for the manufacturer, Novo Nordisk, to implement a Risk Evaluation and Mitigation Strategy (REMS) program to ensure that the benefits of liraglutide

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Pirfenidone in Idiopathic Pulmonary Fibrosis

By: Jesse Castillo, Pharm.D.

Background: Idiopathic pulmonary fibrosis (IPF) is a fatal form of interstitial lung disease with no known cause; it is characterized by fibrosis of lung tissue that results in restricted ventilation from impaired gas exchange, poor quality of life, and ultimately death within 2-5 years.^{1,2} The prevalence of IPF in the United States is estimated to be as high as 63 per 100,000 people.¹ In October 2014, the Food and Drug Administration (FDA) approved two novel and mechanistically different drug therapies for treatment of IPF, pirfenidone (Esbriet®: InterMune, Inc.)

and nintedanib (Ofev®: Boehringer Ingelheim).³⁻⁵ This article will discuss the use of pirfenidone in patients with IPF.

How Does Pirfenidone Work?: The precise mechanism of action has not been fully elucidated; however, pirfenidone may regulate the activity of transforming growth factor β (TGF- β) and tumor necrosis factor α (TNF- α), thus inhibiting fibroblast proliferation, collagen synthesis and accumulation, and reducing cellular histological

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outweigh the risks.⁴ This REMS involved a communication plan to healthcare providers and professional societies about the risk of acute pancreatitis and thyroid cancer and required submissions of REMS assessments to the FDA for a follow-up period of 7 years.⁴ Pregnant and nursing women were excluded from the liraglutide trials that were pivotal for the approval of Victoza[®] and Saxenda[®].^{2,3} Victoza[®] is rated pregnancy category C, although a study examining liraglutide in pregnant women for the prevention of gestational diabetes is currently underway.^{3,5} In contrast, Saxenda[®] is rated pregnancy category X because weight loss offers no potential benefit to a pregnant woman.²

Liraglutide Weight Loss Trial: Liraglutide for weight loss maintenance was evaluated in SCALE[™], a phase 3, 56-week, randomized, double-blind, placebo-controlled trial.⁶ Adult patients with a BMI ≥ 30 kg/m² or ≥ 27 kg/m² with a comorbidity of dyslipidemia or hypertension were eligible. Patients were randomized 1:1 to liraglutide 3 mg subcutaneously daily or placebo after losing $\geq 5\%$ of body weight in the lead-in period. A 500 kcal/day deficient diet, continued physical activity, face-to-face counseling, and medical monitoring every 4 weeks were required. A total of 422 participants lost $\geq 5\%$ of weight at screening, with a mean of $6.0\% \pm 0.9\%$ or 6.3 kg ± 1.6 kg. Of those randomized to liraglutide (n=212), 75% (n=159) completed the 56-week trial compared to 69.5% (n=146) of placebo (n=210). At week 56, participants who received liraglutide lost an additional mean $6.2\% \pm 7.3\%$ of randomization weight compared to $0.2\% \pm 7.0\%$ with placebo (p<0.0001). More participants on liraglutide maintained $\geq 5\%$ weight loss compared to placebo (81.4% vs. 48.9%; p<0.0001). Additionally, more liraglutide patients lost $\geq 5\%$ of randomization weight (50.5% vs. 21.8%; p<0.0001).⁴ No cases of acute pancreatitis or medullary thyroid carcinoma were reported in either the liraglutide or placebo groups. Thyroid neoplasms were reported by three participants in the liraglutide group, but all were considered unlikely to be related to the treatment because of the proximity of occurrence to the first dose or a pre-existing condition. The occurrence of cardiac disorders was similar between the liraglutide and placebo groups. More participants in the liraglutide group experienced gastrointestinal disorders compared to placebo (74% vs. 45%, respectively). The authors concluded that liraglutide 3 mg daily combined with diet and exercise was well-tolerated and effective in maintaining weight loss over 56 weeks.⁴

Dosing and Administration: The initial dose of Saxenda[®] is 0.6 mg subcutaneously once daily for the first week and titrated up by 0.6 mg every week, based on tolerability, to a maximum dose of 3 mg by week 5.³ The dose titration schedule is summarized in Table 1.

Table 1: Saxenda[®] Dose Titration Schedule^{3*}

Week	Daily Dose
1	0.6 mg
2	1.2 mg
3	1.8 mg
4	2.4 mg
5 and onward	3 mg

* If unable to tolerate dose titration, delay dose escalation for an additional week. If a patient cannot tolerate the 3 mg dose, discontinue Saxenda[®], as efficacy has not been established at lower doses.

Bottom Line: The SCALE[™] trial has demonstrated that liraglutide along with diet and exercise produced significant weight loss which was maintained over a 56 week period. However, the medication has been associated with the risk of pancreatitis and thyroid cancer requiring a REMS assessment. Additionally, unlike other weight loss options, it requires subcutaneous administration. In determining whether to utilize Saxenda[®], clinicians and patients will ultimately need to decide whether the benefits outweigh the risks.

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markers of fibrosis.^{6,7} Pirfenidone is also believed to exert anti-inflammatory properties by decreasing the accumulation of inflammatory cells resulting from a variety of stimuli.⁷

Clinical Trials and Guidelines: In order to obtain new drug approval for pirfenidone, data from the CAPACITY* trials, published in 2011, were submitted to the FDA. However, conflicting results reported in these trials regarding pirfenidone's effectiveness in preventing deterioration of lung function prompted the FDA to require further studies.⁷ Based on the results of the CAPACITY trials, the 2011 ATS/ERS/JRS/ALAT* International Guidelines on IPF gave a weak recommendation against the use of pirfenidone for treatment of IPF.⁸ This recommendation can be interpreted as not supporting the widespread use of pirfenidone in the majority of patients; however, its use may be considered for a minority of IPF patients.⁸ The results from the ASCEND* trial, published in 2014, confirmed the slowing of disease progression in the pirfenidone group as evidenced by a significant reduction in the decline of predicted forced vital capacity (FVC), an increase in the number of patients with no decline in FVC, and a significant reduction in the decline in 6 minute walk test distance.⁹ Additionally, a pre-specified pooled patient analysis from the ASCEND and CAPACITY trials, showed pirfenidone to significantly reduce the risk of all-cause mortality and IPF-related mortality.⁹ Based on the results of these trials, the drug was approved by the FDA.

Adverse Effects: Some common ($\geq 10\%$) adverse reactions of pirfenidone include gastrointestinal (GI) related effects, dizziness, rash, headache, and photosensitivity.^{3,9} Pirfenidone has been shown to elevate liver enzyme levels. Patients should protect themselves against sunlight/sunlamp exposure by wearing sunscreen and protective clothing while on pirfenidone.

Dosage and Administration: Pirfenidone will be available as 267-mg capsules. The recommended dosage of pirfenidone is three capsules three times daily with food for a total daily dose of 2403 mg.³ In order to limit side effects, pirfenidone therapy should be initiated with a dose titration over a 2-week period; the titration schedule is listed in Table 1.

Table 1: Titration Schedule for Pirfenidone^{3*}

Treatment Days	Dosage
Days 1 through 7	One capsule TID
Days 8 through 14	Two capsules TID
Days 15 onward	Three capsules TID

*If pirfenidone is discontinued for 14 days or longer, the titration schedule should be re-initiated.

Drug Interactions and Monitoring/Dosage Adjustments:

Concomitant use of pirfenidone with medications which significantly inhibit CYP1A2, such as fluvoxamine and high-dose ciprofloxacin (750 mg twice a day) is not recommended.³ However if therapy with these medications is unavoidable, pirfenidone dosage should be reduced to one capsule three times a day for concomitant use with a strong CYP1A2 inhibitor and two capsules three times a day with high-dose ciprofloxacin.³ Baseline liver function tests should be obtained prior to initiation, subsequently every month for the first 6 months, and then every 3 months thereafter.³ The dose of pirfenidone may need to be modified or therapy discontinued based on liver enzyme levels accompanied by symptoms of hepatic dysfunction or hyperbilirubinemia. It should be used with caution in patients with renal impairment.³ There is no recommended dosage adjustment for patients with renal insufficiency. However it is not recommended in patients with end-stage renal disease or for those on dialysis.

Bottom line: Pirfenidone is one of the first pharmacologic agents FDA-approved for the treatment of IPF. Pirfenidone may slow the decline of lung function hopefully prolonging survival in patients with IPF.

Acronym Definitions:

* ATS=American Thoracic Society; ERS=European Respiratory Society; JRS=Japanese Respiratory Society; ALAT=Latin America Thoracic Association; CAPACITY=Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research and Efficacy and Safety Outcomes; ASCEND=Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis

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Agents for Hereditary Angioedema

By: Long Trinh, Pharm.D.

Introduction: Hereditary angioedema (HAE) is an autosomal dominant disease caused by a deficiency in C1 esterase inhibitor (C1-INH) activity.^{1,2} Hereditary angioedema accounts for about 2% of all clinical angioedema cases affecting approximately 1 in 50,000 individuals.² The disease is characterized by recurrent episodes of nonpruritic, nonpitting edema of the skin, respiratory and gastrointestinal tracts.¹ The average HAE patient experiences approximately 20 attacks per year which can be life-threatening if the upper airway is affected.² The mortality rate of HAE-induced laryngeal edema is 25- to 40-%.

Pathophysiology and Common Triggers of HAE: C1 esterase inhibitor has a regulatory role in the complement, coagulation, and kallikrein-kinin (contact-system) cascades.^{1,2} Deficiency in functional C1-INH activity elevates plasma bradykinin, which is the key mediator of the swelling and the painful symptoms of HAE. Diagnosis and confirmation of the disease involves assays of C4 and C1-INH levels and function.^{1,3} Patients with HAE typically have low C4 with normal C1 and C3 levels. Quantitative evaluation of C4 is the first diagnostic step used to rule out HAE.¹⁻³ Subsequent measurement of C1-INH confirms the diagnosis.^{1,2} HAE type I and type II results from a reduction in C1-INH level or a functional deficiency of C1-INH, respectively.¹⁻³ HAE type I comprises approximately 85% of the cases of HAE, while type II occurs in about 15% of those afflicted with this disorder. Some HAE attack triggers include minor trauma, dental procedures, infection, stress, puberty, menstruation, pregnancy, and certain medications.¹⁻³

Management Options for HAE: Various management steps which can be taken to help prevent and/or treat HAE attacks are as follows^{3,4}:

- **Avoid medications which trigger HAE attacks:** Estrogen-containing oral contraceptives, hormone replacement therapy, and ACE inhibitors; plasminogen activators are triggers but their benefit may outweigh the risk of use.
- **Prophylactic options:** The goal of prophylactic management of HAE is to prevent and minimize the frequency of an attack. The first-line prophylactic agent is the plasma-derived C1-INH concentrate, Cinryze®. Other agents recommended for prophylaxis if Cinryze® is not available, include attenuated androgens (e.g., danazol) and antifibrinolytics (e.g., oral tranexamic acid).

- **Acute treatment options:** Treatment of an acute attack generally consists of C1-INH concentrates (Cinryze®, Berinert®, Ruconest®) or ecallantide (Kalbitor®) a kallikrein antagonist, or icatibant (Firazyr®), a bradykinin antagonist. These agents work by reducing the physiologic action of bradykinin. Patients with HAE do not respond adequately to antihistamines and glucocorticoids. Epinephrine only has a modest effect on relieving an HAE attack.

Select Agents for HAE: The C1-INH concentrate Cinryze® was approved by the Food and Drug Administration (FDA) in 2008 for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE.⁵ Berinert®, which was FDA-approved in 2009, was the only C1-INH concentrate available for the treatment of acute HAE attacks until the recent approval of Ruconest® in 2014.⁶ Since Berinert® is plasma-derived, administration of hepatitis B vaccine is recommended prior to its use.⁶ Ruconest® is a novel recombinant C1-INH concentrate produced in transgenic rabbits and therefore, lacks the risk of viral transmission.⁷ However, since Ruconest® is derived from an animal source it carries a high risk of allergic or anaphylactic reactions. Consequently, prior to treatment with Ruconest®, patients should be evaluated for immunoglobulin E (IgE) antibodies against rabbit allergens. Additionally, it is recommended that IgE antibody testing should be repeated annually or after ten treatments, whichever occurs first. Icatibant and ecallantide are both administered subcutaneously, whereas the C1-INH concentrates are administered intravenously.⁵⁻⁹ Anaphylaxis has been reported following the administration of ecallantide; therefore, ecallantide can only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema.⁸ Icatibant is currently the only agent on the market approved for subcutaneous self-administration at the onset of an acute HAE attack.⁹ Key characteristics of various agents for prophylaxis and/or treatment of HAE are summarized in Table 1.

Bottom Line: Hereditary angioedema is caused by a deficiency in C1-INH activity resulting in an elevation of bradykinin levels. Several types of triggers can precipitate an HAE attack. Treatment of an HAE attack consists of C1-INH concentrates, ecallantide, or icatibant; these therapies help reduce the physiologic effects of bradykinin reducing the symptoms of angioedema. All of these agents have certain

limitations. The use of Cinryze® is restricted on the Cleveland Clinic Health-System (CCHS) Formulary to the Department of Allergy and Immunology for the prophylaxis of HAE in the outpatient setting. Any inpatient orders for Cinryze® for the treatment of an acute HAE attack must be approved by the Drug Information Center. Berinert®, Kalbitor®, Firazyr®, and Ruconest® are currently non-formulary.

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Table 1: Medications Used for Prophylaxis and/or Treatment of HAE⁵⁻⁹

Drug Manufacturer (Year Approved by FDA)	Therapeutic Category	FDA- approved Indication	FDA- approved Age (years)	Dose	Route of ADM	Limitations
Cinryze® ViroPharma (2008)	Plasma-derived C1-INH	Prophylaxis*	≥12	1000 units every 3-4 days	IV	Pretreatment hepatitis B (in combination with hepa- titis A) vaccination recom- mended to prevent blood- borne pathogens
Berinert® Behring (2009)				20 units/kg	IV	
Ecallantide (Kalbitor®) Dyax (2009)	Kallikrein antagonist	Treatment	≥12	30 mg (may repeat within 24 hours)	SC	Only administered by a healthcare professional; requires three injections of 10 mg /1 mL Dose = 30 mg/3 mL
Icatibant (Firazyr®) Shire (2011)	Selective bradykinin B2 receptor antagonist		≥18	30 mg (may repeat every 6 hours; NTE three injections within 24 hours)	SC	Injection site reactions occurred in 97% of patients in clinical trials
Ruconest® Salix (2014)	Recombinant human C1-INH		≥12	50 units/kg over 5 minutes (maximum 4200 units)†	IV	Pretreatment and repeated IgE antibody testing against rabbit required; effectiveness not established in patients with laryngeal attacks

ADM=Administration FDA=Food and Drug Administration HAE=Hereditary Angioedema IV=Intravenous NTE=Not to Exceed

SC=Subcutaneous

*Used off-label for treatment

† < 84 kg dose is 50 units/kg; ≥ 84 kg dose is 4200 units