OREGON DUR BOARD NEWSLETTER©

AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug_policy/newsletter

February 2011 Volume 13, Issue1

An Update in Therapeutic Options for Diabetes

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The prevalence of diabetes continues to increase despite advances in detection and therapy. According to the Centers for Disease Control and Prevention, as many as 1 in every 3 adults will have diabetes by 2050.[1] A number of therapeutic options are available for management of glycemic variances associated with diabetes yet no agent has demonstrated clear superiority.[2] This review will focus on three new classes of agents; an amylin analog, dipeptidyl peptidase-4 (DPP-4) inhibitors or incretin enhancers and glucagon-like peptide-1 (GLP-1) agonists or incretin mimetics.

Current pharmacological recommendations for patients with type 1 diabetes are to initiate an intensive insulin regimen. Rapid, short, intermediate, long acting and premixed insulin products should be considered and titrated to optimal patient response. Insulin sensitizers may be considered as an adjunct to insulin therapy, however, no conclusive benefit has been demonstrated in type 1 patients.[3] The American Diabetes Association treatment recommendations for patients with type 2 diabetes are lifestyle modifications and metformin for step 1 therapy. For step 2 therapy, step 1 recommendations with the addition of either a sulfonylurea or basal insulin are suggested. Less well validated tier 2 therapies are the addition of pioglitazone, a GLP-1 agonist, or pioglitazone and a sulfonylurea to step 1 recommendations. Step 3 recommendations include the addition of intensive insulin to step 1 treatments.[2]

Amylin Analog

Pramlintide: Pramlintide is synthetic analog of amylin, a neuroendocrine hormone produced by pancreatic beta cells, which helps control postprandial glucose levels. Pramlintide is injected immediately prior to major meals causing decreases in postprandial glucagon secretion by delaying the peak of carbohydrate absorption. Effects on postprandial glucose allow for reductions in the amount of short acting insulin required.[4]

Pramlintide was studied up to 52 weeks in patients with type 1 and type 2 diabetes. Data was gathered from trials studying pramlintide as monotherapy and as an adjunct to insulin, with and without other oral antidiabetic agents. Studies demonstrated a glycosylated hemoglobin (HbA1c) lowering from baseline of 0.29% to 0.58% in patients with type 1 diabetes. Baseline HbA1c means ranged from 8.3%-8.9%.[5,6] The greatest glucose lowering effects were seen at 26 weeks, while less glucose lowering was observed at 52 weeks. Studies in patients with type 2 diabetes, with baseline HbA1c means from 7.9% - 9.2%, showed HbA1c lowering of 0.35% to 1.1% from baseline.[7-10] In an active control trial, comparing pramlintide to titrated rapid-acting insulin analogs (RAIA) (on background basal insulin and prior oral antihyperglycemic drugs) no statistical difference was demonstrated between the groups (1.1% vs. 1.3%, p=0.46).[7]

Weight Loss: Both type 1 and type 2 diabetic patients experienced weight loss or weight neutral effects with pramlintide therapy. When pramlintide was studied in comparison to placebo and insulin, a statistically significant weight loss of 1.7 kg at 6 months for type 1 and type 2 patients was demonstrated. In a small cohort of patients followed for five years, weight loss effects waned and patients with type 1 diabetes gained weight, suggesting a transient effect on weight loss.[4]

Adverse Events: The most prevalent treatment-emergent adverse events seen with pramlintide include headache, anorexia, vomiting and most commonly nausea (45%-95% compared to placebo rates of 12% to 36%).[4] Withdrawal rates were high, ~30% in the pramlintide group, which were dose related and mostly due to nausea.[5-10] In active control studies a greater incidence of severe hypoglycemia was shown with pramlintide therapy when patients were taking mealtime insulin with no insulin reduction. Reducing the insulin dose eliminated severe hypoglycemia, however, as a result pramlintide carries a black box warning of an associated risk of severe hypoglycemia, especially in patients with type 1 diabetes. Patients are instructed to reduce their short-acting insulin by 50% upon initiation of pramlintide therapy.[4] Pramlintide therapy did not alter fasting lipid parameters.[6]

Place in Therapy: The American Diabetes Association (ADA) considers pramlintide a third line agent and The American Association of Clinical Endocrinologists (AACE)/ American College of Endocrinology (ACE) recommends this class as an adjunct to insulin in patients receiving prandial insulin.[2,11] Pramlintide is a treatment option in patients for whom weight loss is particularly desirable and for those who are close to their glycemic goal. Due to the high incidence of adverse advents and no long term outcome data, widespread use cannot be advocated at this time.

Incretin Enhancers (DPP-4 Inhibitors)

The DPP-4 inhibitors are incretin enhancers indicated for patients with type 2 diabetes. The incretin effect enhances nutrient-stimulated release of intestinal peptides that are released in response to glucose or other gut nutrients. Specifically, the DPP-4 inhibitors inhibit the degradation of endogenous incretins resulting in enhanced glucose dependent insulin secretion and reduced glucagon secretion.[12,13]

Sitagliptin: A Cochrane Review found sitagliptin monotherapy to lower HbA1c by a difference of 0.77% when compared to placebo.[14] Reductions demonstrated by sitagliptin monotherapy proved less than comparative agents, metformin and glipizide.[15-17] In patients with a mean HbA1c of 7.7%, on background metformin therapy, studies comparing sitagliptin to glipizide found no significant difference in HbA1c lowering between the two therapies. The glipizide doses in this study were only titrated to around 50% of the maximally effective dose, due to hypoglycemia limitations. After 52 weeks both sitagliptin 100mg/day and glipizide 5-20mg/day lowered HbA1c from baseline to a similar extent, -0.51% and -0.57%, respectively.[18] Results were similar when comparing sitagliptin to rosiglitazone.[19] Studies using sitagliptin as additive therapy to metformin, pioglitazone, or glimepiride resulted in greater HbA1c reductions than the addition of placebo.[15,17,20,21] Sitagliptin is available as a combination product with metformin, called Janumet®.[22]

Saxagliptin: In placebo-controlled studies with saxagliptin monotherapy HbA1c reductions from baseline ranged from -0.43% to -0.9%, in patients with mean HbA1c values of 7.9%.[23,24] When saxagliptin was studied as add-on therapy to metformin, glyburide or a thiazolidinedione HbA1c reductions from baseline ranged from -0.54% to -0.94%, in patients with a mean baseline HbA1c ranging from 8.0% - 9.6%.[25-28] Study durations only went out to 24 weeks, with one trial at 12 weeks showing greater glucose lowering than studies of longer duration. A systematic assessment of cardiovascular outcomes of eight randomized, phase 2/3 trials suggested a potential reduction in cardiovascular events in patients treated with saxagliptin.[29] Saxagliptin is also available in a combination product with metformin called Kombiglyze XR® approved in November of 2010.[30]

Weight Loss: Studies with DPP-4 inhibitors demonstrated slight weight loss, slight weight gain or a weight neutral effects. In studies comparing sitagliptin to metformin or glipizide weight changes varied from -0.9kg to +0.6kg. Similar changes were demonstrated with saxagliptin when used in combination therapy as an add-on to glyburide, metformin, or thiazolidinedione.[25-28]

Adverse Events: DPP-4 treatment is most commonly associated with nasopharyngitis, upper respiratory infections, urinary tract infections and headache. DPP-4 agents are well tolerated with total withdrawal rates being slightly lower for sitagliptin and saxagliptin compared to placebo. Rates of hypoglycemia were also similar for both DPP-4 inhibitors and placebo groups. Increased rates of hypoglycemia were demonstrated when

sitagliptin and saxagliptin were used with insulin or insulin secretagogues and dose reduction is recommended.[12,13] An increased risk of respiratory infections has been demonstrated in clinical trials.[12] DPP-4 are cell membrane proteins, expressed in many tissues including immune cells, therefore, there is a potential for DPP-4 inhibitors to interfere with immune function. Sitagliptin has been associated with acute pancreatitis in post-marketing reports, however, there is no good evidence of cause and effect at this time.[12] *Janumet* and *Kombiglyze XR* carry a black box warning because of the potential for lactic acidosis associated with the metformin component. Improvement in triglycerides, LDL and HDL cholesterol levels have been demonstrated in studies with DPP-4 inhibitors. No consistent lipid profile benefits have been seen.[31]

Place in Therapy: The DPP-4 inhibitors are considered third line by the ADA, based on glycemic effectiveness and relative cost.[2] The AACE/ACE considers DPP-4 inhibitors preferred agents, after metformin, as monotherapy or add-on therapy.[11] The Cochrane Review of DPP-4 inhibitors for type 2 diabetes mellitus reported no advantages of DPP-4 inhibitors over existing therapies.[14] Data on mortality, diabetic complications as well as long term cardiovascular outcomes and safety data are lacking. With studies lasting only 30 weeks, postmarketing data will be vital to access the effects of DPP-4 inhibitors on immune function. Animal models suggest beta-cell preservation with chronic use of DPP-4 inhibitors but additional studies are needed to determine if this can be extrapolated to humans.[32] DPP-4 inhibitors may be an option for patients close to their HbA1c goal and are unable to tolerate other hypoglycemic agents due to adverse effects, including hypoglycemia.

Incretin Mimetics (GLP-1 Agonists)

GLP-1 agonists are receptor agonists that are used in patients with type 2 diabetes as an adjunct to diet and exercise to improve glycemic control. The GLP-1 agonists stimulate GLP-1 receptors to increase insulin production in response to glucose, which decreases postprandial glucagon release and slows gastric emptying.[33,34]

Exenatide: A systematic review of five randomized control trials of exenatide demonstrated a HbA1c reduction from baseline of 1.01% ; 95% CI -1.18% to –0.84%.[31] In placebo controlled trials in which patients were uncontrolled despite metformin, sulfonylurea or thiazolidinedione therapy, exenatide lowered HbA1c from baseline -0.78% to -1.3% (mean baseline HbA1c 7.8% - 8.5%).[35-39] Studies comparing exenatide to insulin glargine, on background oral therapy, found no difference between the two treatments.[40,41] Exenatide was also shown to be non-inferior to insulin aspart in an open-label study.[42] A head-to-head trial examined the efficacy of exenatide 10 mcg twice daily to liraglutide 1.8mg once daily and found greater lowering of HbA1c with liraglutide, treatment difference of -0.33; 95% CI -0.47 to -0.18.[43] In an open-label study lasting 82 weeks, exenatide treatment resulted in improvement in cardiovascular markers; blood pressure and lipids.[44] A once-weekly formulation of exenatide is in development, which will be marketed under the name *Bydureon*. FDA approval is expected by the beginning of 2012.[45]

Liraglutide: In placebo controlled studies, liraglutide lowered HbA1c values to a greater extent than placebo as monotherapy and as add-on treatment to oral agents. An active control study comparing liraglutide with insulin glargine found significantly greater reductions from baseline HbA1c values with liraglutide 1.8mg daily (-1.33% compared to -1.09%, p=0.0015).[46] Studies comparing liraglutide with glimepiride, without metformin therapy, showed liraglutide to have statistically significantly greater reductions in HbA1c.[47] In a 26 week study in which liraglutide and glimepiride groups were given metformin 1g twice daily, the treatment groups were found to be non-inferior, with similar decreases in HbA1c.[48] Liraglutide also showed additional HbA1c lowering when added to a metformin and rosiglitazone regimens.[49] In a head to head study of liraglutide compared to sitagliptin, with both groups on metformin, liraglutide was found to lower HbA1c to a greater extent, with an estimated mean treatment difference of -0.60%, p<0.0001.[50]

Weight Loss: Treatment with GLP-1 analogues have resulted in statistically significant weight loss compared to active treatments (WMD -2.37kg; 95% CI -3.95, -0.78). Weight loss appears to be dose-dependent and does not wane over time in studies up to 30 weeks. Weight loss occurred in patients with and without nausea, suggesting that weight loss is independent of nausea.[31]

Adverse Events: Nausea, vomiting and diarrhea were the most common adverse event in exenatide treated patients, declining after 8 weeks.[31] Withdrawal rates due to adverse events were higher with exentatide compared to placebo, RR 3.8, CI 2.29 to 6.33. Liraglutide was also associated with gastrointestinal adverse events, predominantly nausea and diarrhea, with adverse events withdrawal rates similar to exenatide. The incidence of hypoglycemia was similar with insulin and exenatide and is higher with exenatide, compared to placebo in patients on background sulfonylurea therapy. Severe hypoglycemia occurred rarely (0.4%) and only when exentatide was administered concomitantly with a sulfonylurea.[33] Liraglutide demonstrated less minor hypoglycemia compared to glimepiride and similar rates when compared to insulin glargine. However, one study showed higher rates of major hypoglycemia (2.2%) with liraglutide when compared with insulin glargine (0%). When compared to exenatide, liraglutide demonstrated significantly less hypoglycemia.[51] Postmarketing reports of pancreatitis have been documented in patients taking exenatide. A weak association of pancreatitis and liraglutide was noted in one study comparing glimepiride and liraglutide. Currently, there is no convincing data to suggest a clear cause and effect relationship. Liraglutide carries a black box warning for thyroid C-cell tumors, found in rodents exposed to the drug. It is recommended that liraglutide is not used in patients with a personal or family history of certain types of thyroid cancers.[34] Overall, studies with GLP-1 analogues demonstrated little effect on lipid parameters.[31]

Place in Therapy: As labeling suggests, the GLP-1 analogues are not recommended as first line agents but in the appropriate patients they can be a useful option for optimizing glycemic control while promoting weight loss. The ADA considers the GLP-1 analogues tier-2 agents, helpful for those patients experiencing hypoglycemia or in which weight loss is important. Additionally, they suggest that GLP-1 analogues be used in conjunction with lifestyle modifications and metformin.[2] The AACE/ACE recommends GLP-1 analogues as one of their preferred agents, after metformin, because of effectiveness and low risk of hypoglycemia, used alone or in a multi-drug treatment regimen. The AACE/ACE preferences the GLP-1 analogues over the DPP-4 inhibitors due to better postprandial glucose reductions and weight loss.[11] Animal studies suggest beta cell preservation and stimulation of beta cell proliferation, however, it is unknown if this can be expected in humans.[32]

Summary: The importance of glucose reducing microvascular complications has been demonstrated in multiple studies. New treatment options have been proven to lower HbA1c, but clear superiority has not been definitively proven over existing agents. The adverse event profiles of newer agents may offer some advantages compared to current therapies, however, post-approval surveillance is needed to determine long term effects and limitations. Additionally, head to head studies would further delineate the roles of these new therapies in diabetic patients.

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