Incretin-Based Therapies: What Do We Need To Know?

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Short Communication

According to the Canadian Diabetes Association, 2.7 million Canadians (~7.6% of population) were affected with diabetes in 2010 and these numbers will potentially rise to 4.2 million (~10.8% of population) in 2020 demonstrating the need to better control diabetes progression and ultimately lower the above statistics [1] (http://www.diabetes.ca/documents/get-involved/WEB_Eng_CDA_Report_.pdf).

It is essential to note that the progressive nature of type 2 diabetes requires the combination of lifestyle modification (diet and exercise) and antihyperglycemic agents in order to achieve adequate glycaemic control [2]. Recently, two therapeutic classes were introduced to the Canadian market to modulate incretin hormones (hormones released in the intestine in response to food intake) [3]. These two therapeutic classes are the glucagon-like peptide 1 (GLP-1) analogues and the dipeptidyl peptidase-4 (DPP-4) inhibitors, which are the focus of the present communication.

To date, two GLP-1 analogues are approved for use in Canada: liraglutide (victoza™ by Novo Nordisk) and exenatide (byetta™ by Eli Lilly). Similarly, two DPP-4 inhibitors are currently in use in Canada: saxagliptin (onglyza™ by Bristol-Myers Squibb Company and AstraZeneca) and sitagliptin (januvia™ by Merck Frosst). Both GLP-1 analogues and DPP-4 inhibitors stimulate insulin secretion, inhibit glucagon secretion in a glucose-dependent manner [4,5] and have a low risk of hypoglycaemia [6].

GLP-1 analogues differ from normal natural GLP-1 in that they are resistant to degradation by DPP-4 and therefore they have longer half life(s) (hours versus minutes) [7]. Distinctive features of GLP-1 analogues include their ability to induce significant weight loss (approximately 3 kg in a patient concurrently taking sulfonylurea or metformin) by suppressing food intake and gastric emptying [8], GLP-1 analogues improve systolic blood pressure and lipid profiles with superior efficacy to liraglutide over exenatide [6]. Nausea is the most common adverse effect with GLP-1 therapy and is reported in exenatide therapy more than in liraglutide therapy [6]. GLP-1 analogues are administered as subcutaneous injections (liraglutide 0.6-1.8 mg once daily without regards to meals, while exenatide is administered in 5-10 µg doses twice daily at anytime within the 60 minutes prior to the morning and evening meals).

DPP-4 inhibitors, on the other hand, prevent the degradation of endogenous incretins such as GLP-1, and thereby potentiate their actions [7]. DPP-4 inhibitors are very well tolerated weight-neutral medications that are taken orally once daily without regards to food (saxagliptin 5 mg once daily and sitagliptin 100 mg once daily).

Both GLP-1 analogues and DPP-4 inhibitors are used as monotherapy or in combination with metformin alone or together with sulfonylureas in patients with type 2 diabetes who do not achieve adequate glycaemic control. GLP-1 agonists if used as monotherapy lower A1C by 1% [9], while DPP-4 inhibitors monotherapy decreases A1C level by 0.7-1% [10]. When GLP-1 analogues are added to metformin therapy, an additional 0.4-0.8% reduction in A1C occurs with exenatide [6] and an additional 1-2% reduction in A1C occurs with liraglutide [11]. On the other hand, when DPP-4 inhibitors are added to the maximum tolerated dose of metformin, an additional 0.78% further reduction in A1C is achieved [12].

In conclusion, despite the better tolerability of DPP-4 inhibitors, GLP-1 analogues are superior in achieving significant weight loss and lower A1C levels. Of the GLP-1 analogues, liraglutide demonstrated superior efficacy, less nausea and less hypoglycaemia with once daily dosing.

References


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