Review: Incretin therapy improves glycemic control more than placebo in patients with type 2 diabetes

Amori RE, Lau J, Pittas AG. **Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis.** JAMA. 2007;298:194-206.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Endocrinology ★★★★★☆☆

QUESTION

In adults with type 2 diabetes, is incretin therapy effective and safe for glycemic control?

METHODS

Data sources: MEDLINE (1966 to May 2007), Cochrane Central Register of Controlled Trials (2007, Issue 2), conference abstracts (2005 to 2006), drug-prescribing documents, relevant Web sites, and bibliographies of relevant studies.

Study selection and assessment: English-language, randomized, controlled trials (RCTs) ≥ 12 weeks in duration that compared incretin therapy (glucagon-like peptide 1 [GLP-1] analogues or dipeptidyl peptidase 4 [DPP4] inhibitors) with a control (placebo or another hypoglycemic agent) in nonpregnant adults with type 2 diabetes and reported hemoglobin A_{1c} (HbA_{1c}) level as an outcome. 29 RCTs (n = 11 942, mean age range 51 to 59 y) met the selection criteria. 9 involved GLP-1 analogues, and 20 involved DPP4 inhibitors. Study quality assessment was based on group comparability at baseline, allocation concealment, intention-to-treat analysis, and loss to follow-up.

Outcomes: Change in HbA_{1c}. Secondary outcomes included change in weight, hypoglycemia, and other adverse events.

MAIN RESULTS

GLP-1 analogues. GLP-1 analogues reduced HbA_{1c} levels more than placebo and had higher rates of hypoglycemia; exenatide and insulin did not differ (Table). GLP-1 analogues caused more weight loss (Table) and gastrointestinal side effects than controls (nausea, relative risk increase [RRI] 192%, 95% CI 102 to 324; vomiting, RRI 232%, CI 151 to 341; and diarrhea, RRI 123%, CI 72 to 189). *DPP4 inhibitors.* DPP4 inhibitors reduced HbA_{1c} more than placebo but not as much as other agents (Table). Weight gain was greater with DPP4 inhibitors than placebo (Table).

CONCLUSIONS

In type 2 diabetes, incretin therapy is more effective than placebo for glycemic control; results of comparisons with other hypoglycemic agents are inconsistent. GLP-1 analogues are associated with weight loss and DPP4 inhibitors with weight gain.

Sources of funding: National Institute of Diabetes and Digestive and Kidney Diseases and Dr. Gerald J. and Dorothy R. Friedman New York Foundation for Medical Research.

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Incretin therapy (GLP-1 analogues or DPP4 inhibitors) vs control (placebo or other HGAs) in nonpregnant adults with type 2 diabetes*

Outcomes	Number of trials (n)	Comparisons	Weighted mean difference (95% CI)	I^2†
Change in HbA_{1c} level	6 (1285)	GLP-1 vs placebo	–1.0% (–1.1 to –0.8)‡	44%
	2 (1036)	Exenatide (GLP-1) vs insulin	–0.06% (–0.22 to 0.10)	59%
Weight change	8	GLP-1 vs control	–2.4 kg (–4.0 to –0.8)	98%
			RRI (CI)	NNH (CI)
Hypoglycemia	5 (1228)	Exenatide (GLP-1) vs placebo	130% (8 to 388)	11 (4 to 179)
	2 (1050)	Exenatide (GLP-1) vs insulin	2.0% (–54 to 126)	NS
			Weighted mean difference (CI)	I^2†
Change in HbA_{1c} level	16 (4190)	DPP4 vs placebo	–0.7% (–0.8 to –0.6)‡	77%
	4 (2899)	DPP4 vs HGAs	0.21% (0.02 to 0.39)§	66%
Weight change	13	DPP4 vs placebo	0.5 kg (0.3 to 0.7)	0%
			RRR (CI)	NNT (CI)
Hypoglycemia	20 (7311)	DPP4 vs control	3.0% (–86 to 50)	NS

*DPP4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1; HbA_{1c} = hemoglobin A_{1c}; HGAs = hypoglycemic agents; NS = not significant; other abbreviations defined in Glossary. RRR, RRI, NNT, NNH, and CI calculated from data in article. Data pooled using a random-effects model.
†I^2 represents low (25%), moderate (50%), and high (75%) heterogeneity among trials. ‡Favors incretin therapy. §Favors HGA.

COMMENTARY

GLP-1 increases the secretion of insulin and suppresses the secretion of glucagon; in pharmacologic doses, it delays gastrointestinal transit and decreases appetite. These effects, which counter abnormalities commonly found in patients with type 2 diabetes, have fueled the development of incretin-based therapies. Because the enzyme DPP4 degrades GLP-1 quickly (1), researchers have sought GLP-1 receptor agonists (e.g., exenatide) or modifications to GLP-1 that make the modified drug more resistant to DPP4 (e.g., liraglutide) (2). The "gliptins" inhibit DPP4, thus raising levels of GLP-1 and a similar hormone, glucose-dependent insulinotropic polypeptide (3).

The review by Amori and colleagues offers some interesting insights about the use of these medications in patients with type 2 diabetes. There has been some excitement about the potential for weight loss associated with use of GLP-1 receptor agonists, although on average, the magnitude of such losses is small. Furthermore, this class of medication is associated with a significant incidence of gastrointestinal adverse effects.

On the other hand, DPP4 inhibitors are essentially weight-neutral and are not associated with gastrointestinal side effects. Amori and colleagues rightly point out that, in clinical trials, DPP4 inhibitors were associated with an increased incidence of nasopharyngitis. Although this is a relatively minor symptom, it highlights potential concerns about the long-term safety of gliptins given the widespread distribution of DPP4 and its importance in immune surveillance (4, 5).

Clinicians and patients must temper their enthusiasm for the use of these medications because they are expensive and their glucose-lowering efficacy is similar to more established therapies for type 2 diabetes. Furthermore, in the absence of long-term safety data, use of incretin-based therapies should be weighed against the potential for harm.

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References

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