

Combination therapy of GLP-1 analogues and insulin: do the benefits outweigh the costs?

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In the current issue of *the Netherlands Journal of Medicine*, Van Velsen *et al.* describe a small trial showing the benefit of adding a GLP-1 analogue to insulin in obese patients with type 2 diabetes using the maximum allowed or tolerated dosages of metformin and a sulphonylurea derivative.¹ The study clearly shows how impressive results of adding a GLP-1 analogue to insulin can be: the patients lost on average 14.3 km of weight, the HbA1C decreased by 5.5 mmol/mol (0.5 %) and patients could lower the dosage of insulin used by on average 75 IU. Patients used either a once daily, a twice daily or a full basal insulin-bolus regime. A recent meta-analysis on a regime of basal insulin and a GLP-1 analogue in a total of 4348 participants in *The Lancet* showed similar although less outspoken results as those of Van Velsen *et al.*: patients had lost on average 3.2 kg at the end of the study and the HbA1C decreased by 0.44% (5 mmol/mol).²

As stated in the accompanying editorial in *The Lancet*, the very first study on GLP-1 analogues included patients on insulin.³ The lack of postprandial increase in blood glucose level was considered an artifact at first. Now, the combination of a GLP-1 analogue and insulin is more and more recognised as a potent strategy resembling normal physiology best. GLP-1 analogues simulate the incretin GLP-1 but are more resistant to degradation by dipeptidylpeptidase-4 (DPP-4): among other functions, they inhibit gastric emptying, stimulate post-prandial insulin secretion, increase satiety and suppress glucagon secretion.⁴ Another argument for adding a GLP-1 analogue to insulin when oral therapy is at maximum dosage would be a protective effect on preservation of beta cell mass. However, although in rodents decline in beta cell mass can be halted and possibly even increased by GLP-1 analogues, it is difficult to confirm this in human trials.^{5,6} A beneficial effect on beta cell *function* has been shown in smaller functional studies, but beta cell mass is difficult to assess.^{6,7}

The combination of GLP-1 analogues with insulin has been approved by the European Medicine Agency (EMA) and the American Food and Drug Administration (FDA), but is not reimbursed in all countries. In the Netherlands, for instance, GLP-1 agonists are currently only reimbursed in obese patients (body mass index (BMI) > 35 kg/m²) using metformin and a sulphonylurea derivative in the maximally tolerated dosage. The combination with insulin was reimbursed in the period after the introduction but redrawn in 2011. The Dutch Diabetes Patient Federation successfully fought this decision, enabling patients who already used this combination to continue. New prescriptions were no longer reimbursed. Recent studies including the meta-analysis in *The Lancet* might re-open this discussion.

Clearly, this discussion is about the balance between costs and (long-term) benefits: the efficacy of the combination therapy on HbA1C and especially body weight is clear, but at what price? Despite strictly limited use, the costs of GLP-1 analogues and DPP-4 inhibitors last year made up 68% of the total amount spent on non-insulin therapy for type 2 diabetes in the Netherlands.⁸ When considering translation of the combination of a GLP-1 analogue and insulin to daily practice, what would be most desirable would be to add a GLP-1 analogue to once daily insulin, possibly in a fixed-dose combination limiting the burden to one subcutaneous injection a day.^{3,9} Current studies showing promising results used a combination of liraglutide with insulin degludec, the most expensive insulin.¹⁰

Regarding the long-term benefits: first studies show that GLP-1 can be considered safe with regard to cardiovascular events and from *in vitro* and animal studies positive effects on cardiovascular outcomes are expected.^{11,12} However, long-term results on decreasing microvascular and macrovascular complications have to be awaited, for instance the results of the current placebo-controlled

LEADER trial on the effect of liraglutide on cardiovascular endpoints in 9340 diabetes type 2 patients.¹³

To conclude, adding a GLP-1 analogue to insulin treatment shows clear benefits by enabling weight loss and decreasing the need for insulin. Future fixed-dose combinations might reduce the burden for patients to one subcutaneous injection with long-acting insulin and GLP-1 analogue. It has to be decided what price is acceptable to reach these advantages. Knowledge on long-term benefits such as reduction in microvascular or macrovascular complications is clearly needed to take stock of the pros and cons.

REFERENCES

1. Van Velsen EF, Lamers J, Blok V, van Leendert RJM, Kiewiet-Kemperet RM. A prospective study of concomitant GLP-1 analogue and insulin use in type 2 diabetes in clinical practice. *Neth J Med*. 2014;10:523-7.
2. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. *Lancet*. 2014. [Epub ahead of print]
3. Young LA, Buse JB. GLP-1 receptor agonists and basal insulin in type 2 diabetes. *Lancet*. 2014. [Epub ahead of print]
4. Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metab*. 2013;17:819-37.
5. Xu G, Stoffers DA, Habener JF, Bonner-Weir S. Exendin-4 stimulates both beta-cell replication and neogenesis, resulting in increased beta-cell mass and improved glucose tolerance in diabetic rats. *Diabetes*. 1999;48:2270-6.
6. Lamont BJ, Andrikopoulos S. Hope and fear for new classes of type 2 diabetes drugs: is there preclinical evidence that incretin-based therapies alter pancreatic morphology? *J Endocrinol*. 2014;221:T43-61.
7. Bunck MC, Corner A, Eliasson B, et al. Effects of exenatide on measures of beta-cell function after 3 years in metformin-treated patients with type 2 diabetes. *Diabetes Care*. 2011;34:2041-7.
8. Statistics DfFp. Meer kosten voor nieuwe diabetesmiddelen. *Pharmaceutisch Weekblad*. 2013;148:44.
9. Buse JB, Vilsboll T, Thurman J, et al. Contribution of Liraglutide in the Fixed-Ratio Combination of Insulin Degludec and Liraglutide (IDegLira). *Diabetes Care*. 2014;37:2926-33.
10. Gough SC, Bode B, Woo V, et al. Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naïve patients with type 2 diabetes. *Lancet Diabetes Endocrinol*. 2014. [Epub ahead of print]
11. Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular risk: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab*. 2014;16:38-47.
12. Saraiva F, Sposito AC. Cardiovascular effects of Glucagon-like peptide 1 (GLP-1) receptor agonists. *Cardiovasc Diabetol*. 2014;13:142.
13. Steinberg WM, Nauck MA, Zinman B, et al. LEADER 3-Lipase and Amylase Activity in Subjects With Type 2 Diabetes: Baseline Data From Over 9000 Subjects in the LEADER Trial. *Pancreas*. 2014;43:1223-31.