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Addition of incretin therapy to metformin in type 2 diabetes

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Incretin-based therapies offer a new approach for the management of type 2 diabetes, with a mechanism of action distinct from any existing class of glucose-lowering agents.[1] These drugs improve the body's ability to control blood glucose by increasing active concentrations of glucagon-like peptide-1 (GLP-1). Two approaches have been used to enhance the action of GLP-1. First, incretin mimetics (exenatide) or analogues (liraglutide) act as agonists at the GLP-1 receptor to mimic the effect of endogenous GLP-1, but are resistant to degradation by dipeptidyl peptidase-4 (DPP-4). Second, drugs that specifically inhibit DPP-4 (sitagliptin, vildagliptin, saxagliptin) are used to increase the half-life of endogenous GLP-1 that is secreted in response to food intake. Both approaches have proven efficacy for reducing the concentration of glycosylated haemoglobin (HbA_{1c}), without inducing severe hypoglycaemic episodes or promoting weight gain.[1] The drugs can be used alone or in combination with other oral glucose-lowering agents, such as metformin, sulphonylureas, andthiazolidinediones.

Almost all published randomised trials of incretin therapies compared the new compound with a placebo or a reference glucose-lowering agent, but head-to-head comparisons between two incretin-based therapies are scarce. Onetrial compared 1.8 mg liraglutide once daily with 10 µg exenatide twice daily, and showed greater efficacy and better tolerance with liraglutide.[2] 2 mg exenatide (longacting release) once weekly was more effective and bettertolerated than 10 µg exenatide twice daily.[3] No long-term comparisons of GLP-1 receptor agonists with DPP-4 inhibitors have been published, except in abstract form.[4] Therefore evidence is lacking to clearly position GLP-1 receptor agonists versus DPP-4 inhibitors after failure to manage type 2 diabetes with metformin.[5]

Thus Richard Pratley and colleagues' 26-week, randomised, parallel-group, open-label trial,[6] published in *The Lancet* today, is of great interest. Added to metformin, 1.2 mg and 1.8 mg liraglutide once daily significantly improved blood glucose control (change in HbA_{1c} from baseline: -1.24%, 95% Cl -1.37 to -1.11 for 1.2 mg; -1.50%, -1.63 to -1.37 for 1.8 mg) versus 100 mg sitagliptin once daily (-0.90%, -1.03 to -0.77; $p<0.0001$ for both comparisons). Furthermore, reductions in bodyweight were greater with 1.2 mg and 1.8 mg liraglutide (-2.86 kg, -3.39 to -2.32 for 1.2 mg; -3.38 kg, -3.91 to -2.84 for 1.8 mg) than with sitagliptin (-0.96 kg, -1.50 to -0.42; $p<0.0001$ for both comparisons). These results confirm previous reports of either liraglutide[2,7] or sitagliptin[8-10] in patients with type 2 diabetes that was not well controlled with diet and metformin. Further, similar findings were recorded with exenatide twice daily,[3,11] exenatide (longacting release) once weekly,[2-4] and DPP-4 inhibitors vildagliptin[12] and saxagliptin[13] (table).

Findings from today's study show the superiority of 1.8 mg versus 1.2 mg liraglutide for reduction of HbA_{1c}, butthis result has not been recorded in previous studies (table).[7] Only the 1.8 mg dose of liraglutide was assessed in LEAD-6,[2] in which liraglutide once daily was shown to be superior to 10 µg exenatide twice daily for reduction of HbA_{1c}. Therefore 1.2 mg liraglutide should be considered as the starting dose in most patients with type 2 diabetes, with recommendations for titration up to 1.8 mg if target HbA_{1c} concentrations are not reached. However, no study has been published in which patients who were insufficiently controlled on 1.2 mg liraglutide had a significant improvement in glucose control from an increased dose of 1.8 mg liraglutide.

The superiority of liraglutide versus sitagliptin for blood glucose control and weight reduction was probably due to increased circulating concentrations of the GLP-1 agonist, leading to different pharmacological effects, as shown with exenatide.[14] Even though Pratley and colleagues recorded superior treatment satisfaction with 1.8 mg liraglutide than with sitagliptin, the gastrointestinal tolerance profile is better with sitagliptin than with liraglutide, and one pill of sitagliptin daily might be judged as easier to administer than one subcutaneous injection of liraglutide daily. The increased cost of liraglutide should be compared with the benefit provided by improved glucose control and weight reduction.

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Table: *Main randomised trials assessing efficacy of DPP-4 inhibitors or GLP-1 receptor agonists in patients with type 2 diabetes who had inadequate glycaemic control on metformin*

	Number of patients	Study duration (weeks)	Baseline HbA_{1c}	Reduction in HbA_{1c}*	Reduction in bodyweight (kg)*
DPP-4 inhibitors					
100 mg sitagliptin once daily					
Charbonnel et al (2006)[8]	464	24	7.96%	-0.67%	-0.70
Scott et al (2008)[9]	94	18	7.70%	-0.73%	-0.40
Nauck et al (2007)[10]	588	52	7.40%	-0.67%	-1.50
Bergenstal et al (2009)[4]	166	26	8.50%	-1.00%	-0.90
Pratley et al (2010)[6]	219	26	8.5%	-0.90%	-0.96
50 mg vildagliptin twice daily					
Ferrannini et al (2009)[12]	1396	52	7.30%	-0.44%	-0.20
5 mg saxagliptin once daily					
De Fronzo et al (2009)[13]	191	24	8.10%	-0.68%	-0.87
GLP-1 agonists					
10 μg exenatide twice daily					
De Fronzo et al (2005)[11]	113	30	8.18%	-0.78%	-2.8
Drucker et al (2008)[3†]	147	30	8.30%	-1.50%	-3.6
Buse et al (2009)[2‡]	231	26	8.20%	-0.79%	-2.87
2 mg exenatide (longacting release) once weekly					
Drucker et al (2008)[3§]	148	30	8.30%	-1.90%	-3.70
Bergenstal et al (2009)[4]	160	26	8.50%	-1.55%	-2.70
1·2 mg liraglutide once daily					
Nauck et al (2009)[7]	100	26	8.30%	-1.10%	-2.60
Pratley et al (2010)[6]	221	26	8.4%	-1.24%	-2.86
1·8 mg liraglutide once daily					
Nauck et al(2009)[7]	100	26	8.40%	-1.00%	-2.80
Buse et al (2009)[2‡]	233	26	8.20%	-1.12%	-3.24
Pratley et al (2010)[6]	218	26	8.4%	-1.50%	-3.38

*Result at end of follow-up (intention to treat, last observation carried forward) versus baseline. †34% of patients on metformin alone. ‡27% of patients on metformin alone. §38% of patients on metformin alone.

Some important information is still unknown, but could help clinicians to choose the best incretin therapy to manage type 2 diabetes after failure with metformin. We do not know how the efficacy of GLP-1 receptor agonists versus DPP-4 inhibitors will vary long term during the progressive decline in β-cell function that is responsible for loss of glucose control, and the development and progression of chronic diabetic complications. Long-term safety also remains an open question. In our opinion, the range of type 2 diabetes is so heterogeneous that treatment probably needs to be tailored to individuals ratherthan strictly standardised.[5] Such an approach would need to take into consideration all biological, clinical, and psychosocial characteristics of every patient.

AJS and CHU Sart-Tilman have received fees for AJS's consulting on international advisory boards from Sanofi-Aventis and AstraZeneca/Bristol-Myers Squibb, and on national advisory boards for AstraZeneca/Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novo Nordisk, Sanofi-Aventis, and Novartis. AJS has received honoraria for participating in speakers' groups and expenses for travel and accommodation from AstraZeneca/Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novo Nordisk, Sanofi-Aventis, and Takeda. RPR has received honoraria for participating in speakers' groups from Novo Nordisk, Novartis, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Sanofi-Aventis, and Takeda; and has received expenses for travel and accommodation from Novo Nordisk, AstraZeneca/Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, and Sanofi-Aventis. CHU SartTilman has a grant pending from Novo Nordisk, and has received fees for RPR's consulting on national advisory boards.

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