Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Type 2 diabetes: concerns raised over possible pancreatic adverse effects of incretin-based therapies

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A study has suggested an increased risk of pancreatitis and pancreatic duct metaplasia in people with type 2 diabetes treated with incretin-based therapies. The European Medicines Agency has investigated these findings but has concluded that there are no new concerns for incretin therapies on the basis of available evidence. Healthcare professionals should continue to prescribe these agents in line with the Summary of Product Characteristics and NICE guidance.

Overview and current advice

Incretin-based therapies mimic or enhance the effects of glucagon-like-peptide 1 (GLP-1). GLP-1 is a hormone-like peptide that is released by the intestine in response to a meal. GLP-1 acts by stimulating insulin secretion, suppressing glucagon secretion, inhibiting gastric emptying, and by reducing appetite and food intake. Following secretion, GLP-1 is quickly inactivated by an enzyme, dipeptidyl peptidase-4 (DPP-4). Incretin-based therapies are either injected analogues that are not inactivated by DPP-4 (exenatide, liraglutide and lixisenatide) or oral drugs that inhibit DPP-4 (linagliptin, saxagliptin, sitagliptin and vildagliptin).

Incretin-based therapies have been associated with a risk of developing acute pancreatitis (see the relevant Summaries of Product Characteristics). Recently, concerns have been raised about a possible increased risk of precancerous cellular changes called pancreatic-duct metaplasia.

New evidence

A post-mortem study of pancreatic tissue has raised concerns about possible adverse effects on the pancreas associated with incretin-based therapies. The researchers looked at tissue from 20 age-matched organ donors who, in life, had type 2 diabetes treated with incretin-based therapy (sitagliptin or exenatide, n=8) or other therapy (n=12); and 14 controls who did not have diabetes. Those treated in life with incretin-based therapy had increased pancreatic...
mass, including increased exocrine cell proliferation and dysplasia, compared with the other people who had had diabetes, and the controls.

An investigation, editorial and feature in the British Medical Journal recently discussed the safety concerns around incretin-based therapies. These have been supported by some but criticised by others in readers’ rapid responses and in letters to the journal by Holt, Barnett and O’Hare (see reply by the BMJ’s investigations editor) and Novo Nordisk (manufacturer of liraglutide).

Commentary provided by the NICE Medicines and Prescribing Centre:

Effects on the pancreas were identified as a possible risk for the incretin-based therapies during their initial evaluation, and rare cases of pancreatitis have been reported. The potential increased risk of pancreatitis is already known (see Drug Safety Update March 2009 and September 2012) and warnings are included in the product information for all incretin-based therapies.

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has finalised its review of this issue. The CHMP concluded that presently available data do not confirm recent concerns over an increased risk of pancreatic adverse events with these medicines. Following a review of the publication and consultation of a panel of experts, the CHMP considered that the study itself had a number of methodological limitations and potential sources of bias, most importantly differences between the studied groups with respect to age, gender, disease duration and treatments, which preclude a meaningful interpretation of the results. The CHMP also considered after a review of all available non-clinical and clinical data that there is no change in evidence regarding the risks of pancreatic adverse events associated with the use of incretin-based therapies.

With regard to pancreatic cancer, the CHMP concluded that data from clinical trials do not indicate an increased risk with these medicines. However, the number of events is too small to draw final conclusions. The manufacturers of these medicines are closely monitoring for adverse effects, including effects on the pancreas, and report their findings regularly to the EMA for assessment. Several studies are planned or ongoing, and 2 large independent studies have been under way since 2011 to study the risk profile of diabetes treatments in general, and more specifically their risk profile in relation to the pancreas. First results of these studies, which are funded by the European Commission, are expected in the spring of 2014.

NICE recommends that sitagliptin, vildagliptin, exenatide and liraglutide 1.2 mg daily may be considered in specific circumstances as part of dual therapy and triple therapy for type 2 diabetes. For more information see Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87; currently being updated), exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes (NICE technology appraisal guidance 248) and liraglutide for the treatment of type 2 diabetes mellitus (NICE technology appraisal guidance 203). The NICE Pathway: diabetes brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

Sitagliptin, vildagliptin, linagliptin and saxagliptin, exenatide, lixisenatide and liraglutide will be included in the update of the NICE clinical guideline for the management of type 2 diabetes. TA 203 and TA 248 will be withdrawn once this guidance is updated. The publication date for this guideline is to be confirmed. The NICE Evidence summary: new
medicine on lixisenatide is currently being updated and is expected to be published in September 2013.

References
2. EMA (2013). Investigation into GLP-1-based diabetes therapies concluded [online, accessed 15 August 2013]

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