



Association of British Clinical Diabetologists

ABCD position statement on GLP-1 based therapies and pancreatic damage

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Summary

- A recent “joint investigation by the BMJ and Channel 4’s Dispatches current affairs programme” has brought widespread attention to the possibility that GLP-1 based therapies may cause pancreatic damage.
- A plausible mechanism has been proposed by which GLP-1 based therapies might lead to pancreatitis and even pancreatic cancer. The animal data behind this mechanism is inconsistent and the human histological data is preliminary and open to alternative explanations. Nevertheless a cautious approach would seem reasonable.
- The single observational study in support of the hypothesis that GLP-1 based therapies cause pancreatitis is open to criticism and is not supported by other such observational studies.
- Results from studies involving adverse events reporting systems cannot be relied upon because of “notoriety bias”.
- In the ABCD nationwide audits of GLP-1 receptor agonists (GLP-1RAs) in real clinical use in the UK, use of these agents was associated with improvements in glycaemic control and weight and reduction in other diabetes therapies in particular insulin. Alongside this there were very few reports of pancreatitis and 75% of these had an alternative explanation.
- GLP-1RAs reduce all the major risk factors for cardiovascular disease. Meta-analyses of existing RCTs involving DPP4 inhibitors suggest significant reductions in major cardiovascular events alongside no increase in pancreatitis or cancer. The eight, long-term, cardiovascular safety studies should clarify the issue with regard to risk and benefits of GLP-1 based therapies as they will record not only cardiovascular outcomes but also information on pancreatitis, pancreatic cancer and thyroid cancer.
- The strength of the data in support of GLP-1 based therapies causing pancreatic damage does not justify the alarm that has been caused to patients taking these therapies. By stopping these agents in response to the scare that has been created, harm to patients may occur because of the discontinuation of the agents in whom they were working well.
- Pharmaceutical companies should make all relevant data available for inspection by independent experts.

Introduction

On June 10th 2013 a documentary was broadcast on British television, “Channel 4 Dispatches - Diets, Drugs and Diabetes”. This was followed the same week by a feature article in the British Medical Journal (BMJ) (1) along the same lines. Both the television programme and the article gave evidence raising the possibility that glucagon-like-peptide 1 (GLP-1)-based therapies may be associated with pancreatitis and pancreatic cancer, both implying that this possibility had been underplayed. This feature was one of five items (1-5) on the subject in the issue of the BMJ concerned and the upshot was that the evidence against GLP-1 based therapies was considered sufficient to the extent that “after reflection most patients and clinicians may opt to avoid using GLP-1 based drugs at all, or to avoid them early in the disease or for long periods” (2,5). The subject has been covered in two previous issues of the BMJ this year (6-8). The television documentary, in particular, caused alarm to many patients in the UK who saw it with many patients phoning and attending for advice and discontinuing their therapy and refusing to re-start. ABCD has studied the data which has led to the television documentary and the BMJ articles and also much other data of relevance which was not mentioned in the “joint investigation by the BMJ and Channel 4’s Dispatches current affairs programme” (3).

A plausible mechanism by which GLP-1 based therapies could cause pancreatic damage

Butler and colleagues have proposed a case for a plausible mechanism to explain the proposed increased risk of pancreatitis (9). Some animal studies have shown pancreatic acinar and ductal proliferation in response to GLP-1 therapy with an increase in pancreatic weight. The possibility has been raised that pancreatic “duct proliferation might lead to duct occlusion, occlusion would generate back pressure, and back pressure would stress acinar cells thereby activating and releasing the digestive enzymes that they contain - a well-established causal mechanism for pancreatitis” (9). Furthermore there are concerns that the acinar and ductal proliferation could lead to metaplasia and the possibility of predisposition to pancreatic cancer. A study of the pancreases of organ donors who had received and who had not received GLP-1 based therapies found that in those treated with GLP-1 based therapies there was enlargement of the pancreas with increased exocrine pancreas proliferation,

an increase in the number of pre-malignant lesions, marked alpha cell hyperplasia with potential for evolution into neuroendocrine tumours (9,10).

Uncertainty in the animal and autopsy data

Nauck has pointed out that the changes described in animal studies are not found in all such studies, with different GLP-1 based therapies and use in different species leading to differing results (11). Nevertheless in view of concerns from some studies (9), a cautious approach would seem prudent. Further consideration by Khan of the data with regard to human donor pancreases revealed a number of alternative explanations for the findings (12). For example he pointed out that the patients with diabetes who did not receive GLP-1 based therapies were a much younger age, had greater use of insulin and, with two dying with diabetic ketoacidosis, he raised the possibility that the diabetic controls included some type 1 diabetes patients (12). Both Khan and Nauck pointed out that the changes could have been due to pre-terminal state of the patients (11,12). With regard to the suggestion that GLP-1 based therapies may lead to chronic pancreatitis and pancreatic cancer, they pointed out that after “the millions of patient years of exposure to these agents” one might have expected by now to have seen more reported cases with substantial evidence implicating the GLP-1 based therapies (11,12). Nevertheless the millions of years of exposure are mainly for a relatively short time and as cancers may take years to develop, a cautious approach would again seem prudent.

Uncertainty in other data

A single observational study suggested a doubling of risk of acute pancreatitis with some GLP-1 based therapies (13). Because GLP-1 receptor agonists are associated with reducing weight and DPP4 inhibitors are weight neutral the patients selected for these therapies are likely to be different from those selected for other diabetes therapies such as sulphonylureas, pioglitazone or insulin all of which are associated with weight increase. In this observational study it is therefore difficult to conclude from comparisons between patients treated with GLP-1 based therapies and those not so treated.

Type 2 diabetes patients with obesity are not only more likely to get GLP-1 based therapies but, as obesity is associated with gall bladder disease and hypertriglyceridaemia, they are also more likely to have these, both of which are risk factors for acute pancreatitis (14-17). The authors found obesity, gall bladder disease and hypertriglyceridaemia were all increased in their pancreatitis cases and they attempted to adjust for these confounders using multivariate analysis (13). Because patients treated with GLP-1 based therapies are, through the process of selection for treatment-type, fundamentally different from those not so treated, like is not being compared with like, and no amount of adjustment for confounders can create matching samples (18). Caution needs to be exercised therefore, over making conclusions based on such a multivariate analysis. Others have suggested weaknesses of this study and pointed out that several other such observational studies have not found an association between pancreatitis and GLP-1 based therapies (11).

Two studies looking at reports of pancreatitis in the US food and drug administration adverse events reporting system have found increased patients reported as having pancreatitis on some GLP-1 based therapies compared to those on older therapies (8,19,20). However, such studies cannot be relied upon because of “notoriety bias” (21).

ABCD nationwide audits of GLP-1 receptor agonists (GLP-1RAs)

ABCD has data from two nationwide audits of exenatide and liraglutide in real clinical use in the UK. From these we know that in the UK patients treated with these agents tend to be very overweight (in keeping with higher risk of acute pancreatitis) with very poor glycaemic control (22,23). In the exenatide audit the occurrence of acute pancreatitis was specifically asked about at follow up. In the liraglutide audit “any possible side effects” were asked for.

In association with use of GLP-1RAs in these audits HbA1c reduced at 6 months on average by between 0.75% and 0.93%, and weight by between 3.7 kg and 6.5kg (23), and there was also reduction in other diabetes therapies in particular insulin (24,25).

The total incidence of definite or possible reported pancreatitis in the audits were 0.120 and 0.108 cases per 100 patient years of exposure in the exenatide (26) and liraglutide (27) audits respectively. The audits had the strength that they allowed detailed information about reported cases to be obtained – contributors to the audit reporting the cases were contacted and full detail obtained from the hospital notes. It was noteworthy that in most reported cases there were other causes for the pancreatitis, in particular gallbladder disease alcoholism and hypertriglyceridaemia (26,27). After this detailed investigation of each reported case, the exenatide audit (6717 patients) and the on-going liraglutide audit (6010 patients as of 1 July 2013) each had one unexplained case representing incidences of unexplained pancreatitis in the ABCD audits of 0.030 and 0.027 cases per 100 patient years of exposure to exenatide (26) and liraglutide respectively (27). It should also be borne in mind that many cases of acute pancreatitis are “idiopathic” (16,17) so the GLP-1 receptor agonists (GLP-1RAs) do not necessarily have to be invoked even in the cases without another explanation.

Long-term cardiovascular safety studies

Diabetes substantially increases the risk of major cardiovascular complications (28,29) such that most patients with diabetes die with cardiovascular disease (30). Therefore the potential impact of any therapy on the threat of cardiovascular disease needs to be taken into consideration when the risks and benefits of that therapy are being discussed. Studies have shown that GLP-1RAs reduce all the major risk factors for cardiovascular disease (31-33). Meta-analyses of RCTs involving DPP4 inhibitors suggest that these may be associated with reduced risk of major adverse cardiac events (34,35) without increased risk of cancer or pancreatitis (34), though these results should be interpreted with caution because the trial durations were short. There are currently eight long-term cardiovascular safety studies on-going (12). These should clarify the issue with regard to risk and benefits of GLP-1 based therapies as they will record not only cardiovascular outcomes but also information on the putative risks of GLP-1 based therapies such as pancreatitis, pancreatic cancer and thyroid cancer.

The top line result from the first to report, the RCT with saxagliptin (study name SAVOR-TIMI-53), has already been released and showed that saxagliptin “met the primary safety objective of non-inferiority, and did not meet the primary efficacy objective of superiority, for a composite endpoint of

cardiovascular death, non-fatal myocardial infarction or non-fatal ischaemic stroke, when added to a patient's current standard of care (with or without other anti-diabetic therapies), as compared to placebo. These preliminary SAVOR-TIMI-53 data are being analyzed and the study results will be submitted to the European Society of Cardiology (ESC) for potential presentation at the ESC Congress in September" (36). Thus it is likely that in September 2013 we will have the detail of safety data with regard to the DPP4 inhibitor, saxagliptin, in particular with regard to pancreatitis. The other studies as they follow, and if necessary meta-analysis of them, should clarify further the issues of risks and benefits.

Alarm to patients

Whilst it is legitimate for the Dispatches TV programme and the accompanying BMJ article to raise concerns about the issues concerning non-disclosure of pharmaceutical companies, it is to be regretted that in the process of doing this, they should cause such alarm amongst patients in view of the questionable strength of the data in support of the safety concerns raised. ABCD has received reports from many clinical teams throughout the UK reporting alarmed patients phoning or attending for reassurance (by June 28th 2013, 34 centres had contacted ABCD to report this), patients discontinuing their GLP-1 based therapies (by June 28th 2013, 17 centres had reported this to ABCD). Sudden discontinuance of therapy is a significant safety concern to patients and results in a rise of patients requiring to be put on insulin. It is particularly disappointing that the "joint investigation by the BMJ and Channel 4's Dispatches current affairs programme" (3) has chosen to raise this alarm at this time when the data from long-term safety studies, including pancreatitis, will be available so imminently. It is reassuring that the regulators seem more balanced in their view and have not issued any warnings prior to review of all data, and indeed the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has finalised a review of GLP-1 based diabetes therapies and concluded that there were "no new concerns for GLP-1 therapies identified on the basis of available evidence" (37).

Commercial secrecy

Perhaps the major concern in the recent BMJ articles (1-5) and the Dispatches television programme was over whether pharmaceutical companies disclose in full the evidence involving the risks of their agents. ABCD fully supports the notion that pharmaceutical companies should make all their data available for inspection by independent experts.

Conclusions

The American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) and the International Diabetes Federation (IDF) have recently produced joint recommendations regarding GLP-1 based therapies, pancreatitis and pancreatic cancer (38). Based on assessment of the same evidence as considered here by ABCD, they have concluded that “at this time, there is insufficient information to modify current treatment recommendations”. ABCD fully supports this position. All therapies for diabetes have risks, but when considering the risks of therapies for diabetes it should be remembered that uncontrolled diabetes itself carries considerable risks. GLP-1 based therapies have been shown to decrease HbA1c and to reduce weight (GLP-1RAs) or to be weight neutral (DPP4 inhibitors) It seems likely that these changes would produce clinical benefit in the longer term, though this has not as yet been proven.

Whilst regulatory bodies digest the existing data and that to be released over the next 6-12 months, and beyond, there is a need for diabetes specialist teams to deal with the immediate concerns from patients unleashed by the media coverage and offer balanced advice. Montori in the BMJ (5) concludes that after reflection most doctors and clinicians may wish to avoid using these drugs at all or to avoid them early in the disease or for long periods. ABCD suggests that this advice is inappropriate at present. We do however suggest that clinicians review patients on these therapies and ensure that the choice to start them over traditional therapies was based on sound therapeutic and patient centred goals, and that reasonable benefits have been achieved; this being a maxim that can be applied to any newer treatment.

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Conflict of interest statements

REJR has received speaker fees, consultancy fees and/or educational sponsorship from a number of companies including in alphabetical order, Bristol Myers Squibb / Astra Zeneca Alliance, Eli Lilly, GlaxoSmithKline, Novo Nordisk, Sanofi-Aventis and Takeda.

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SR has declared no conflict of interests

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