Gastroenterology
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6 March 2011
Ref.: KsHJ/KBF/MKT

Potentially damaging controversial analysis to be published in Gastroenterology

Dear Professor Rustgi,

It has come to our attention that the manuscript *Incidence of Pancreatitis and Cancer Among Patients Given Glucagon Like Peptide-1 Based Therapy* by Michael Elashoff, Aleksey V. Matveyenko, Belinda Gier, Robert Elashoff and Peter C. Butler has been accepted for publication and is available online as Article in Press.

We have considerable concern about the publication of results and conclusions from analysis based on the USFDA post-marketing safety surveillance database despite USFDA cautioning drawing conclusions from such analysis. The hypothesis is driven by speculation from case reports and from results in few genetically manipulated rodents, which have not been confirmed by the extensive randomized controlled trials or preclinical programs conducted by Novo Nordisk and other companies developing therapies based on incretin physiology – evidence which has been extensively reviewed by FDA. Elashoff et al do not provide a balanced review of this existing evidence base in their hypothesis, their article contains much speculation and draws conclusions from data that the FDA cautions is not intended for use in drawing inferences about adverse event rates. We believe the same rigour is required in assessment of data from clinical experience as has been applied in the approval process. Evidence from randomized controlled clinical trials and matched cohort studies need to be part of any risk assessment, and this evidence was ignored by Elashoff et al.

The manuscript by Elashoff et al reports an analysis of the USFDA Adverse Event Reporting System (AERS) data on post-marketing safety surveillance. Based on the

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results of the analysis the study reports the odds ratio for pancreatitis is increased 6 fold with exenatide and sitagliptin compared to a selection of oral anti-diabetic medications and that the findings are significant ($p<0.0000000000000002$). Also both pancreatic cancer and all other cancers are reported to be similarly significantly increased. The authors conclude that the findings are consistent with case reports and animal studies.

According to FDA[1] the voluntary reporting system collecting reports from health care professionals and consumers alike and is used by FDA to monitor new safety concerns and is reviewed by FDA. FDA highlights that due to several factors, the AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

It is surprising that Elashoff et al find a six fold increase in cases of pancreatitis. In order to seek regulatory approval of liraglutide (Victoza®), Novo Nordisk completed the largest clinical phase 3a programme ever conducted for a diabetes drug. Despite some studies and extension arms being non-blinded no significant differences in the risk of pancreatitis were observed in any studies as well as in meta-analysis of all trials performed in total in 4600 patients treated with liraglutide.

In the conclusion Elishoff et al state that the findings are consistent with case reports and animal findings, however we believe this conclusion is strongly biased as Elishoff et al are referring to 2 small animal studies. One study is from the authors own group using a genetically modified human amyloid rat model which is not available for other groups to use and whose human relevance is unknown. Also, the study uses only sitagliptin only, and no attempt was apparently made to document increased GLP-1 in this animal model[23]. However, the authors ought to also have mentioned that other animal studies contradict these findings. A study published in Diabetes studied sitaglipin, exenatide and liraglutide in mice. Liraglutide and exenatide actually induced an anti-inflammatory response in the exocrine pancreas; sitagliptin had no effect, and even in a chemically induced model of pancreatitis was there no effect of exenatide[4]. Also, a recent study examined exenatide in numerous animal models, including several well know models of diabetes, and showed no signs of pancreatitis[5].

Novo Nordisk has as part of toxicology testing performed extensive animal studies using a very high number of animals investigating the potential existence of pancreatitis. No animals had a macroscopically identified pancreatitis, and very few animals had microscopically identified pancreatitis without any clear relationship to vehicle and liraglutide dose.

MICE	Male					Female				
Liraglutide (mg/kg/day)	0	0.03	0.2	1.0	3.0	0	0.03	0.2	1.0	3.0
No. examined	79	67	67	67	79	79	67	66	66	76
No. with microscopic pancreatitis	3	2	1	1	1	0	3	3	3	3

RATS	Male				Female			
Liraglutide (mg/kg/day)	0	0.075	0.25	0.75	0	0.075	0.25	0.75
No. examined	50	50	49	50	50	50	50	50
No. with microscopic pancreatitis	0	0	0	0	0	0	0	0

MONKEYS	Male			Female		
Liraglutide (mg/kg/day)	0	0.25	5	0	0.25	5
No. examined	5	5	5	5	4	5
No. with microscopic pancreatitis	0	0	0	0	0	0

[6]

Mice and rats dosed for 2 years. Monkeys dosed for 87 weeks.
Doses correspond to up to 36 and 60 fold human doses.
No animals had macroscopic pancreatitis.

Furthermore, going back to human analysis, Elashoff et al do not mention that the results are in contrast to database analysis performed on healthcare claims databases and research databases which are scientifically better suited for exploring hypothesis. In these studies no differences has been found between sitagliptin/exenatide and other diabetic therapies in terms of risk of developing pancreatitis[7][8][9][10] .

The incretin therapies have been a valued addition to the diabetes treatment options in providing efficacious glucose normalisation, weight loss or no increase in weight as opposed to most other diabetic therapies and importantly a very low risk of drug induced hypoglycaemia. In clinics worldwide patients continue to face challenges in achieving and maintaining appropriate glucose control and increased concern amongst patients and health care providers about the safety of available drug options will lead to further deterioration of public health.

Novo Nordisk welcomes pharmacovigilance to ensure the safety of people with diabetes, but conclusions on safety concerns must be sufficiently documented in order not to have unfortunate effects on medical practice and therapy acceptance.

In 1998 Wakefield et al[11] published an infamous manuscript in The Lancet. The publication stood for extended time despite immediate concerns raised on the validity

of conclusions. Understandable, but inappropriate, public scare about MMR vaccinations lead to deterioration of public health and discredit to the scientific community.

On March 4th a position statement[12] was issued by the German Diabetes Society, DDG, and DiabetesDE stating new initiations on therapies with GLP-1 receptor agonists and DPP-4 inhibitors should only take place in very special circumstances and that all patients currently treated with these drugs should be informed about the findings to appear in Gastroenterology.

We would like to inform you as Editor-in-Chief of Gastroenterology that we have performed an initial analysis aimed to confirm the results presented by Elashoff et al. We agree with the Elashoff et al manuscript that bias is a concern if there is a public awareness of a potential side-effect. Therefore we have solely aimed to confirm the part of the analysis investigating the period before 2007 where FDA warned about a potential increase in pancreatitis cases in exenatide treated patients.

Unfortunately, the Elashoff et al publication does not reveal sufficient details about the analysis to assure it is repeated precisely. In our initial analysis, we have however used the exact same definitions of case / control groups and case / control events and otherwise simplisticly counted events observed in connection with either drug and counted identically for both exenatide and control drugs.

Elashoff et al	Exenatide	Control drug
Pancreatitis event	148	17
Control event	634	320

OR=4.39 (p<0.0000000001)

Novo Nordisk	Exenatide	Control drug
Pancreatitis event	89	79
Control event	870	727

OR=0.94 (p=0.77)

There are clear discrepancies between our initial confirmatory analysis and those of Elashoff et al which we are not able to explain.

On behalf of Novo Nordisk, in order to ensure the most optimal guidance to patients and public reaction, we would urge Gastronenterology to withhold the publication of Elashoff et al until it has been confirmed by an independent statistical analysis.

Dr. Kirstine Brown Frandsen, MD, Corporate Vice President of Global Medical Affairs (kbf@novonordisk.com, +45 30791124) will be standing by for further information or dialogue. Please feel free to contact us.

Best regards,

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[7] Dore et al. Curr Med Res Opin 2009;25:1019-27

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