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Metformin, hot topic in cancer research

Richard Philip

Metformin, predominantly given as a first-line drug for type 2 diabetes, is now causing a stir in the area of cancer research.

Epidemiological studies have shown that diabetics treated with the drug have their cancer rate reduced by roughly half compared to the general population.

"Cancer epidemiologists pay a lot of attention when we see that kind of a finding and try to prove that it's an artifact or that there was some kind of mistake because reduction of cancer mortality by 50 percent is really something that we've never seen before as a consequence of any prevention strategy," said Professor Michael Pollak, a professor in the departments of medicine and oncology at McGill University, Montreal, Quebec, Canada.

He cautioned that it is still too early to jump to any conclusions because all the data that metformin reduces cancer risk or cancer mortality are retrospective and not from prospective randomized controlled trials, and hence cannot be regarded as formal proof.

Laboratory studies, however, have supported the epidemiological findings. In one study, mice that were given tobacco carcinogens had a reduced chance of having lung cancer if they had been pretreated on an ongoing basis with metformin, Pollak stated.

Further studies are being carried out to determine if metformin can reduce cancer in non-diabetics.

In the treatment of diabetes, metformin fundamentally acts in the liver where it leads to the activation of AMP-activated protein kinase (AMPK), a key regulator of lipid and glucose metabolism. This results in reduced glucose secretion by the liver and as a consequence of this, insulin levels fall.

Scientists have hypothesized that metformin's insulin reduction may be responsible for the inhibition of the subset of cancers whose growth is stimulated by insulin.

Because cancer cells also contain AMPK, there is a question as to whether metformin could act directly on tumor cells and have value even in non-diabetics, Pollak said.

But for this theory to be plausible, scientists will have to know the proper concentration of metformin that should be in the tumor for a cancer reduction effect to occur.

Metformin is taken orally and accumulates preferentially in the liver. It is therefore a controversial question whether a tumor would have a high enough concentration of metformin for it to have a local action, Pollak explained.

"When we take tumor cells and put them on a plastic dish in laboratory culture and we do a dose-response curve to metformin we can find the metformin concentration that will really inhibit the tumor growth. But we don't know whether those concentrations are achievable by the standard doses in the clinic," he added.

Pollak noted that there is fairly good insight that metformin is not going to work uniformly in all tumors in all people. Scientists would therefore have to determine what molecular subtype of breast, colon or lung cancer, [for example] metformin would be effective in.

"If we wanted to do intelligent clinical trials of metformin for cancer treatment either in diabetics or even in non-diabetics we shouldn't probably just go and give unselected patients metformin," Pollak said.

"Although some groups are actually proposing to run into it quickly because they are so excited, many scientists believe that we have to understand more before we can actually be ready for clinical trials of this agent that would be optimally designed," he concluded.

Liraglutide, well-tolerated, improves glucose control and reduces weight

Type 2 diabetics whose blood sugar was not controlled by metformin experienced a reduction in HbA_{1c} levels and progressive weight loss – which were both maintained for up to 1 year – after receiving additional therapy with liraglutide, researchers reported.

The data came from a 52-week extension of the 1860 trial, which compared the human glucagon-like peptide-1 (GLP-1) analogue liraglutide to the dipeptidyl-peptidase-4 (DPP-4) inhibitor sitagliptin, as an adjunct to metformin therapy.

In the 26-week, pre-extension phase of the study, patients received 1.2 mg or 1.8 mg of liraglutide via injections once a day or 100 mg of sitagliptin in tablet form once a day.

Results of this part of the trial, published earlier this year, showed that patients who received high- or low-dose liraglutide had significantly better HbA_{1c} control and weight loss compared to patients who received the sitagliptin tablets. [*Lancet* 2010:375;1447-56]

In the extension phase of the study, patients remained on their randomized therapy. The current results confirm that glucose-lowering and weight reduction with liraglutide are maintained for 52 weeks.

However, during the first 26 weeks of the trial more patients taking liraglutide experienced nausea. During the extension phase, however, the rates of nausea were low with all the treatments – under 2 percent.

"Although liraglutide was initially associated with higher rates of nausea compared to sitagliptin, it was generally well tolerated and reduced HbA_{1c} and body weight to greater extent than sitagliptin, resulting in overall patient satisfaction," said Dr. Richard Pratley, a professor of medicine, and director of the Diabetes and Metabolism Translational Medicine Unit at the University of Vermont College of Medicine in Burlington, Vermont, US, who presented the findings.

Professor Anthony Barnett, a professor of medicine and clinical director in the Department of Diabetes and Endocrinology at the University of Birmingham and Heart of England NHS Foundation Trust, said it is important to explain to patients that nausea may be an issue with GLP-1 agonists. "In my clinical experience, these drugs then, are very well tolerated and adherence becomes much less of a problem. But certainly you do get a dropout sometimes in the first few weeks of the treatment," he noted.

Patients' satisfaction with treatments was assessed using the Diabetes Treatment Satisfaction Questionnaire. There was an increase in overall treatment satisfaction with liraglutide compared to sitagliptin at 26 weeks and at the end of the 52-week extension period. Better glucose control and weight reduction were the main reasons for this.

"The idea was that perhaps injectables would be disadvantageous, but it turns out that it [liraglutide] wasn't perceived as being any less convenient or flexible than oral medications," said Pratley.

When patients hear they can potentially lose weight with a GLP-1 agonist it becomes less of an issue that the drug is given by injection, he added. "They don't ask, what size needle it is, they don't ask where you have to inject it." *– RP*

Linagliptin beneficial in diabetics with renal impairment

Linagliptin, a DPP-4 inhibitor currently in late-stage development as a once-daily oral tablet for type 2 diabetics has all the benefits of its class and the added advantage that it is not primarily excreted by the kidney, making it useful for diabetics with renal impairment.

Many type 2 diabetics are at risk of or already have renal impairment and require special clinical consideration. Treatments are needed that can still be used when renal function declines, said Professor Anthony Barnett, a professor of medicine and clinical director of the Department of Diabetes and Endocrinology at the University of Birmingham and Heart of England NHS Foundation Trust in the UK.

Linagliptin, like the other DPP-4 inhibitors, has the benefits of effective blood glucose lowering, weight neutrality, good tolerability and low risk of causing hypoglycemia.

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>
> *– Professor Anthony Barnett*

However, currently available DPP-4 inhibitors are mainly discharged via the kidney and therefore require dose adjustment, or are not recommended for patients with moderate renal impairment, explained Barnett.

Linagliptin, on the other hand, is predominantly excreted through the enterohepatic system.

Barnett noted that there are many patients who are not able to benefit from the gliptin class of drugs because they have renal problems.

"That really is a big issue for us in clinical practice," he said.

He noted that the clinical data for linagliptin seen to date suggest a benefit due to its primarily non-renal route of excretion.

"The convenience of a drug not needing additional monitoring of kidney function or not needing dose adjustment as kidney function declines, could improve patient compliance as well as make life easier for the health professional," he said. *– RP*