THERAPY

IBD — a potential adverse effect of DDP4 inhibitors in T2DM

Dipeptidyl peptidase 4 (DPP4) inhibitors are increasingly being used to treat patients with type 2 diabetes mellitus (T2DM); however, new research suggests that this class of drugs could increase the risk of incident inflammatory bowel disease (IBD).

"For the present study, we were interested in assessing the impact of DPP4 inhibitors on autoimmunity, given the role of DPP4 in immune function," explains lead author Devin Abrahami. The researchers used data from Clinical Practice Research Datalink, a primary care database from the UK, to identify 141,170 patients with T2DM who started antidiabetic treatment between 1 January 2007 and 31 December 2016. They then compared the use of DPP4 inhibitors with use of other antidiabetic agents, taking into account additional factors such as smoking, alcohol use and BMI.

Over 552,413 person-years of follow-up, 208 cases of incident IBD were recorded. Adjusted hazard ratios revealed that use of DPP4 inhibitors was associated with a 75% increased risk of IBD. The hazard ratios increased with duration of use, peaking after 3–4 years and decreasing after >4 years. The researchers conducted several secondary analyses, and the findings remained consistent.

Although the absolute risk of IBD with use of DPP4 inhibitors is low, the authors caution that clinicians should consider not prescribing these agents to patients who are already at increased risk of IBD and that gastrointestinal symptoms in patients receiving DPP4 inhibitors should be closely monitored.

"Additional research is needed to replicate our findings," states senior author Laurent Azoulay. "However, our findings open the doors to investigate the effect of these drugs on other autoimmune conditions where DPP4 is thought to be involved."

Claire Greenhill

ORIGINAL ARTICLE Abrahami, D. et al. Dipeptidyl peptidase-4 inhibitors and incidence of inflammatory bowel disease among patients with type 2 diabetes: population based cohort study. *BMJ* https://doi.org/10.1136/bmj.k872 (2018)

DIABETES

Acute effects of glucagon on the liver

Studies on the effects of glucagon on the liver typically focus on the role of gluconeogenic genes and their products, but these genes and proteins do not explain the acute effects of glucagon on hepatic metabolism. Now, a new study reports that elevated levels of glucagon promote the release of glutamine from the liver and increase gluconeogenesis. In addition, the authors show that reducing glutamine metabolism in the liver reduces the severity of hyperglycaemia.

"Among the early studies on the hepatic actions of glucagon, there are numerous reports detailing rapid metabolic changes, some studies even showed increases in glutamine metabolism," explains Russell Miller, lead author on the study. "In the present study, we used stable isotope-based mass spectrometry, which tracks heavy isotopes through metabolic pathways, to analyse the metabolic changes that occur in the liver in response to glucagon."

The team found that hepatic glucose release following stimulation with glucagon was concomitant with a large increase in hepatic glutaminolysis. Further analysis revealed that a marked proportion of this metabolized glutamine contributed to the carbons of glucose generated during the glucagon-stimulated gluconeogenesis.

The authors then genotyped cryopreserved human hepatocytes and identified the L581P variant of liver-expressed glutaminase 2 (GLS2) as a gain-of-function variant. Importantly, loss-of-function of GLS2 in mice recapitulated the L581P GLS2 phenotype observed in humans (low fasting levels of glucose and increased plasma levels of glutamine).

"There are a number of paths forward," concludes Miller. "Levels of plasma glutamine and the L581P GLS2 variant could potentially be used in future clinical work to inform therapeutic approaches to type 2 diabetes mellitus. For example, plasma levels of glutamine could possibly be used to identify populations of patients who will respond to treatment with a glucagon antagonist."

Alan Morris

ORIGINAL ARTICLE Miller, R. A. et al. Targeting hepatic glutaminase activity to ameliorate hyperglycemia. *Nat. Med.* https://doi.org/10.1038/nm.4514 (2018)

CANCER

Inhibiting glycolysis in tumour cells

The therapeutic outcomes of patients with cancer might be improved by combining tumour glycolysis inhibition with adoptive T cell therapy, according to new research. The study is the first to provide clinical evidence to support the immune regulatory role of tumour glycolysis in controlling the effectiveness of adoptive T cell therapy for cancer treatment.

"We previously found, following an independent metabolomic library screen, that tumour glycolysis could be a potential mechanism of tumour resistance to T cell-mediated killing," explains lead author Weiyi Peng. "These results prompted us to study the relationship between tumour glycolysis and resistance to adoptive T cell therapy."

In the present study, the authors evaluated the relationship between the expression of glycolysis-related genes and T cell infiltration in two independent cohorts of tumour specimens from patients with refractory melanoma who had been treated with adoptive T cell therapy. Peng and colleagues demonstrated, for the first time, that melanomas from patients who were refractory to adoptive T cell therapy exhibit increased glycolytic activity. Their results highlight the potential of combining tumour glycolysis inhibition with adoptive T cell therapy to improve therapeutic outcomes of patients with melanomas.

The researchers are now working to test whether their findings are generalizable to other types of immunotherapies, including immune checkpoint inhibitors, and to different cancer types with high glycolytic activity, such as lung cancer. "We also need to define the mechanisms by which targeting tumour glycolysis can improve the antitumour immune responses," concludes Peng. "We are very interested in the future clinical development of combining T cell-based immunotherapy with therapeutics that inhibit tumour glycolysis in patients with melanomas."

Alan Morris

ORIGINAL ARTICLE Cascone, T. et al. Increased tumor glycolysis characterizes immune resistance to adoptive T cell therapy. *Cell Metab.* https://doi.org/10.1016/j.cmet.2018.02.024 (2018)