Gliptins: joint pain and exposure to NSAIDs

Joint and muscle pain are part of the adverse effect profile of gliptins. In France, *Prescrire* carried out a study, using data from the mandatory national health insurance system, showing that patients taking gliptins are more frequently exposed to nonsteroidal anti-inflammatory drugs (NSAIDs) than patients taking other hypoglycaemic drugs for type 2 diabetes. They are therefore more often exposed to the adverse effects of NSAIDs, without any demonstrated advantage with respect to their diabetes.

Joint and muscle pain form part of the adverse effect profile of gliptins, such as *sitagliptin*, which are dipeptidyl peptidase 4 (DPP-4) inhibitors used as hypoglycaemic drugs in type 2 diabetes (1). In 2015, the US Food and Drug Administration (FDA) drew attention to reports of disabling pain attributable to gliptins (2). In 2017, a meta-analysis of 67 comparative trials showed an increased risk of joint pain in the gliptin group compared to patients in a control group who were not taking a gliptin (estimated relative risk (RR) of 1.13 with a 95% confidence interval of 1.04 to 1.22; p=0.003) (3).

Does this adverse effect translate into a greater use of analgesics? To address this question, *Prescrire* examined data from a representative sample of the population covered by the French health insurance system (EGB) (**a**).

Comparison of gliptins versus other hypoglycaemic drugs. The sample is constructed and maintained so as to represent 1/97th sample of the population covered by mandatory health insurance (5). In the sample, exposure to drugs is estimated from the prescriptions dispensed in community pharmacies and then submitted for reimbursement.

The study first identified patients who received at least three prescriptions in one year, during the period 2012-2016, for either a gliptin or one or more other hypoglycaemic drugs commonly used for type 2 diabetes (oral hypoglycaemics, *insulin glargine*, *insulin detemir*, *exenatide*, or *liraglutide*) (6). It then identified which of these patients, in the year following at least one of these hypoglycaemic drug prescriptions, had received at least two prescriptions for a systemic nonsteroidal anti-inflammatory drug (NSAID), a weak opioid (*tramadol*, *codeine*, powdered *opium*, alone or in combination), or *nefopam*.

On average, each year during this period, about 30% of patients exposed to a gliptin were also exposed to at least one NSAID, versus about 24.5% of patients exposed to a different hypoglycaemic drug. This difference was statistically significant (p<0.001), including when age and gender were taken into account.

About 20% of patients in the gliptin group were exposed to a weak opioid analgesic, as was the case in the group taking other hypoglycaemic drugs. Exposure to *nefopam* was about 0.7% in both groups.

In practice This epidemiological observation does not prove the existence of a cause-and-effect relationship, but it does constitute a signal which is consistent with the results of clinical trials showing that gliptins carry a risk of joint pain. It is likely that this pain can cause enough discomfort to lead diabetic patients to use NSAIDs, thus adding their adverse effects, particularly renal and cardiovascular effects, to those of gliptins. However, it has not been demonstrated that gliptins reduce the long-term complications of diabetes, whereas they carry a risk of serious adverse effects. Their use should be avoided.

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***a-** EGB for "échantillon généraliste de bénéficiaires" (ref 4).*

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