Prescribing gliptins: Enthusiasm should be coupled with caution

Sir,

We read an article titled "Choosing a gliptin" by Gupta and Kalra published in the October issue of this journal. Though they recommend its use, some concern still remains.

Dipeptidyl peptidase-4 (DPP4; also known as CD26) is a ubiquitous, membrane-bound enzyme that has roles in nutrition, metabolism, the immune and endocrine systems, bone marrow mobilization, cancer growth, and cell adhesion (http://www.genecards.org/cgi-bin/carddisp.pl? gene=DPP4). Importance of this enzyme can be emphasized by a study in DPP4-deficient rats which showed hyperglycemia, dyslipidemia, and increased serum creatinine in accordance with decreased creatinine clearance as compared with wild-type rats after STZ treatment.[1] DPP4 is crucial for regulating the expression of factors related to steroid metabolism, such as Cyp51, Sc4mol, and Hsd17b2, and DPP4 deficiency or inhibition may cause dyslipidemia.[2]

Recently; Elashoff *et al.*[3]examined the US Food and Drug Administration's (FDA) database of reported adverse events for those associated with the DPP4 inhibitor sitagliptin and the glucagon-like peptide-1 (GLP-1) mimetic exenatide, from 2004 to 2009. Use of sitagliptin or exenatide increased the odds ratio for reported pancreatitis sixfold as compared with other therapies ($P < 2 \times 10^{-16}$). FDA has issued repeat safety alert in 2009 in view of 88 new cases of pancreatitis following sitagliptin use between 2006 and 2009.

Pancreatic cancer was also more commonly reported among patients who took sitagliptin or exenatide as compared with other therapies ($P < 0.008$, $P < 9 \times 10^{-5}$). Recent animal studies showing chronic silent pancreatitis as a consequence of GLP-1 mimetic therapy also raise concern. Moreover, because pancreatitis is a known risk factor for pancreatic cancer, long-term GLP-1 receptor activation might lead to increased risk for pancreatic cancer.[4] In fact, pancreatitis following sitagliptin is mainly chronic pancreatitis, and also chronic pancreatitis is risk factor for pancreatic carcinoma whose incidence increases with increasing duration of pancreatitis. Thus, the cases that we are seeing now may only be the tip of iceberg. Pancreatic carcinoma and chronic pancreatitis may become more apparent in the future when we will have patients exposed to drug for a long enough period. In addition, the available reports showing no relation of gliptins with pancreatitis were sponsored by pharmaceutical companies and arguably have a limited capacity to detect adverse outcomes.[5]

Moreover, DPP4 expression has been related with autoimmune arthritis, malignant cell prevention, and dissemination. It has also been suggested that immunomodulatory effects of DPP4 inhibition might increase the risk for all cancers. Recent research in animal models links DPP4 inhibition to melanoma, prostate cancer, ovarian cancer, neuroblastoma, and lung cancer. Low levels of DPP4 in malignancy are associated with dissemination or metastasis. We should not forget that chronic GLP-1 receptor activation may lead to changes in multiple tissues where GLP-1 receptors are expressed, and we are still not aware of all physiologic roles played by GLP-1 receptor activation. Hence, till more data are available, we have stopped prescribing DPP4 inhibitors in our oncology patients. Careful post-marketing surveillance for adverse effects, and continued evaluation in longer-term studies is required to determine the role of this new drug class One must remain vigilant and stay tuned, or otherwise we may end up with our fingers burnt similar to what happened with use of rosiglitazone and other drugs in not so distant past.

Thus, enthusiasm to prescribe this drug should be coupled with caution.

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