

BULLOUS PEMPHIGOID INDUCED BY DIPEPTIDYL PEPTIDASE-4(DPP-4) INHIBITORS: A PHARMACOVIGILANCE-PHARMACODYNAMIC/PHARMACOKINETIC ASSESSMENT THROUGH AN ANALYSIS OF THE VIGIBASE®

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Introduction: Dipeptidyl Peptidase-4(DPP-4) inhibitors have emerged recently as a putative triggering factor of Bullous Pemphigoid (BP); however, the strength of this association and the mechanism whereby it occurs remain unclear.

Material and methods: first, we performed case/non-case analyses in VigiBase® to examine the potential signal of BP [expressed as the reporting odds ratio (ROR) and its 95% confidence interval] for DPP-4inhibitors. Secondly, we performed linear regression analyses to explore the association between DPP-4inhibitor signals for BP and their affinities towards different target enzymes (DPP-2, DPP-4, DPP-8and DPP-9) and their volume of distribution (Vd).

Results: A significant BP signal was found for DPP-4inhibitors. The ROR for pooled DPP-IV inhibitors was 168.5(95% CI: 156.1–181.3). Among individual DPP-4inhibitor, the highest RORs were found for teneligliptin 898.3(95% CI: 734.7–1098.4), omarigliptin 672.3(95% CI: 376.7–1199.9) and lowest for saxagliptin 18.9(95% CI: 11.5–30.9) and sitagliptin 44.4(95% CI: 38.6–51.1). We found a marginally significant linear correlation between the BP signal and gliptin affinity at DPP-4(slope=1.316[-0.4385–3.21], $p=0.067$, $R^2=0.40$) but not the other enzyme targets, nor for Vd.

Discussion and conclusion: Our case/non-case analyses suggest that there is a strong signal of the risk of bullous pemphigoid due to DPP-4inhibitor exposure, indicating a 'class effect' associated with this potentially serious disease. This risk is higher than the risk for any other drugs reported as a plausible cause in the occurrence of BP, including other anti-hyperglycaemic drugs. The results reported herein suggest a clinical relevance of gliptins selectivity for DDP-4in the development of BP as a result of exposure to these drugs. Future preclinical and clinical studies are needed for a better understanding of this correlation.