Falsely Accused? Insufficient Evidence to Conclude that Sitagliptin is a Cause of Chronic Cough

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A decade ago, a single-center case series was published describing 15 patients with type 2 diabetes who presented with cough, dyspnea and fatigue after initiation of therapy with sitagliptin [1]. Notably, all 15 subjects had evidence of allergic rhinitis, and 13 were maintained on an angiotensin-converting enzyme (ACE) inhibitor, a class of drugs with a well-established, causal relationship to chronic cough through a mechanism of enhancement of cough reflex sensitivity [2]. Since then, not a single report of sitagliptin-associated cough can be found on a National Library of Medicine (PubMed) search. An informal poll of the Directors of 17 subspecialist Cough Centers worldwide (6 in the United States; 5 in the United Kingdom; 1 each in Canada, China, Germany, Italy, Japan and South Korea) yielded no reports by any clinician of ever having had a case of presumed or suspected sitagliptin-associated cough (personal communication).

With this background, we found it remarkable that in the most recent CHEST cough management guidelines, an investigation algorithm pathway is provided in which sitagliptin is prominently featured alongside ACE inhibitors as a potential cause of chronic cough [3]. Furthermore, the legend of the algorithm includes the statement: “Always evaluate whether sitagliptin as well as ACE inhibitors are contributing to the patient’s cough” [3]. The sole reference provided in the CHEST guidelines to support a causal role for sitagliptin in chronic cough is the aforementioned case

series published in 2010 [1]. Given our concern that sitagliptin had been granted a disproportionate level of importance, we aimed to further elucidate this issue by investigating the mechanism of action and evaluating the evidence supporting any potential link of sitagliptin with chronic cough. We reviewed placebo-controlled meta-analyses of early and late phase clinical trials as well as real-life data from the International Drug Monitoring Program of the World Health Organisation (WHO) and medical product safety reporting information from the United States Food and Drug Administration (FDA).

Sitagliptin was the first approved (in 2006) dipeptidyl peptidase-4 (DPP-4) inhibitor and is used as monotherapy or as a component of combination therapy for the treatment of patients with type 2 diabetes [4]. DPP-4 is a ubiquitous enzyme found on numerous cell types, but for the purpose of improving glycemic control, inactivates the incretin hormones (glucagon like peptide-1 (GLP1), and glucose-dependent insulinotropic polypeptide (GIP)), thereby resulting in a rise in insulin from the beta cells of the pancreas and a reduction in glucagon from pancreatic alpha cells. Other mechanisms have also been postulated but the net effect is improved glycemic control [5].

DPP-4 is thought to have other physiological functions involving numerous other enzyme substrates and receptor expression on a wide array of immune cells including T cells, B cells, natural kills cells, as well as subsets of macrophages [6]. Furthermore, neuropeptides such as substance P and bradykinin, which are relevant to the mechanism of ACE inhibitor-induced cough [2], are also considered potential enzymatic substrates for DPP-4 and hence inhibiting this enzyme with sitagliptin may increase levels of such neurotransmitters and increase neuronal sensitization. Based on these reasons, the early phase development of sitagliptin was met with some pre-emptive caution for the occurrence of possible infections and cough [7].

Early meta-analysis of pooled studies of DPP-4 inhibitors found them to be very well tolerated with low absolute

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rates of adverse events [8]. By combining all available data, a small increased risk of nasopharyngitis was demonstrated (6.4% for all DPP-4 inhibitor vs 6.1% for comparator; risk ratio, 1.17; 95% CI 0.98–1.40), driven mainly by sitagliptin [1.38 (1.06–1.81)]. However, there was no difference in the incidence of cough [RR 1.07 (0.65–1.78)], influenza [RR 0.87 (0.64–1.19)], or upper respiratory tract infection [0.99 (0.81–1.21)], even in the sitagliptin group comparison [8].

A subsequent meta-analysis of trials of longer duration (18 to 104 weeks) comparing all DPP-4 inhibitors with placebo (44 trials), a comparator from another class of anti-diabetic agents (20 trials), or another DPP-4 inhibitor (3 trials) again demonstrated a slight increased risk of nasopharyngitis compared with placebo (6% vs. 5.3%, RR 1.13, 95% CI 0.99–1.29), which was predominantly driven by the sitagliptin subgroup (5.3 vs. 4.1 percent; RR 1.35, 95% CI 1.03–1.77) [9]. Reassuringly, the risk of upper respiratory tract infections was not significantly elevated in any of the DPP-4 groups. Similarly, the most recent phase 3 placebo controlled study of sitagliptin randomised 14,671 patients with a median follow-up of 3 years. There was no difference in incidence of respiratory tract infections, and no mention of cough, nasopharyngitis, or sinusitis in the study adverse event [AE] reporting [10]. Furthermore, no mention was made of such AEs in the other DPP-4 phase 3 studies [11–14].

In a previous study, real world data based on reporting of infections in the WHO Vigibase Adverse Drug Reaction (ADR) database were analyzed using a nested case–control methodology, with biguanides as the control or reference group for comparison. In this analysis, there was an overall increased risk of infections compared to biguanides [RR 2.2 (95% CI 1.9–2.7)], mainly driven by an increased risk of upper respiratory tract infections (including nasopharyngitis and sinusitis) [RR 12.3 (8.6–17.5)]. Cough was not specifically mentioned, and no increased risk of lower respiratory tract infections or urinary tract infections was observed [15]. Vigibase is a spontaneous reporting system, essentially a repository for reports of suspected ADRs collected by national drug authorities in over 110 countries and spanning over 100,000 different medicinal products. Hence under-reporting, reporting bias and the Weber effect (peak AE reporting at the end of the 2nd year post regulatory approval) must be considered. Review of the database (<https://www.vigiaccess.org>) (accessed 1/9/2020) revealed 28,574 sitagliptin-associated ADRs, of which 337 were for cough. To provide context, the widely-used diabetic medication metformin had 75,718 reported ADRs, of which 643 referred to cough. The antitussive dextromethorphan had 155 ADRs reporting associated cough (of a total of 9589 ADRs), whereas lisinopril, an ACE inhibitor clearly causally associated with cough induction [2] had 52,500 reported ADRs, of which 10,178 were for cough. *MedWatch*, the

medical product safety reporting program of the FDA, listed no sitagliptin-associated reports for the years 2017–2019 (<https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program>; accessed 1/9/2020).

Based on this review of the literature, we conclude that there is a slight increased risk of nasopharyngitis with the use of sitagliptin compared with placebo. However, we did not find sufficient evidence to associate an increased risk of acute cough, chronic cough or lower respiratory tract infection with sitagliptin or any other DPP-4 inhibitor.

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