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Safety of Dipeptidyl Peptidase-4 Inhibitors in COVID-19: An Update

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ABSTRACT

Background: Safety of use of dipeptidyl peptidase-4 (DPP-4) inhibitors in patients with type 2 diabetes and coronavirus disease 2019 (COVID-19) is unclear. Objective: To review the most recent data regarding safety of use of DPP-4 inhibitors before and during hospitalization of patients with type 2 diabetes and COVID-19.

Methods: PUBMED search until February 16, 2021. Search terms included COVID-19, DPP-4 inhibitors, sitagliptin, CD26, mortality, diabetes. Retrospective studies, pertinent animal investigations and pre-print studies are reviewed.

Results: All available studies related to the use of DPP-4 inhibitors in patients with COVID-19 are retrospective. Very limited and conflicting data exist regarding susceptibility of patients using DPP-4 inhibitors to COVID-19. In one Italian study, use of the DPP-4 inhibitor, sitagliptin prior to hospital admission, was associated with reduction in mortality in patients with type 2 diabetes and COVID-19. In addition, the use of sitagliptin before hospitalization was associated with greater number of hospital discharges, improvement of clinical status, reduced risk of transfer to intensive care unit (ICU) and need for mechanical ventilation compared with patients who were not receiving sitagliptin. In 3 studies, pre-admission use of DPP-4 inhibitors was continued in most patients after admission. Two of these 3 studies did not show significant mortality benefit with the use of DPP-4 inhibitors, whereas the third and smallest study demonstrated significant reduction in in-hospital mortality. Results of 2 meta-analyses showed a neutral effect of DPP-4 inhibitors on mortality in patients with type 2 diabetes and COVID-19 admitted to the hospital.

Conclusions: Overall, use of DPP-4 inhibitors in patients with type 2 diabetes and COVID-19 may be safe whether these agents were stopped or continued after hospital admission. A possible beneficial effect of DPP-4 inhibitors on mortality cannot be excluded. Randomized trials are urgently needed to clarify the efficacy and safety of DPP-4 inhibitors in patients with COVID-19 with and without type 2 diabetes.

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Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors such as sitagliptin are oral anti-diabetic agents approved by the Federal Drug Administration (FDA) for treatment of type 2 diabetes [1,2]. DPP-4, also called CD26, is the enzyme causing breakdown of the incretin hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). These 2 incretins normally lower blood glucose levels after meals by stimulation of insulin secretion, inhibition of glucagon production, slowing of gastric emptying, and promotion of early satiety [2]. Thus, inhibition of DPP-4 by DPP-4 inhibitors decreases breakdown of these 2 incretins and prolongs the duration of their anti-hyperglycemic actions [2]. Indeed, many investigators believe that DPP-4 inhibitors may be useful therapeutic agents in patients with COVID-19 with and without type 2 diabetes [3-5]. The rationale of using DPP-4 inhibitors as treatment for COVID-19 is based on 2 hypotheses. First, COVID-19 is caused by a coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2). The latter virus uses angiotensin converting enzyme 2 (ACE2) as receptor and the transmembrane protease serine 2 (TMPRSS2) as co-receptor for host cell binding and penetration [6]. In the meantime, Vankadari and Wilce have shown that CD26 could be also involved in binding of SARS-Cov-2 to its target cells [7]. Therefore, inhibition of CD26 by DPP-4 inhibitors could virtually inhibit viral penetration into host cells. Second, both animal and human studies have shown that sitagliptin might exert anti-inflammatory actions [8,9]. Thus, sitagliptin administration results in inhibition of several pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and C reactive protein (CRP) [8,9]. In fact, before the COVID-19 pandemics, Satoh-Asahara et al have shown that sitagliptin therapy was associated with significant increase in expression of the anti-inflammatory cytokine interleukin-10 (IL-10) in patients with type 2 diabetes, a finding that further supports the inflammation-suppressive effects of DPP-4 inhibitors[8]. Accordingly, this drug class could virtually inhibit the severe inflammatory reaction and cytokine storm that occur in COVID-19 and represent a major cause of death. The main purpose of this

article is to review most recent studies regarding effects of DPP-4 inhibitors in patients with type 2diabetes and COVID-19 on mortality and other clinical outcomes.

Effect of DPP-4 inhibitors on susceptibility to develop COVID-19

Data regarding use of DPP-4 inhibitors and susceptibility to COVID-19 are very scant and inconsistent. Fadini et al explored whether users of DPP-4 inhibitors might have low risk of COVID-19 infection by comparing the frequency of users of DPP-4 inhibitors in COVID-19 patients with type 2 diabetes versus age- and sex-matched patients with type 2 diabetes without diagnosis of COVID-19 [10]. They found no significant difference between the 2 patient groups, 10.6% and 8.8%, respectively [10]. On the contrary, in a Chinese case-control retrospective study, Yan et al [11] reported that use of DPP-4 inhibitors was associated with increased risk of COVID-19 infection; odds ratio (OR) being 6.02 (95% CI, 2.3-15.5). Meanwhile, they found that use of DPP-4 inhibitors was not associated with increased clinical severity of COVID-19 [11]. These data, however, should be interpreted with caution as the number of patients who were using DPP-4 inhibitors was small, 9 and 6 patients in the study of Fadini et al and Yan et al, respectively[10,11].

Effect of DPP-4 inhibitors intake prior to hospitalization on clinical outcomes in COVID-19

Solerte et al evaluated the effects of sitagliptin administration before hospital admission on mortality of patients with type 2 diabetes and COVID-19 pneumonia[12]. This investigation included 338 consecutive patients of whom 169 subjects were taking sitagliptin as part of their anti-diabetic therapy (sitagliptin group) and an equal group of 169 subjects were receiving other diabetes therapy (the control group) [12]. After admission, all oral anti-diabetic agents, including sitagliptin, were discontinued and patients were switched to insulin therapy as per recommendations of American Diabetes Association (ADA) [13]. The use of sitagliptin at the time of hospitalization was associated with significant reduction in mortality; 18% and 37% in the sitagliptin group and control group, respectively (P= 0.0001) [12]. After adjustment for clinically relevant factors (age, sex, comorbidities, and ongoing treatments), pre-admission treatment with sitagliptin was associated with decreased in-hospital death with an odds ratio (OR) of 0.44 (95% CI, 0.29-0.66; P=0.0001) [12]. The beneficial effect of sitagliptin therapy did not significantly change as a function of age, gender, body mass index, and hemoglobin A1c levels [12]. Other primary end points in the study of Solerte et al included the number of discharged patients and overall amelioration in clinical status [12]. Thus, a greater number of patients were discharged at 30 days in the sitagliptin group compared with the control group, 120 and 89 patients, respectively (P=0.008) [12]. In addition, greater proportions of patients in the sitagliptin group than in the control group had overall improvement of clinical score, 60% and 38%, respectively (P=0.0001) [12]. Moreover, pre-admission sitagliptin intake was associated with decreased risk of mechanical ventilation; hazard ratio (HR) 0.27 (95% CI, 0.11-0.65; P=0.003), and ICU admission; HR 0.51 (95% CI, 0.27-0.95; P= 0.03), compared with the control group [12]. Interestingly, consistent with the anti-inflammatory action of DPP-4 inhibitors, patients who were receiving sitagliptin prior to admission had significant reduction in serum markers of inflammation such as CRP and procalcitonin as well as significant increase in lymphocytic count compared to the control group [12].

Effect of continuing DPP-4 inhibitors administration after admission on clinical outcomes in COVID-19

In three studies, pre-admission use of DPP-4 inhibitors was allowed to continue in most patients after hospital admission [14-16]. The French CORONADO study was the largest retrospective investigation (n=2,449) that evaluated the impact of DPP-4 inhibitors on a composite primary outcome that consisted of need for mechanical ventilation or death 7 days in patients with COVID-19 and type 2 diabetes [14]. In the CORONADO study, approximately 81% of patients continued taking DPP-4 inhibitors after admission [14]. The primary outcome occurred at similar rates in users and non-users of DPP-4 inhibitors, 27.7% and 28.6%, respectively (P=0.67) [14]. Likewise, frequency of the individual components of the primary outcome was similar in users and non-users of DPP-4 inhibitors [14]. Noh et al from South Korea examined the difference in all-cause mortality between users and non-users of DPP-4 inhibitors in patients with diabetes and COVID-19 (n=586). No significant difference in all-cause mortality was observed, HR 0.74; 95% CI 0.43-1.26 [15]. Similarly, difference in prevalence of severe manifestations of COVID-19 was not significant, HR 0.83; 95% CI 0.45-1.53 [15]. In an Italian study, Mirani et al found that use of DPP-4 inhibitors was independently associated with reduction in mortality in hospitalized patients with type 2 diabetes and COVID-19. Thus, after adjustment for age and sex, among users of DPP-4 inhibitors, HR was 0.13 (95% CI, 0.02-0.92) [16]. However, in the latter study, only 11 patients were using DPP-4 inhibitors [16]. Overall, the results of these 3 studies provide reassurance about safety of continuation of administration of DPP-4 inhibitors in hospital among patients with type 2 diabetes and COVID-19 [14-16].

Effects of DPP-4 inhibitors on clinical outcomes of COVID-19: results of meta-analyses

Kow and Hasan performed a meta-analysis of 6 observational studies including 1,531 patients with COVID-19 admitted to the hospital. No significant difference in risk of death or severe COVID-19 was observed among patients using pre-admission DPP-4 inhibitors compared with non-users, OR 1.15, 95% CI 0.64-2.06) [17]. In another meta-analysis of 7 retrospective studies, Bonora et al [18] reached similar conclusion. Thus, the risk ratio of COVID-19 mortality among users of DPP-4 inhibitors relative to non-users was not significant, being 0.81 (95% CI 0.57-1.15) [18]. Although these 2 meta-analyses did not indicate any safety signal regarding use of DPP-4 inhibitors, it was limited by the observational nature of included studies with significant heterogeneity among them and multiple definitions of "severe" COVID-19. In addition, no information was provided regarding the status of use of DPP-4 inhibitors after admission to the hospital. Table 1 summarizes main findings of studies that examined effects of DPP-4 inhibitors on clinical outcomes in patients with type 2 diabetes and COVID-19 admitted.

Table 1: Association of DPP-4 inhibitors with mortality and other clinical outcomes in patients with type 2 diabetes and COVID-19 admitted to the hospital

Reference	Solerte et al [12]	Mirani et al [16]	Noh et al [15]	Roussel et al [14]	Kow and Hasan [17]	Bonora et al [18]
Country	Italy	Italy	South Korea	France	Multi-national	Multinational
Design	Case-control, multicenter	Case series, single center	Retrospective	Retrospective, secondary analysis of the CORONADO Study	Meta-analysis of 6 observational studies	Meta-analysis of 7 observational studies
Patients all hospitalized with type 2 diabetes and COVID-19	169 patients on sitagliptin, and 169 patients on standard care	79 patients on no DPP-4 inhibitors and 11 patients on DPP-4 inhibitors	453 patients on DPP-4 inhibitors vs 133 patients on no DPP-4 inhibitors (metformin and insulin monotherapy excluded)	596 patients on DPP-4 inhibitors and 1,853 patients on no DPP-4 inhibitors	Total number of patients 1,531. Number of patients using DPP-4 inhibitors not reported	612 patients on DPP-4 inhibitors and 1703 patients on other glucose-lowering agents
Effect of DPP-4 inhibitors on mortality	18% mortality sitagliptin vs 37% other patients, HR 0.44 (95% CI, 0.29-0.66; P=0.0001)	Reduction in mortality with DPP-4 inhibitors HR 0.13 (95% CI, 0.02-0.92, P=0.042).	Non-significant reduction in mortality with DPP-4 inhibitors vs no DPP-4 inhibitors: adjusted HR 0.74 (95% CI, 0.43-1.26).	Primary outcome (composite of mortality need of mechanical ventilation) was similar in users of DPP-4 inhibitors 27.7% vs non-users 28.6%, P=0.68.	Non-significance difference in death or severe disease between users of DPP-4 inhibitors compared with non-users: pooled OR 1.15 (95% CI 0.64-2.06)	Non-significance difference in death which occurred in 18% of patients on DPP-4 inhibitors vs 19.7% of patients on no DPP-4 inhibitors RR 0.81, (95% CI 0.57-1.15)
Effect of DPP-4 inhibitors on other clinical outcomes	Improvement in clinical outcomes 60% sitagliptin vs 38% other patients (P=0.0001) & number of hospital discharges sitagliptin 120 vs other patients 89 discharges (P=0.0008).	Not reported	Non-significant reduction in risk of severe manifestations of COVID-19. Adjusted HR 0.74, 95% CI 0.45-1.53)	No difference between users and non-users of DPP-4 inhibitors in need of mechanical ventilation.	Not reported	Not reported
Status of DPP-4 inhibitors after admission	DPP-4 inhibitors were stopped after admission	DPP-4 inhibitors were continued after admission in all patients	More than 90% of patients continued their diabetes therapy after admission	Approximately 81% of patients continued DPP-4 inhibitors after admission	Not reported	Not reported

Abbreviations: HR: hazard ratio, OR: odds ratio, RR: relative risk, ICU: intensive care unit.
Studies including less than 10 patients receiving DPP-4 inhibitors are not presented.

Limitations of available studies

The main limitation of available studies of DPP-4 inhibitors in COVID-19 is their non-randomized retrospective design. The latter design cannot prove a causative role of sitagliptin in mortality reduction. In addition, retrospective studies are frequently limited by imbalance between the study groups at baseline in many confounding factors that may affect outcomes. For instance, in the study of Solerte et al , glycemic control was significantly better in the sitagliptin group than in the control group during hospitalization, as well as at follow-up at day 30, with means blood glucose concentrations at 30 days of 139 and 170 mg/dl, respectively[12]. Since poor glycemic control during hospital stay was shown to be independently associated with poor prognosis in COVID-19 patients, this difference in blood glucose values might partly explain the favorable prognosis observed in the sitagliptin group [12].

Conclusions and current directions

In general, available data suggest that use of DPP-4 inhibitors in patients with type 2 diabetes and COVID-19 admitted to the hospital may be safe. The balance of evidence overall supports a neutral effect on clinical outcomes when these agents are continued after admission. Meanwhile, the study of Solerte et al [12] that showed significant clinical benefits of pre-admission use of sitagliptin suffers from multiple limitations. Nevertheless, there are plausible mechanisms whereby DPP-4 inhibitors could be useful agents for treatment

of COVID-19 including their anti-inflammatory actions, and possibly interference with SARS-Cov-2 penetration into host cells through CD26 inhibition. Results of ongoing randomized trials with sitagliptin and linagliptin are eagerly awaited to clarify safety and efficacy of DPP-4 inhibitors in hospitalized patients with COVID-19 [18]. It would be interesting in such trials to include patients with and without type 2 diabetes to see to what extent potential beneficial effects of DPP-4 inhibitors are independent of their anti-diabetic actions.

References

1. Januvia (sitagliptin) tablets. Prescribing information. Merk & CO., INC., Whitehouse Station, NJ 08889, USA. 2006.
2. Mikhail N (2011) Safety of dipeptidyl peptidase 4 inhibitors for treatment of type 2 diabetes. Curr Drug Safety 6: 304-309.
3. Dastan F, Abedini A, Shahabi S (2020) Sitagliptin repositioning in SARS-CoV-2: Effects on ACE-2, CD-26, and inflammatory cytokine storms in the lungs. Iran J allergy Asthma Immunol 10-12.
4. Mozafari N, Azadi S, Mehdi-Alamdarlou S, et al. (2020) Inflammation: A bridge between diabetes and COVID-19, and possible management with sitagliptin. Med Hypotheses 143: 110-111.
5. Solerte SB, Di Sabatino A, Galli M, Fiorina P (2020) Dipeptidyl peptidase-4 (DPP-4) inhibition in COVID-19. Acta Diabetol 57: 779-783.
6. Hoffmann M, Kleine-Weber H, Schroeder S, et al. (2020) SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 181: 271-280.
7. Vankadari N, Wilce JA (2020) Emerging Wuhan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. Emerg Microbes Infect 9: 601-604.
8. Satoh-Asahara N, Sasaki Y, Wada H (2013) A dipeptidyl peptidase-4 inhibitor, sitagliptin, exerts anti-inflammatory effects in type 2 diabetic patients. Metabolism 62: 347-51.
9. Marques C, Mega C, Gonçalves A (2014) Sitagliptin prevents inflammation and apoptotic cell death in the kidney of type 2 diabetic animals. Mediators Inflamm 2014:538737.
10. Fadini GP, Morieri ML, Longato E (2020) Exposure to dipeptidyl-peptidase-4 inhibitors and COVID-19 among people with type 2 diabetes: A case-control study. Diabetes Obes Metab 22: 1946-1950.
11. Yan H, Valdes AM, Vijay A (2020) Role of drugs used for chronic disease management on susceptibility and severity of COVID-19: A large case-control study. Medrxiv.
12. Solerte SB, D'Addio F, Trevisan R (2020) Sitagliptin Treatment at the Time of Hospitalization Was Associated With Reduced Mortality in Patients With Type 2 Diabetes and COVID-19: A Multicenter, Case-Control, Retrospective, Observational Study. Diabetes Care 43: 2999-3006.
13. American Diabetes Association (2020) Diabetes care in the hospital: Standards of Medical Care in diabetes 43: 193-201.
14. Roussel R, Darmon P, Pichelin M, Goronflot T, Abouleka Y, et al.(2021) CORONADO investigators. Use of Dipeptidyl Peptidase-4 inhibitors and prognosis of COVID-19 in hospitalized patients with type 2 diabetes: a propensity score analysis from the CORONADO study. Diabetes Obes Metab.
15. Noh Y, Oh IS, Jeong HE, Filion KB, Yu OHY etal (2021) Association Between DPP-4 Inhibitors and COVID-19 Related Outcomes Among Patients With Type 2 Diabetes. Diabetes Care dc201824.
16. Marco Mirani, Giuseppe Favacchio, Flaminia Carrone, Nazarena Betella, Emilia Biamonte et al. (2020) Impact of Comorbidities and Glycemia at Admission and Dipeptidyl Peptidase 4 Inhibitors in Patients With Type 2 Diabetes With COVID-19: A Case Series From an Academic Hospital in Lombardy, Italy. Diabetes Care 43: 3042-3049.
17. Kow CS, Hasan SS (2020) A meta-analysis on the preadmission use of DPP-4 inhibitors and risk of a fatal or severe course of illness in patients with COVID-19. Therapie https://dx.doi.org/10.1016%2Fj.therap.2020.12.015.
18. Bonora BM, Avogaro A, Fadini GP (2021) Disentangling conflicting evidence on DPP-4 inhibitors and outcomes of COVID-19: narrative review and meta-analysis. J Endocrinol Invest.
19. Wu J, Huang J, Zhu G, Wang Q, Lv Q, et al. (2020) Elevation of blood glucose level predicts worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study. BMJ Open Diabetes Research and Care http://dx.doi.org/10.1136/bmjdrc-2020-001476.