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Strength of Evidence to Support the Possible Therapeutic Effect of DPP-4 Inhibitors in COVID-19

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ABSTRACT

The aim of this study was to demonstrate, with limited retrospective data, that inhibitors of dipeptidyl peptidase-4 (DPP-4), such as sitagliptin, may reduce mortality in patients with type 2 diabetes hospitalized with COVID-19. This benefit was confirmed in a limited number of 9 patients [6-9]. However, DPP-4 inhibitors have the potential to be effective agents for the treatment of COVID-19, including its anti-inflammatory effects, and may interfere with the invasion of SARS-CoV-2 into host cells by inhibiting CD26. Randomized trials are urgently needed to elucidate the therapeutic role of DPP-4 inhibitors in hospitalized patients with COVID-19. In these trials, it will be necessary to evaluate patients with type 2 diabetes and those without type 2 diabetes to understand the extent to which DPP-4 is beneficial.

KEYWORDS

Diabetes; COVID-19; DPP-4 inhibitors; Sitagliptin; Mortality; CD26.

1. 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. DPP-4, also called CD26, is the enzyme causing breakdown of the incretin hormones glucagonlike 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. It follows that inhibition of DPP-4 by DPP-4 inhibitors decreases breakdown of these 2 incretins and prolongs the duration of their anti-hyperglycemic actions [1,2]. Many authors believe that DPP4 inhibitors could be useful therapeutic agents in patients with COVID-19 with and without type 2 diabetes [3-5]. The purpose of this manuscript is to review available studies related to the relationship between DPP-4 inhibitors and COVID-19.

2. Effect of Dpp-4 Inhibitors on Mortality in COVID-19

To the best of authors' knowledge, only 4 observational studies examined the effects of pre-admission administration of DPP-4 inhibitors on mortality and clinical outcomes in patients with type 2 diabetes and COVID-19. In addition, one study addressed the relationship of use of DPP-4 inhibitors with development of COVID-19 [6,10]. Overview and main findings of these studies are summarized in table 1. The first study conducted by Solerte et al specifically evaluated the effects of sitagliptin on mortality, as primary outcome. 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) [6]. 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) [11]. 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). Thus, after adjustment for clinically relevant factors (age, sex, comorbidities, and ongoing treatments), pre-admission treatment with sitagliptin was associated with a decreased odds-ratio (OR) for in-hospital death; OR 0.44 (95% CI, 0.29-0.66; P=0.0001). The beneficial effect of pre-admission sitagliptin therapy did not significantly change as a function of age, gender, body mass index, and hemoglobin A1c levels. In another 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. The hazard ratio (HR), adjusted for age and sex, among users of DPP-4 inhibitors was 0.13 (95% CI, 0.02-0.92). Interestingly, the latter study was the only available investigation in which administration of DPP-4 inhibitors was continued after hospital admission. Using national claims data related to COVID-19 in Korea, Rhee et al reported that use of DPP4 inhibitors was associated with significant reduction in intensive care or death among patients with diabetes and COVID-19, adjusted OR 0.36 (95% CI, 0.13-0.97). Meanwhile, in a small Italian retrospective study, Fadini et al reported on 85 patients with type 2 diabetes and COVID-19 admitted to the hospital, 9 of whom were taking a DPP-4 inhibitor prior to admission. The authors found no significant differences in mortality rates between users and non-users of DPP-4 inhibitors, 11.1% and 13.9%, respectively; P=0.82. Corresponding rates of ICU admissions were also not significant, 19.2% and 33.3%, respectively; P=0.32. Clearly, it is difficult to draw any conclusion from these results due to the small number of users of DPP-4 inhibitors in this study [6-9].

Effect of Sitagliptin on Other Clinical Outcomes of COVID-19 Other primary end points in the study of Solerte et al [6] included the number of discharged patients and overall amelioration in clinical status. Thus, a greater number of patients were discharged at 30 days in the sitagliptin group than in the control group, 120 and 89 patients, respectively (P=0.008). Moreover, 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). Furthermore, the study of Solerte et al [6] showed that 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. In a small retrospective Chinese study, Yan et al [10] found that use of DPP-4 inhibitors was not associated with clinical severity of COVID-19.

Effect of Sitagliptin on Other Clinical Outcomes of COVID-19 Solerte et al [6] observed that patients who were receiving sitagliptin prior to admission had significant reduction in serum markers of inflammation such as C-reactive protein (CRP) and procalcitonin as well as significant increase in lymphocytic count compared to the control group.

3. Effect of Dpp-4 Inhibitors on Risk to COVID-19

Fadini et al [9] 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. They found no significant difference between the 2 patient groups, 10.6% and 8.8%, respectively. On the contrary, in a Chinese case-control retrospective study, Yan et al [10] reported that use of DPP4 inhibitors was associated with increased risk of COVID-19 infection; OR being 6.02 (95% CI, 2.3-15.5), but not with increased clinical severity of COVID-19. These data, however, should be interpreted with caution as the number of patients who were using DPP-4 inhibitors was only 6 patients.

4. Limitations of the 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, i.e. association does not mean causation. 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: 139 and 170 mg/dl, respectively [6]. 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].

5. Mechanisms of the Possible Protective Effects of Dpp-4 Inhibitors in COVID-19

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) that uses the angiotensin converting enzyme 2 (ACE2) as receptor and the transmembrane protease serine 2 (TMPRSS2) as co-receptor for host cell binding and penetration. However, Vankadari and Wilce have shown that CD26 could be also involved in binding of SARS-Cov-2 to its target cells. 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 antiinflammatory actions. Thus, sitagliptin administration results in inhibition of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and CRP [14-16]. Accordingly, sitagliptin could virtually inhibit the severe inflammatory reaction and cytokine storm that occur in COVID-19 and represent a major cause of death. This hypothesis is in agreement with the findings Solerte et al [6] who observed that patients who were receiving sitagliptin prior to admission had significant reduction in serum markers of inflammation such as CRP and procalcitonin. In addition, in patients with type 2 diabetes, Satoh-Asahara et al [15] have shown that sitagliptin therapy was associated with significant increase in expression of the anti-inflammatory cytokine interleukin-10 (IL10), a finding that further supports the inflammation-suppressive effects of sitagliptin.

6. Metformin and COVID-19 Related Mortality

Multiple retrospective studies have shown significant mortality reduction in patients admitted with COVID-19 who were taking metformin, possibly due to its anti-inflammatory effects. The most comprehensive data in this respect was derived from the recent meta-analysis conducted by Kow and Hassan [18]. In the latter study, the authors analyzed data (up to August 8, 2020) of 5 studies including 8,121 patients with diabetes and COVID-19 who were using metformin prior to hospital admission. Pooled analysis revealed a significantly reduced risk for mortality with the use of metformin prior to admission, pooled odds ratio (OR) being 0.62 (95% CI, 0.43-0.89) compared to patients with diabetes who were not using metformin [17,18]. Interestingly,

this mortality benefit of metformin was not demonstrated in the studies of DPP-4 inhibitors mentioned above. Thus, in the study of Solerte et al [6], pre-admission therapy with metformin did not have any effects on clinical outcomes. Meanwhile, in the study of Mirani et al [7], there was a trend towards mortality reduction among COVID-19 patients who were taking metformin prior to hospitalization. Yet, this trend did not reach statistical significance; adjusted OR 0.55, 95% CI (0.27-1.11). Nevertheless, further data are needed as studies of both DPP-4 inhibitors and metformin suffer from similar limitations with respect to their non-randomized designs.

Table 1. Retrospective studies of DPP-4 inhibitors in COVID-19

Reference	**Solerte et al [6]**	**Mirani et al [7]**	**Rhee et al [8]**	**Fadini et al [9]**	**Yan et al [10]**
Country	Italy	Italy	South Korea	Italy	China
Design	Case-control, multicenter	Case series, single center	Claims of COVID-19 in National Review and Assessment Service data base	Retrospective	Case control analysis
Patients	338 hospitalized patients with type 2 diabetes, 169 on sitagliptin	90 hospitalized patients with diabetes including 11 patients on DPP-4 inhibitors	263 patients on DPP-4 inhibitors vs 569 patients on no DPP-4 inhibitors	9 hospitalized patients on DPP-4 inhibitors vs 76 patients on no DPP-4 inhibitors	6 patients on DPP-4 inhibitors and 52 diabetic patients on no DPP-4 inhibitors, and 48,667 control subjects
Effect of DPP4 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).	Reduction in risk of death or ICU admission, OR 0.36 (95% CI, 0.13-0.97).	No significant difference in mortality: DPP-4 inhibitors 11.1% vs no DPP-4 inhibitors 13.9% (P=0.82).	Not reported
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	Not reported	No difference in ICU admissions: DPP-4 inhibitors 33.3% vs no DPP-4inhibitors 19.2% (P=0.32)	No significant association of use of DPP-4 inhibitors and severity of COVID-19
Comments	Reduction in procalcitonin and C-reactive protein in sitagliptin group	Only study in which use of DPP-4 inhibitors were continued after admission	This database is representative of the Korean population		PPP-4 inhibitors associated with Increased risk of COVID-19. OR 6.02 (95% CI, 2.3-15.5)

7. Conclusions and Current Directions

It is tempting to speculate that DPP-4 inhibitors such as sitagliptin may have protective effects in COVID-19. This concept is based on results of 3 retrospective investigations showing substantial reduction in mortality in patients with COVID-19 and type 2 diabetes taking DPP-4 inhibitors prior to hospitalization. The decrease in mortality was associated with significant improvement of clinical status and decrease in need for ICU transfer and mechanical ventilation. Moreover, in one study, the DPP-4 inhibitor was continued during hospitalization. Indeed, the latter study reported the highest reduction in mortality in association their anti-diabetic effects. demonstrate such benefits in a limited number of 9 patients [6-9]. 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. Randomized trials are urgently needed to clarify the therapeutic role of DPP-4 inhibitors in

hospitalized patients with COVID-19. It is worthwhile to evaluate patients with and without type 2 diabetes in these trials to see to what extent the beneficial actions of DPP-4.

References

Januvia (2006) tablets. Prescribing information. Merk & CO, INC., Whitehouse Station, NJ 08889, USA.

Mikhail N (2011) Safety of dipeptidyl peptidase 4 inhibitors for treatment of type 2 diabetes. Curr Drug Safety 6: 304-309.

Dastan F, Abedini A, Shahabi S, et al. (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 19: 10-12.

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: 110111.

Solerte SB, Di Sabatino A, Galli M, Fiorina P (2020) Dipeptidyl peptidase-4 (DPP-4) inhibition in COVID-19. Acta Diabetol 57: 779-783.

Solerte SB, D'Addio F, Trevisan R, et al. (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 29: dc201521.

Mirani M, Favacchio G, Carrone F, 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, Epub ahead of print.

Rhee SY, Lee J, Nam H, et al. (2020) Effects of a DPP-4 inhibitor and RAS blockade on clinical outcomes of patients with diabetes and COVID-19. Medrxiv.

Fadini GP, Morieri ML, Longato E, et al. (2020) Exposure to dipeptidyl-peptidase-4 inhibitors and COVID-19 among people with type 2 diabetes: A case-control study. Diabetes Obes Metab.

Yan H, Valdes AM, Vijay A, et al. (2020) Role of drugs used for chronic disease management on susceptibility and severity of COVID-19: A large case-control study. Medrxiv.

American Diabetes Association (2020) Diabetes care in the hospital: Standards of Medical Care in diabetes-2020. 43: S193-S201.

Wu J, Huang J, Zhu G, 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 8: e001476.

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.e8.

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.

Satoh-Asahara N, Sasaki Y, Wada H, et al. (2013) A dipeptidyl peptidase-4 inhibitor, sitagliptin, exerts anti-inflammatory effects in type 2 diabetic patients. Metabolism 62: 347-51.

Marques C, Mega C, Gon?alves A, et al. (2014) Sitagliptin prevents inflammation and apoptotic cell death in the kidney of type 2 diabetic animals. Mediators Inflamm 538737.

Cameron AR, Morrison VL, Levin D, et al. (2016) Antiinflammatory effects of metformin irrespective of diabetes status. Circ Res 119: 652-665.

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