



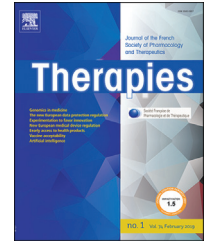
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LETTER TO THE EDITOR

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

KEYWORDS

Covid-19;
 DPP-4 inhibitors;
 Mortality

Abbreviations

CI confidence interval
 COVID-19 coronavirus disease 2019
 DPP-4 dipeptidyl peptidase-4

We read with interest the review by Bouhanick et al. [1] which discussed the association between diabetes mellitus and coronavirus disease 2019 (COVID-19). Particularly, the authors have summarized the available evidence on the use of several classes of glucose-lowering agents in patients with COVID-19, and they postulated that dipeptidyl peptidase-4 (DPP-4) inhibitors could influence the course of COVID-19 via their anti-inflammatory actions. While the medical community had been struggling to search for a potential cure in patients with COVID-19, we believe that DPP-4 inhibitors should be trialled for their efficacy to reduce the risk of death and/or severe disease in this patient population. Since there have been few studies which addressed the issue, we aimed to perform a meta-analysis to summarize the overall effect of DPP-4 inhibitors on the clinical outcomes in patients with COVID-19.

We searched PubMed, Google Scholar, Scopus, and medRxiv (a preprint repository) databases, up to 17 November 2020, for studies of any design evaluating the risk of a fatal or severe course of COVID-19 among DPP-4 inhibitor users compared to non-DPP-4 inhibitors users, with the following keywords and their MeSH terms: "COVID-19", "SARS-CoV-2", "dipeptidyl-peptidase-4", "DPP-4", and "gliptin", without language restrictions. The inclusion criteria were studies that investigated the preadmission use of DPP-4 inhibitors on the risk of a fatal or severe course of COVID-19 and reported adjusted measures of association. We excluded editorials or narrative reviews without original data. In addition, studies that provided no adjusted estimation were also excluded. Each included article was

independently evaluated by two authors (CSK and SSH) who extracted the study characteristics and adjusted measures of effect. The quality of observational studies was evaluated using the Newcastle-Ottawa scale. The outcome of interest was the development of a fatal or severe course of COVID-19. Adjusted odds ratios or relative risks and the corresponding 95% confidence intervals from each study were pooled in a random-effects model using Meta XL, version 5.3 (EpiGear International, Queensland, Australia) to produce pooled odds ratio and 95% confidence interval. The I^2 statistic was performed to estimate the magnitude of heterogeneity.

We were able to retrieve six studies [2–7] of observational design that corresponded to our inclusion and exclusion criteria. Study characteristics are depicted in Table 1. Altogether, the meta-analysis included over 1,531 patients with COVID-19. Except the study by Dalan et al. [6] which is of moderate quality (Newcastle-Ottawa scale of 5), the remaining five studies [3–5,7,8] are deemed good quality with a Newcastle-Ottawa scale of 7 to 8. There was non-uniformity in the definition of the severe disease in patients with COVID-19 utilized across the six included studies. In both the studies by Chen et al. [2] and Yan et al. [6], severe illness was defined based on the diagnosis and treatment plan for COVID-19 issued by the National Health Commission of China.

In the study by Kim et al. [3], severe illness was defined based on the use of high-flow nasal cannula, mechanical ventilation, continuous renal replacement therapy, extracorporeal membrane oxygenation, and admission to intensive care units. In the study by Rhee et al. [4], severe illness was defined based on the presence of procedure code for endotracheal intubation or mechanical ventilation, or the charge of an intensive care unit management fee. In the study by Dalan et al. [5], severe illness was defined based on admission to intensive care units. In the study by Pérez-Belmonte et al. [7], severe illness was defined based on admission to intensive care units, the use of invasive and non-invasive mechanical ventilation, or in-hospital death.

Our meta-analysis revealed no significant difference in the risk for the development of a fatal or severe course of illness with preadmission use of DPP-4 inhibitors in patients with COVID-19, relative to non-use of DPP-4 inhibitors (Fig. 1; pooled odds ratio = 1.15; 95% confidence interval 0.64–2.06; $I^2 = 54\%$). The potential role of DPP-4 inhibitors in patients with COVID-19 has been a subject of ongoing debate. DPP-4 inhibitors including gemigliptin, linagliptin, and evogliptin, have demonstrated their potential in the *in silico* molecular docking analysis to inhibit the main

Table 1 Characteristics of included studies.

Study	Country	Design	Total number of patients	Age (median/mean unless otherwise specified)	Severe/Fatal course of illness ^a			Covariates adjustment	NOS
					DPP-4 inhibitors users (n/N; %)	Non-DPP-4 inhibitors users (n/N; %)	Adjusted estimate (95% CI)		
Chen et al. [2]	China	Retrospective, single center	120	DPP-4 inhibitor users = 66.0 Non-DPP-4 inhibitor users = 65.0	N/A	N/A	OR = 1.81 (0.51-6.37)	Age, serum albumin level, serum creatinine level, C-reactive protein level, blood glucose level	8
Dalan et al. [5]	Singapore	Retrospective, single center	76	N/A	N/A	N/A	RR = 5.14 (1.49-17.70)	Age, sex, ethnicity, use of anti-hypertensive medications, other diabetes Medications, statins, haemoglobin A1c, systolic and diastolic blood pressure, body mass index	7
Kim et al. [3]	Korea	Retrospective, multicenter	235	All patients = 68.3	N/A	N/A	Severe illness: OR = 1.05 (0.44-2.49) Mortality: OR = 1.47 (0.45-4.78)	Age, sex, comorbidities	7
Rhee et al. [4]	Korea	Retrospective database review	832	DPP-4 inhibitor users = 63.7 Non-DPP-4 inhibitor users = 61.0	25/569 (4.4)	9/263	OR = 0.36 (0.14-0.97)	Age, sex, comorbidities, co-medications	7
Yan et al. [6]	China	Retrospective, multicenter	58	All patients = 49.2 (14.2)	1/6 (16.7)	20/52 (38.5)	OR = 0.32 (0.02-2.18)	Age, sex, body mass index	5
Pérez-Belmonte [7]	Spain	Retrospective, multicenter	210	DPP-4 inhibitor users = 80.0 Non-DPP-4 inhibitor users = 79.4	45/105 (42.9)	42/105 (40.0)	OR = 1.12 (0.65-1.95)	Age, sex, history of smoking, comorbidities, Barthel Index score, Charlson Comorbidity Index score, co-medications, admission blood glucose, serum creatinine, transaminase levels	7

CI confidence interval; DPP-4 dipeptidyl peptidase-4; NOS Newcastle-Ottawa Scale; OR odds ratio; RR relative risk.

^a In both the studies by Chen et al. [2] and Yan et al. [6], severe illness was defined based on the Diagnosis and Treatment Plan for COVID-19 issued by the National Health Commission of China. In the study by Kim et al. [3], severe illness was defined based on the use of high-flow nasal cannula, mechanical ventilation, continuous renal replacement therapy, extracorporeal membrane oxygenation, and admission to intensive care units. In the study by Rhee et al. [4], severe illness was defined based on the presence of procedure code for endotracheal intubation or mechanical ventilation, or the charge of an intensive care unit management fee. In the study by Dalan et al. [5], severe illness was defined based on admission to intensive care units. In the study by Pérez-Belmonte et al. [7], severe illness was defined based on admission to intensive care units, the use of invasive and non-invasive mechanical ventilation, or in-hospital death.

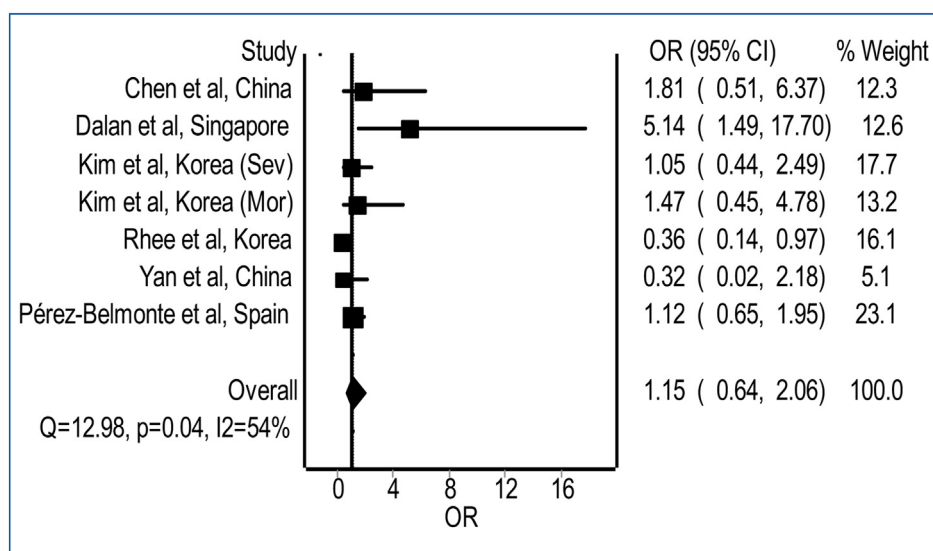


Figure 1. Pooled odds for a fatal or severe course of illness in COVID-19 patients with preadmission use of DPP-4 inhibitors relative to non-use of DPP-4 inhibitors. (heterogeneity: $I^2 = 54\%$; $P = 0.04$). CI: confidence interval; DPP-4: dipeptidyl peptidase-4; OR: odds ratio.

protease of severe acute respiratory syndrome coronavirus 2, which plays a pivotal role in viral gene expression and replication [8]. Nevertheless, DPP-4 plays also a vital role in the regulation of the immune system via activation of T cells through the nuclear factor- κ B pathway and thus its inhibition may adversely affect the immune response to viral infection, especially when lower levels of T cells have been reported to correlate with severity of COVID-19 [9,10].

Our meta-analysis had a moderate heterogeneity ($I^2 = 54\%$), contributed substantially by the study from Dalan et al. [5] due to wide confidence interval reported. Although our meta-analysis was limited by a relatively small number of patients included and wide confidence interval, it does indicate no safety signal thus far associated with the use of DPP-4 inhibitors in patients with COVID-19. Whether DPP-4 inhibitors could be beneficial to the prognosis of patients with COVID-19 requires further confirmation in large-scale prospective studies.

Disclosure of interest

The authors declare that they have no competing interest.

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Éruption eczématiforme après le vaccin par Pfizer-BioNTech COVID-19[☆]

Eczematiform eruption after Pfizer-BioNTech COVID-19 vaccine

Mots clés Éruption eczématiforme ; Vaccin ; ARN messenger ; COVID19 ; Effet secondaire

Keywords Eczematiform eruption; Vaccine; mRNA; COVID19; Adverse event

Abréviations

COVID-19 maladie à coronavirus 2019

IgE immunoglobulines E

PA paquet-année

SARS CoV-2 *severe acute respiratory syndrome coronavirus-2*

Les vaccins à base de nanoparticules lipidiques contenant de l'ARNm (LNP) sont de nouvelles molécules utilisées par Pfizer-BioNTech et Moderna, pour lutter contre la maladie à coronavirus en 2019 (COVID-19). Ces vaccins ciblent la protéine « spike » du virus (« protéine spicule » ou « protéine S »). Cette protéine est située à la surface de l'enveloppe du *severe acute respiratory syndrome-coronavirus-2* (SARS-CoV-2), et lui permet de se fixer à un récepteur cellulaire, l'enzyme de conversion de l'angiotensine 2 puis de pénétrer dans les cellules de l'organisme [1,2].

Les essais cliniques et les vaccinations en cours montrent des niveaux de protection élevés et des effets indésirables de gravité variable. Cependant, certains types d'effets indésirables rapportés, notamment cutanés, restent encore mal définis. Dans l'essai clinique de phase III du vaccin Pfizer-BioNTech COVID-19 [3] et dans le premier rapport de morbi-mortalité post-commercialisation du vaccin [4], les principales manifestations cutanées rapportées étaient de type anaphylactique (urticaire et l'exanthème érythéma-



Figure 1. Éruption eczématiforme des membres inférieurs.

teux diffus) et des réactions allergiques non anaphylactiques (réaction au site d'injection, prurit et éruptions cutanées sans description sémiologique) [4–6].

Baden et al ont rapporté des réactions immédiates au site d'injection après la première dose de Pfizer-BioNTech. Récemment Jedlowski et al ont rapporté un exanthème morbilliforme après chaque dose d'injection du vaccin Pfizer-BioNTech [7]. Nous rapportons ici le premier cas à notre connaissance d'une réaction eczématiforme diffuse survenue 8 jours après la première injection du vaccin Pfizer-BioNTech, et récidivant 4 jours après l'administration de la seconde dose.

Observation

Il s'agit d'un homme de 80 ans, en bon état général, ayant comme antécédent une hypertension artérielle traitée par amlodipine depuis plusieurs années, un tabagisme à raison de 60 paquet-année (PA). Le patient n'avait aucun antécédent d'eczéma, d'atopie, ni d'allergie connue. Dans les 2 h suivant l'injection le patient a présenté une fébricule à 38 °C et des céphalées qui ont régressé après 72 h. Huit jours plus tard, le patient a présenté une éruption prurigineuse composée de macules et de plaques érythémato-squameuses mal limitées au niveau du tronc et des 4 membres (Fig. 1). La surface cutanée atteinte était estimée à 20 %. Il n'y avait pas d'atteinte muqueuse ni phanérienne. Le patient était apyrétique, et ne présentait aucun signe systémique. La prise en charge initiale avec antihistaminiques et une crème anti-mycosique n'a conduit à aucune amélioration.

[☆] Ce cas a été déclaré au Centre régional de pharmacovigilance et de pharmaco épidémiologie Centre-Val de Loire le 22 février 2021 et enregistré sous le numéro 210767.