Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Fenofibrate as a COVID-19 modifying drug: Laboratory success *versus* real-world reality

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To the Editor,

It is of interest to note the benefits of statin therapy on mortality in hospitalised COVID-19 patients in the meta-analysis of retrospective observational studies by Kollias and colleagues [1]. Their analysis does highlight potential mechanisms, beyond lipid metabolism, of widely prescribed lipid lowering drugs.

Two studies on fenofibrate, a widely prescribed fibrate drug used in the management of dyslipidaemia, have detailed intracellular effects on SARS-CoV-2 beyond its established benefits on plasma lipids [2,3]. The first study confirmed the effects of fenofibrate on virus replication in human lung epithelial cells [2]. Fenofibrate reversed the changes induced by the SARS-CoV-2 virus on intracellular upregulation of glycolysis and lipogenesis, thereby blocking the metabolic footprint for viral replication. By contrast, other drugs that also affect lipid or glucose targets: rosiglitazone, metformin, and empagliflozin, did not have the same viral inhibitory effect [2]. The second study confirmed the inhibition by fenofibrate of the receptor binding domain for ACE2 to prevent SARS-CoV-2 infection [3]. These two separate laboratory findings have been proposed as modes of action for fenofibrate to be considered as a therapeutic option to downgrade COVID-19 infection [2,3].

There is additional evidence for fibrates affecting other viruses via anti-inflammatory and immunomodulatory activities, including: the influenza virus [4], herpes simplex [5] and Japanese murine encephalitis [6]. However, there is limited clinical and real-world data supporting these laboratory observations.

From the UK-based Oxford-Royal College of General Practitioners (RCGP) Research & Surveillance Centre (RSC) national database [7] covering a primary-care population of over 15 million in England and Wales, we undertook a real-world fenofibrate observational study. Data was pseudonymised at the time of extraction. The study was conducted under approvals from Royal College of General Practitioners Research Surveillance Centre scientific advisory committee and University of Oxford, Medical Sciences Interdivisional Research Ethics Committee. The study was conducted in a cohort with coding for first confirmed COVID-19 diagnosis and evaluated the association of established fenofibrate (either 160 mg, 200 mg or 267 mg dose) therapy to post-COVID-19 diagnosis 28 day all-cause mortality and new-onset loss of smell (a recently described important clinical COVID-19 symptom). Date at which COVID-19 was first confirmed using codes from the COVID-19 ontology. All analyses were undertaken using the statistical software R (ver. 3.5.3).

Patients with COVID-19 positive coding and on fenofibrate therapy were matched to similar patients with COVID-19 not prescribed fenofibrate therapy. Matching was achieved using propensity scores, matching 1:5 ratio, with a caliper set at 0.2 of the standard deviation of the logit of the propensity score. Propensity scores were based on a logistic regression model including factors associated with worse COVID-19 outcomes: age, male gender, ethnicity, obesity (BM1 $\geq$ 30), diabetes, history of hypertension, cardiovascular disease (ischaemic heart disease, ischaemic stroke or peripheral vascular disease) and smoking status.

From a cohort with confirmed first COVID-19 diagnosis (n = 477,803), we identified 596 cases on a minimum three-month fenofibrate treatment, and compared to a non-fibrate group, propensity score matched (5:1) (n = 2,980) for risk factors for severe COVID-19 disease. In a Kaplan Meier analysis, there was no divergence in survival curves for 28 day all-cause mortality between the fenofibrate group and the non-fenofibrate group (Hazard Ratio [95% CI] 1.07 [0.75–1.55], p = 0.68.). There was also no observed difference (Hazard Ratio [95% CI)] 0.99 [0.55–1.76], p = 0.96) between fenofibrate and matched non-fenofibrate groups for new-onset loss of smell. This large primary-care based observational study is one of the first to report the effects of fenofibrate on COVID-19 infection in real-world clinical practice, but did not corroborate a treatment benefit for post-COVID-19 diagnosis 28-day mortality and new-onset loss of smell.

The detailed evidence for a positive effect from laboratory-based studies with fenofibrate suggests that randomised controlled trials are required to properly evaluate whether fenofibrate, as well as statin treatment, with low acquisition costs, have COVID-19 disease-modifying potential in hospitalised patients and in routine clinical practice.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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