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.

Pharmacological Research 163 (2021) 105285

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Letter to the Editor in response to the article 'Candidate drugs against SARS-CoV-2 and COVID-19'

Dear Editor,

McKee and colleagues published in Pharmacological Research in 2020 an interesting review article on new and repurposed drugs for COVID-19 treatment. The careful reading of this relevant article brought to mind a series of considerations that we report in the letter.

COVID-19 constitutes a worldwide wartime-like health, societal and economic emergency and many drugs, including biological ones, have been repurposed for the treatment of this disease [1]. Drugs repurposing reduces discovery and development times and decreases overall costs, as well as most preclinical and clinical tests including safety and pharmacokinetic profiles, which were already performed.

One of the most severe complications of COVID-19 consists in sepsis-like inflammation that may evolve into "*hyperinflammation*" [2]. Inflammation and immunological make-up of men and women present numerous and relevant sexual dimorphisms [2]. Interestingly, ageing affects women's and men's immune systems differently, as old men exhibit a "*stronger inflammatory*" response than old women [2]. In line with the above observations, COVID-19 has more devastating effects in older men [2].

Infectious and inflammatory diseases alter drug metabolism predominantly down-regulating the drug metabolizing enzymes (cytochrome P450 (CYP) enzymes, phase II enzymes etc.) [3]. In animals "*hyperinflammation*" effects on CYP enzymes expression appear to be sex and CYP enzymes expression dependent [3], while, at best of our knowledge, we still don't know if sex controls this process in humans. Changes in pharmacokinetics can lead to adverse drug reactions (ADR), drug-drug interactions and a decrease in drug efficacy. Therefore, we wonder if the drug kinetic obtained in healthy individuals or in patients without a massive inflammatory reaction is transferable to COVID-19 patients of both sexes.

The majority of approved drugs, including COVID-19 repurposed drugs, are metabolized by CYP3A4 enzyme, and women have more protein and metabolize CYP3A4 substrates more quickly than men [4]. As inflammatory response is bigger in men with COVID-19 than in women [2], it is possible to speculate that men could have a greater inhibition of CYP450 enzymes that, together with a greater activity of CYP34A in women, could contribute to generate sexual dimorphism in the pharmacokinetics of COVID-19 treatments.

In addition, among drugs repurposed for COVID-19 there are some biologicals that alone or in combination with small synthetic drugs may interferes with the inflammatory pathways. Consequentially, biologics therapy can change the expression and activity of the drug metabolizing enzymes depending on the pro-or anti-inflammatory properties of the biologic drug [3]. For example, tocilizumab, repurposed drug for COVID-19, elevates metabolism of simvastatin in rheumatoid arthritis patients [3].

Although things are slowly changing, especially in phase 3 trials, early stage trials are still heavily male-biased [4]. Consequentially, information deriving from early stage is mainly missing in women, however there are cases where information is missing in men and this lack of acknowledgement reflects on repurposed drugs.

Finally, many of drugs repurposed for COVID-19 prolong the QT interval including the remdesivir (an anti-Ebola agent), that is the only drug approved by FDA for the treatment of COVID-19 [5]. As already mentioned, many of repurposed drugs are metabolized by CYP3A4 which can be down-regulated by inflammation (which is bigger in old men) and or by combination therapy with inhibitors of CYP3A4, therefore the risk of QT-prolongation and drug-induced cardiac death could be enhanced [4]. This point is crucial because Covid-19 patients often have myocardial damage that might be a trigger for enhanced arrhythmic risk [2]. In line with this, a descriptive comparison of drugs used in COVID-19 and in non-COVID-19 indications (performed using global ADR database VigiBase) evidences more ADR reports (with exception of chloroquine) in men than in women in line with a greater risk for COVID-19 in men [6]. In men, the main reported ADR is QT-prolongation followed by diarrhea, nausea, hepatitis, and vomiting. In women, the most reported ADR is diarrhea followed by QT-prolongation, nausea, vomiting, and upper abdominal pain. Notably, the literature in non COVID-19 patients sustains that to be a woman is a risk factor for QT-prolongation [4] but Zekarias and collegues's paper does not show it in COVID-19 patients [6].

In our opinion, COVID-19 offers a remarkable opportunity to enrich the pharmacological culture, as studying the repurposed drugs in both men and women represents a real opportunity and not a double-edged sword and this could be useful to avoid the perpetuation of gender bias. Despite all the available technology, once again, only a limited space is reserved to sex and gender, even in a pathology that presents significant sexual differences in lethality, that heavily involves the immune system (essentially sexually dimorphic), and in which the pharmacokinetics of drugs can be substantially different from that obtained in healthy individuals or in subjects suffering from diseases with low inflammatory reaction.

Declaration of Competing Interest

The authors report no declarations of interest.

References

[1] D.L. McKee, A. Sternberg, U. Stange, et al., Candidate drugs against SARS-CoV-2 and COVID-19, Pharmacol. Res. 157 (2020), 104859.
[2] R.H. Manjili, M. Zarei, M. Habibi, et al., COVID-19 as an acute inflammatory disease, J. Immunol. 205 (1) (2020) 12–19.
[3] P. Mallick, G. Taneja, B. Moorthy, et al., Regulation of drug-metabolizing enzymes in infectious and inflammatory disease: implications for biologics-small molecule drug interactions, Expert Opin. Drug Metab. Toxicol. 13 (6) (2017) 605–616.

https://doi.org/10.1016/j.phrs.2020.105285
Received 27 October 2020
Available online 4 November 2020

[4] F. Franconi, I. Campesi, D. Colombo, et al., Sex-gender variable: methodological recommendations for increasing scientific value of clinical studies, Cells 8 (5) (2019).
[5] https://www.fda.gov/drugs/drug-safety-and-availability/fdas-approval-veklury-remdesivir-treatment-covid-19-science-safety-and-effectiveness.
[6] A. Zekarias, S. Watson, S.H. Vidlin, et al., Sex differences in reported adverse drug reactions to COVID-19 drugs in a global database of individual case safety reports, Drug Saf. (2020).

Ilaria Campesi*
Dipartimento di Scienze Biomediche, Università degli Studi di Sassari, 07100 Sassari, Italy
Laboratorio Nazionale di Farmacologia e Medicina di Genere, Istituto Nazionale Biostrutture Biosistemi, 07100 Sassari, Italy

Andrea Montella
Dipartimento di Scienze Biomediche, Università degli Studi di Sassari, 07100 Sassari, Italy

Flavia Franconi
Laboratorio Nazionale di Farmacologia e Medicina di Genere, Istituto Nazionale Biostrutture Biosistemi, 07100 Sassari, Italy

* Corresponding author at: Dipartimento di Scienze Biomediche, Università degli Studi di Sassari, 07100 Sassari, Italy.
E-mail address: icampesi@uniss.it (I. Campesi).