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PARP-inhibitors in a non-oncological indication as COVID-19: Are we aware about its potential role as anti-thrombotic drugs? The discussion is open



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ABSTRACT

In the last three months, the whole scientific community has shifted its focus to the fight against the COVID-2 infection (COVID-19) trying to use different medications to save the patients' life. In some studies, the results were completely inconclusive, as in the case of chloroquine. However, the recent discovery on benefits deriving from use of such anticoagulants for Covid-19 patients, has increased the success of patients' treatment. Among lots of old and new drugs, PARP-inhibitors were not considered as possible option in the treatment of Covid-2 infection, being the latter able to induce the inflammatory and thrombotic cascades. Since PARP-inhibitors are able to reduce and block mechanisms leading to thrombosis and inflammation, they could be used as antithrombotic medications. Therefore, the present brief report is aimed to open the discussion on the potentials of PARP-inhibitors in non-oncological settings, like Covid-19.

Dear Editor,

In the last three months, most research groups have shifted their focus to the fight against the COVID-2 infection (COVID-19). Many scientists worked to understand: a) how the virus is transmitted and able to mutate; b) how it can be sensitive to new and old drugs. Currently, the results obtained in this field resulted as not always promising and, sometimes, completely inconclusive, as in the case of chloroquine [1–4]. However, the recent discovery on benefits deriving from use of such anticoagulants for COVID-19 patients, has increased the success of patients' treatment [5]. In fact, as reported by Poggiali *et al.* [6], since the disseminated intravascular coagulation and coagulopathy can contribute to patients' death, anticoagulant administration has been reported as being associated with decreased mortality in severe COVID-19 pneumonia [6]. Both Tang *et al.* and Poggiali *et al.* [5,6] assessed that low molecular weight heparin (LMWH) regimen seems to be associated with better prognosis in severe COVID-19 patients meeting sepsis-induced coagulopathy criteria or with markedly elevated D-dimer. Along with other experimental treatments, or in combination [4], these findings have dramatically reduced the number of patients needing intensive cares, with a lightening of the workload of the emergency departments and the definitive improvement in the ratio of deaths to infected. The same trend has been observed into Italian hospitals, during the last seven weeks, after the introduction of LMWH as additional medication [6–8]. However, although with some concerns,

mainly related to the schemes of LMWH administration [9], using of prophylactic-doses of LMWH was recommended by the International Society on Thrombosis and Haemostasis (ISTH) for all recovered COVID-19 patients, except for those with an active haemorrhage or with a platelet count $< 25 \times 10^9/L$. [10].

While many drugs are still under investigation in clinical trials [11,12], after a rapid approval by the medical agencies of different countries, no definitive results are reported. In this regard, very recently, a research group focused on different treatments administered to Chinese individuals showing as there is no proven regimen from conventional medicine [13]. Nevertheless, several clinical trials managed patients with lopinavir/ritonavir, ribavirin, beta-interferon, glucocorticoid and supportive treatment with remdesivir undergoing clinical trial [11,13]. After an extensive revision of the latest national and provincial clinical guidelines, retrospective cohort studies, and case series regarding the treatment of COVID-19 by add-on Chinese medicine, Chan *et al.* [11] concluded that, due to the paucity of strongly evidence-based treatments, the current data only suggest that Chinese medicine could be considered as an adjunctive therapeutic option in the management of COVID-19.

In this scenario, where nothing is completely clear, and after reading the paper published by Berger *et al.* [12], I would like to open the discussion on two main topics which were not covered by the current literature.

The first, why no available data are reported about any possible

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relationship between SARS-CoV-2 infection and patients under chemotherapy regimen with poly-ADP ribose polymerase-1 (PARP-1) inhibitors (PARPi)? This empirical consideration, not still supported by literature data, emerged from my experience gained in the last ten years research on the onco-genetic aspects of PARP-inhibition in women suffering from ovarian cancer [14–17]. Noteworthy, patients under anti-PARP-1 regimens [18,19], particularly those with pancreatic, prostate, ovarian and breast cancers (most of them enrolled in clinical trials), might be more protected by the SARS-CoV-2 severe effects, like the thrombotic events. I underline that Bevacizumab administration was reported to be associated to venous thromboembolism in ovarian cancer patients, mostly in those with elevated D-dimer level and high BMI before chemotherapy [20]. Contrastingly, these findings were never reported for Olaparib [17]. Regarding PARP pathway, several studies showed as the inhibition of PARP-1 reduced organ dysfunction in post-myocardial infarction remodelling, ischemia-reperfusion injury, diabetic retinopathy, septic shock, diabetes, and atherosclerosis, attenuating diseases associated with vascular smooth muscle and endothelial dysfunction. The latter is a specific feature of COVID-19 [5,6]. Mathews et al. [21] demonstrated that PARP-1, when activated by oxidative and nitrosative stress, consumes cellular energy and precipitates endothelial cell death. Therefore, inhibition of PARP-1 prevented ROS- and RNS-induced HUVEC death, not only by maintaining cellular energy, but also through a novel mechanism via VEGFR2, Akt, and Bad phosphorylation. All these findings are very interesting when translated to the possible mechanisms surrounding the disseminated intravascular coagulation and coagulopathy processes and leading to either patient's severe symptoms or death related to COVID-19. Noteworthy, the inflammatory process, cytokine storm, and lung injury can result in an increased risk of thrombosis for SARS-CoV-2 positive patients [5,6]. In this setting, use of anti-PARP drugs in non-oncological indications, although still under debate, was reported as being of benefit in inflammatory disorders such as arthritis, psoriasis, colitis, asthma, diabetic complications and cardiovascular diseases [12]. Moreover, although data on total incidence of thrombotic events in COVID-19 are still uncertain, we can assume that individuals with increasing age, obesity, comorbidities and cancer are at higher risk of these events. Based on the scientific evidences regarding a potential anti-inflammatory and anti-thrombotic effect of PARP-1 inhibitors [21], the scientific community should be encouraged to investigate these compounds in the treatment of COVID-19, particularly due to the mitigation effects of all pathways promoting the inflammatory and thrombotic cascades, respectively [21–23].

PARP enzymes (PARP-1 and PARP-2) play a pivotal role in sustaining the genome stability. PARPi are small molecule mimetics of nicotinamide which bind to PARP's catalytic domain to inhibit poly-ADP-ribosylation (PARylation) of target proteins [19]. Considering that different forms of PARP inhibitors are present now on the market (olaparib, veliparib, talazoparib, niraparib and rucaparib) (22), there will be an easy access to these medications for using in either new clinical trials and/or in translational studies.

Moreover, although a risk of genotoxicity can be also associated to PARP-1i long term administration [12], this issues alone should not be a reason to exclude a study drug for testing these molecules in a non-oncological indication, like COVID-19 condition. As for LMWH, also in this case different schemes of administration should be evaluated in order to achieve the best benefit for patients. Therefore, I agree with Berger et al. [12] there are no sufficient reasons to exclude studies based on PARP inhibitors for testing in the most severe forms of COVID-19.

The second, tightly related to the previous one, is why are there no definitive data of association between the number of patients, particularly the elderly ones, under routine anticoagulant/anti-aggregator therapies (such as warfarin and clopidogrel) and COVID-19 outcomes. Theoretically, patients under long-term anticoagulant regimens should have been a little bit more protected from the risk of thrombotic events

as compared to those not using these medications. Since these data are still missing, it is not so easy to accept that LMWH can be safely administered in anti-Covid-19 routine practice, above all following the same regimens of standard anticoagulant therapy [9].

Finally, as recently reported by Ge et al., through *in silico* screening and computational analysis, followed by wet-lab validation, a PARP1i, namely CVL218, currently in Phase I clinical trial, could be of beneficial for the treatment of COVID-19, due to its anti-inflammatory properties [24]. These authors underline as during the life cycle of the coronavirus, PARP-1i may suppress viral replication [24].

The above considerations are far from being provocative, but they are only aimed to stimulate a thought on this specific topic. I would be grateful to the Editor if, through the publication of this paper, it would allow us to open up the debate on the subject.

Declaration of Competing Interest

None.

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