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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
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

Ettore Capoluongo

**ABSTRACT**

In the last three months, the whole scientific community has shifted its focus to the fight against the COVI-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 COVI-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 × 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
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 VEGFFR2, 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. PARPs 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, currently in Phase I clinical trial, could be of benefit 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.

References

[1] Y. Jin, H. Yang, W. Ji, W. Wu, S. Chen, W. Zhang, G. Duan, Virology, epidemiology, pathogenesis, and control of COVID-19, Viruses. 12 (4) (2020).
[2] H.A. Rothan, S.N. Byrareddy, The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak, J. Autoimmun. 109 (2020) 102453.
[3] E.D. Capoluongo, F. Amato, G. Castaldo, The friendly use of chloroquine in the COVID-19 disease: a warning for the G6PD-deficient males and for the unaware carriers of pathogenic alternations of the G6PD gene, Clin. Chem. Lab. Med. (April 24) (2020).
[4] F. Di Gennaro, D. Pizzol, C. Marotta, M. Antunes, V. Racalbuto, N. Veronesi, L. Smith, Coronavirus diseases (COVID-19) current status and future perspectives: a narrative review, Int. J. Environ. Res. Public Health 17 (6) (2020) April 14.
[5] N. Tang, H. Bai, X. Chen, J. Gong, D. Li, Z. Sun, Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy, J. Thromb. Haemost. 18 (May 5) (2020) 1094–1099, https://doi.org/10.1111/j.1538-7836.2020.04710.x.
[6] E. Poggioli, D. Bastoni, E. Ioannidi, V. Arevoli, M. Magnacavallo, Deep Vein Thrombosis and Pulmonary Embolism: Two Complications of COVID-19 Pneumonia? Eur. J. Case. Rep. Intern. Med. 7 (5) (2020) 001646.
[7] H. Fogarty, J. Townsend, C. Ni Chollaghaigh, C. Bergin, I. Martin-Loeches, P. Browne, C.L. Bacon, R. Gaule, A. Gillett, M. Byrne, K. Ryan, N. O’Connell, J.M. O’Sullivan, N. Conlon, J.S. O’Donnell, More on COVID-19 coagulopathy in caucasian patients, Br. J. Haematol. (May 2020) May 12.
[8] A. Remuzzi, G. Remuzzi, COVID-19 and Italy: what next? Lancet 395 (10231) (2020) 1225–1228, April 11.
[9] M. Marietta, V. Coluccio, M. Luppi, More on: ‘COVID-19 coagulopathy in caucasian patients’, Br. J. Haematol. (May 11) (2020).
[10] J. Thachil, N. Tang, S. Gando, A. Falanga, M. Cattaneo, M. Levi, C. Clark, T. Iba, ISTH interim guidance on recognition and management of coagulopathy in COVID-19, J Thromb. Hemost. (2020).
[11] K.W. Chan, V.T. Wong, S.C.W. Tang, COVID-19: an update on the epidemiological, clinical, preventive and therapeutic evidence and guidelines of integrative Chinese western medicine for the management of 2019 novel coronavirus disease, Am. J. Chin. Med. 48 (3) (2020) 737–762.
[12] N.A. Berger, V.C. Besson, A.H. Boulanger, et al., Opportunities for the repurposing of PARP inhibitors for the therapy of non-oncological diseases, Br. J. Pharmacol. 175 (2018) 192–222.
[13] Y.F. Tu, C.S. Chien, A.A. Yarmishyn, Y.Y. Lin, Y.H. Luo, W.Y. Lai, D.M. Yang, S.J. Chou, V.P. Yang, M.L. Wang, S.H. Chiou, A review of SARS-CoV-2 and the ongoing clinical trials, Int. J. Mol. Sci. 23 (7) (2020) 10.
[14] E. Capoluongo, BRCA to the future: towards better testing practice in the era of personalised healthcare, Eur. J. Hum. Genet. 1 (2016) S1–2.
[15] I. Paris, S. Gianci, G. Vizzelli, A. Fagotti, G. Ferrandina, S. Gurdì Alletti, B. Costantini, F. Cosentino, E. Capoluongo, M. Pasqualoni, G. Scambia, Upfront HIPEC and bevacizumab-containing adjuvant chemotherapy in advanced epithelial ovarian cancer, Int. J. Hyperthermia 35 (1) (2018) 370–374.
[16] C. Marchetti, R. De Leo, A. Musella, M. D’Innisano, E. Capoluongo, A. Minucci, P. Benedetti Panic, G. Scambia, A. Fagotti, BRCA mutation status to personalize management of recurrent ovarian Cancer: a multicenter study, Ann. Oncol. 25 (November 12) (2018) 3701–3708.
[17] D. Lorusso, G. Scambia, S. Pignata, R. Sorio, G. Amadio, S. Lepori, A. Mosconi, C. Pisanos, M. Mangili, M. Maltese, R. Sabbatinis, G. Artioli, T. Gamucci, M. Di Napoli, E. Capoluongo, V. Ludovini, F. Raspagliesi, G. Ferrandina, Prospective phase II trial of trabectedin in BRCA-mutated and/or BRCAness phenotype recurrent ovarian cancer patients: the MITO-15 trial, Ann. Oncol. 28 (2015) 370–376.
[18] E. Sachdev, R. Tabatabai, V. Roy, B.J. Rimel, M.M. Mitza, PARP inhibition in Cancer: an update on clinical development, Target. Oncol. 14 (2019) 657–679.
[19] H. Xie, W. Wang, B. Xia, W. Jin, G. Lou, Therapeutic applications of PARP inhibitors in ovarian Cancer, Biomed. Pharmacother. 127 (2020) 110204.
[20] A. Kuk, M. Magnowska, W. Suchy, J. Swierczynska, M.P. Zaborowski, M. Gaca, E.N. Markwitz, Retrospective evaluation of thromboembolism risk in ovarian Cancer patients treated with bevacizumab, Target. Oncol. 12 (2017) 495–503.

[21] M.T. Mathews, B.C. Berk, PARP-1 inhibition prevents oxidative and nitrosative stress-induced endothelial cell death via transactivation of the VEGF receptor 2, Arterioscler. Thromb. Vasc. Biol. 28 (2008) 711–717.

[22] K.E. McCann, Advances in the use of PARP inhibitors for BRCA1/2-associated breast cancer: talazoparib, Future Oncol. 15 (2019) 1707–1715.

[23] N. Curtin, K. Rinyai, J. Thaventhiran, J. Le Quesne, Z. Helyes, P. Bai, Repositioning PARP inhibitors for SARS-CoV-2 infection (COVID-19); a new multi-pronged therapy for ARDS? Br. J. Pharmacol. (May 22) (2020).

[24] Y. Ge, T. Tian, S. Huang, F. Wan, J. Li, S. Li, H. Yang, L. Hong, N. Wu, H. Yuan, L. Cheng, Y. Lei, H. Shu, X. Feng, Z. Jiang, Z. Chi, X. Guo, L. Cai, L. Xiao, Z. Li, C. Yang, Z. Miao, H. Yang, L. Chen, H. Zeng, D. Zhao, F. Zhu, X. Shen, J. Zeng, A data-driven drug repositioning framework discovered a potential therapeutic agent targeting COVID-19, bioRxiv preprint (2020), https://doi.org/10.1101/2020.03.11.9868362020.