JIM Letter to the Editor

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The pathogenesis of microthrombi in COVID-19 cannot be controlled by DOAC: NETosis should be the target

Dear Editor,

We read with interest the data of DOAC-treated patients infected by SARS-CoV-2 compared to the no-DOAC-treated patients. The study by Flam et al [1] is of utmost importance since it sheds light on one of the most controversial aspects of COVID-19 disease: the thrombotic microangiopathy. Autopsy studies disclosed small vessels' thrombotic microangiopathy [2], along with associated venous thrombotic manifestations with or without pulmonary emboli [3]. All these studies have shown that increased D-dimer levels (>1000 ng mL^{-1}) and increased inflammatory markers (very high CRP and IL6 > 80–90 pg mL^{-1}) were present in the critical and severe patients. Yet, none of the patients had clear-cut evidence of haemolytic anaemia or schistocytes, thus suggesting a different thromboangiopathy.

Recent data by Carsana et al [2] and Grasselli et al [3] may allow to interpret the pathogenesis. The AA focused on the pathology of dead patients, and on the pathophysiology of critical ICU - COVID-19–related ARDS and the studies suggest possible pathogenetic events. The major findings were that in severe ARDS of COVID-19, coagulopathy-leukothrombosis (NETosis) and hyperinflammation were two main drivers [2]. In ICU, static lung compliance values were statistically higher, yet a subgroup had a lower compliance than in classical ARDS [3] and the very low compliance, associated with high mortality. D-dimer levels were, as a whole, within the expected median values, yet a subset had very high levels and very high D-dimers (thromboinflammation) also associated with mortality. The latter subset presents, according to several studies, with hyperinflammation (high CRP, high ferritin, high IL6, high IL8- IL8 and IL6 are inducers of NETs) [2,3,4]. Importantly, reports suggest that with D-dimers higher than 1000 ng mL^{-1} but without lung CT emboli, clear-cut hypoperfusion (leukothrombosis) can be demonstrated [5].

We have demonstrated that early COVID-19 pneumonia already has distinct lung hypoperfusion in affected areas, with hyperperfusion around the infiltrating pneumonia [4]. These findings are compatible with microvessel thrombotic complications (NETosis-related), much more than with the classical lung thrombotic microemboli [6].

Unfortunately, DOAC does not disrupt NET-related thrombi, whereas anticoagulant doses of LMWH (low molecular weight heparin) do and recent studies directly investigating the link between heparin and SARS-CoV-2 suggest that heparin can directly bind with the spike protein of the SARS-CoV-2 virus and, therefore, may have indirect antiviral properties. BTK (Bruton tyrosine kinase) inhibitors, besides normalizing quickly CRP and IL6, demonstrated to be promising therapeutic tools, since the inhibition of platelet–neutrophil aggregates and neutrophil FcγRIIA stimulation by Btk inhibitors suppress the generation of neutrophil extracellular traps (NET), a major driver of thrombosis [7]. The recent demonstration of LMWH resistance in ICU patients and the documented low levels of antithrombin III in severe cases suggest that a real personalized approach should be deeply pursued to obtain the full expected outcomes. In conclusion having demonstrated that DOAC does not prevent severe COVID-19 severe outcomes, clinicians and scientists are led to define different and most pathogenetically oriented therapies to better control the microthrombotic angiopathy that characterizes the lung (and other organs) of these patients.

Conflict of interest

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Author contribution

Elisa Gremese and Gianfranco Ferraccioli conceptualized the study and wrote, reviewed and edited the manuscript.

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