Commentary

SARS-CoV-2 coming of age (and with it both previous successes and new problems)

Giovanni C Actis[1], Davide G Ribaldone[1]

1. University Hospital in Turin, Turin, Italy

SARS-CoV-2 and its syndromic tail, (soon become popular under the label -19), have now happily come of age after a glorious rush (though frankly destructive for us) around the world, after pulling out of the stinky shuffle of a poorly identified Chinese market. It seems that those capital events took place sometime in late 2019. Now early in January 2023, i.e., three years later, and well over 6 million victims passed away, one of the few pieces of evidence we have, is revealing that the ground can still be trembling under our feet, if we realize the following. According to a few scientists who might have scrutinized the problem from a little closer point, the unusually high replicating rhythm of the SARS-CoV-2 is laying down the condition for the chance budding out of the "finally perfect" variant, endowed with a 360 degrees field of drug resistance. If anyone would still be hungry for more appalling evidence against our race, it just remains to be stressed that some Corona clones have been characterized to be fully efficient in mimicking the spontaneous viral disease, including the boosted inclination to trigger deadly mega-thrombi in large lung and brain vessels. Thus, in a word: our road to an acceptably safe harbor abreast of deadly zoonoses seems to be still long and rocky. In such untold and dire straits, one can only be reminded to appreciate and re-consider previously forgotten "simple" life values, reappraising the tiny grains of ease that we might stumble in, and save them all, perhaps for even harder challenges. Needless to say, the obscure path ahead should always be illuminated (as much as we can) with the only light of science.

Corresponding authors: Giovanni C Actis, actis_g@libero.it; Davide G Ribaldone, davidegiuseppe.ribaldone@unito.it

 doi.org/10.32388/I187XO.3

Background

After three years, the data now in our hands show that we have been hit (and still we are) by a yet untold killer virus, as reinforced by a rough dashboard: total infected <643. 875.406; fatal outcome <6.6.08230. 12.998.974.878 vaccine maneuvers; 1.1%, toxicity. The relevant pandemic that subsequently broke out was officially named the SARS-CoV-2 pandemic (after the virus). The identification of COVID-19, rapidly reaching top people's favor, does in fact represent a misnomer. The European Medical Authority Board had intended this label for the clinical pictures that may follow the initial SARS infection. No matter what bureaucracy really wanted, this new threat to Mankind's survival early in 2020 had already marked a milestone[1], for the few reasons examined below.

Main Text

1) Apart from the "historic Spanish Flu", in 1918, associated with a world death toll of some 50 million, (the argument for many school studies of all time), very few or no of our contemporary neighbors can readily provide an adequate reply if interviewed on any in-depth question on this yet appalling event. Simply, the Covid 19 just "came out of the blue" for most mortals on earth. 2) The allegedly infectious cause (SARS-CoV-2) is piling up on itself a few tempting curiosity reasons, including 3) a mysterious pre-historic origin[2], which, nevertheless, has not been convincingly disentangled from possible trivial loss of contact between the virus and its watching policeman in a Chinese market shuffle; The Corona(s) seem to be endowed with an utterly potent pro-inflammatory, and pro-coagulative apparatus[3] capable to rapidly place patients in jeopardy and lead supervising Authorities to strongly advise upgrading and placing Coronas to higher levels of defense guard. This circumstance, coupled with an ounce of genuine curiosity, has finally deserved a level of clinical attention, when the degenerative CNS diseases (Alzheimer's, Parkinson's, Creutzfeldt's) were shown recently to have engaged the fastest gear again, preparing to climb harder incidence peaks. We purportedly confined our efforts to achieve closer scrutiny of the relationship between COVID-19-infected hosts. The well-known hyper-inflammatory potential of the COVID agents proved in many cases to be an irresistible temptation to dissect the pro-inflammatory virus role, as opposed to the cell defensive arsenal. An excess of active fibrinogen, in tandem work with a propensity to easy intravascular coagulation, may end up with the devastating formation of intravascular masses of transformed atypical fibrinogen, leading unavoidably to diffuse ischemic damage.[4] At this point, one can readily understand that a punctual classification of the heterogeneous materials floating

within the patient's vessels will be crucial to understanding immediate reactions and immediately following strategies. Large systematic studies mostly based on the master experience of the German Professor Paul Ehrlich in varied times of the 19th century taught us -and thousand of highly committed pathologists- the way to perceive the dramatic difference between microscopic deposition of fibrin powder in "common" atherosclerotic subjects, as opposed to the nascent hyaline networks (harbingers of the giant thrombi dealt with here) that might "(typically") be appreciated in the lumen of cerebral vessels, as belonging to subjects undergoing a diagnostic

autopsy[5] following COVID-19 infection, either spontaneous or (fortunately a minority) in temporal coincidence with a vaccination session. Vascular surgeons have often treasured such autopsy findings because providing clues to the effective choice amongst as many tentative treatments as: injection of dissolving solutions, alone or in combination with

the positioning of intra-vessel filters preventing floating debris to reach and block the blood supply to the heart; careful surgical debridement of the mostly diseased vessel connections. These premises really do involve matters (at an equivalent relevancy level) of legal medicine and emergency vascular correction, with an obvious interdependence. Building up a severity rank will help establish the appropriate level of therapy as a function of the intervention risk; The other crucial point stems from the high level now reached with our etiologic scanners i.e. the detection of involvement of proteins in the pathologic coagulation chains. Thus, we believe that a simple operational take-home message can pivot on the above notes: 1) A classification must be modeled onto a cause-effect interpretation key; 2) Search for the existence of prion-like entities[6] and, if found, a definition of the causative role. In lines of theory, COVID-deriving proteins (the SPIKE holding the utmost importance), can exert the centrally conceived denaturing (coagulative effect) on host proteins through three main interconnected pathways.

A. The exuberant pro-coagulative power carried in by the COVID-expressed protein (the already cited SPIKE, but others also) may well exert the two synergic roles of protein misfolding (specific of prions) and induction of tissue hypoxia. These details are mastered in the smart companion paper[7] authored by Chakraborty *et al.*
B. Other teams, stressing the same points, have imagined an additional source of damage, favored by the delicate intranuclear positioning of the nascent SPIKE protein domains: random bumps of SPIKE debris with sub-cellular host membranes could ignite newly elusive inflammation facilitators.[8]
C. We ourselves,[9] reiterating closer scrutiny of the entire material, were struck by the poorly emphasized possibility

that a fully working coagulative prion may become disguised as a Spike Protein. This construction would imply autonomous roles of COVID proteins, rendering redundant any emphasis on supervening other pathogens in the coagulation cascade, despite the attention on this pathway being stressed by authoritative names.[10]

SPECIFIC DECISION-MAKING in light of the above elucidation

No matter how fussy our criticism can be against the nucleic-acid-based recently launched vaccines, obviously conceived to cripple COVID-pandemic, one must agree that planning a new agent from base 0 would be inadequate at this time of the initial viral attack. Instead, we deem it reasonable to try and theoretically discuss a couple of options.

In our opinion, it would be desirable to progressively loosen the "obsessive" fuss focused until now on the search for a T- cell-based vaccine, tentatively exploring instead, the offer from the innate, non-specific pathways, with a specific eye to: -1) Relative ease of preparation; 2) Species specificity, but no viral specificity i.e large applications over the limitations of T-cell dependent immunity; 3) immediately effective upon injection. We have reported some extra details of a project involving (as a stimulator "fake" virus) the handy use of synthetic polynucleotides (Poly:IC *et al.*), making reference to a few ongoing NIH trials.[11], mirrored in clinics[12]. Last but not least, we cannot neglect worrying breaking news claiming figures that warn that the "pandemic is far from over, "again suggesting a strong need to at least consider the trained immunity alternative[12].

Indeed, it is easy to anticipate that those men/women, battered for months in the absence of any shelter, could have accepted anything presented as an anti-viral weapon. We deem that administration of the SARS virus as a cutaneous patch that can be squeezed under one's fingertips does raise a kind of reassuring "glow" that cannot be released from the pharmacy cartoons fallen from a military jet making its silent path 36 thousand feet amongst fluffy clouds over the operation camp. Relevant data did also reaffirm that acceptance or perplexity do depend on the class of information which people get exposed to, the pre-information mind state, and the ease to trust authorities. All-in-all, at the moment we are feeling most keen at placing our trust in trained -immunity vaccines,[13] as antigen non-specific agents but ready to go, as functional stimulators of Interferon, which in turn can exploit the antiviral efficacy of the NK cells to a large extent. At this point, we believe we are not wrong in guessing the referee's interest to see an add-on part on the current role, together with the projection plans, concentrating on the exploitation of populations of trained-immunity cells in the management of SARS-CoV-2-induced

immune derangements. To perhaps try to terminate this sort of “passionate plea”, we find it adequate to remind that real-life trials have readily demonstrated the best adherence levels from workers deployed in any activity and involved with the decision at any stage, compared to those kept apart from active participation[14]. Finally, we were hit by seeing a delicate psychologic issue almost resolved in a pretty military initiative.

Such programs, which are largely based on a critical role of IFN, will require a pedantic search for the relatively common non-function IFN variant; such variants are known to hamper timely switch from IFN to T-cell mediated responses, a step which, if failing, is known to dramatically detract from the success of any anti-viral immune response.[15]

Needless to say, any pathway, whether present or future, directed to defining all reasonable anti-COVID strategies will have to be strictly revised, reappraised, and reinforced, taking as reference the impending multi-viral attacks as per forecast by the main monitoring organizations.

Conclusively driving home: This neglected, sudden, harsh multi-viral attack last time came close to placing his boots over our neck, and now no more is left before the combat bell tolls again within our still shivering ears. Confident teaming up and individual bravery, before it gets too long, should succeed in preparing the antidote for the next unknown attacker. The future, however, is not ours to see.

(Ongoing paper opened December 8, 22)

References

1. ^ *The end of the COVID-19 pandemic is in sight: WHO | UN News. https://news.un.org>2022/09*
2. ^ *Holmes EC et al, The origins of SARS- Cov2: a critical review. CELL, 2021; 184: 4848-4856.*
3. ^ *Darif D et al, 2021; The pro-inflammatory cytokines in COVID-19 pathogenesis. Microb Pathog, 2021; 153: 1 04799.*
4. ^ *EMA NEWS: European Medicins Agency. COVID-19 Vaccine Janssen: EMA finds possible link to very rare c ases of unusual blood clots with low blood platelets. Risk –benefit ratio remains high 20.04.21*
5. ^ *Bilotta C, Perrone G et al. COVID-19 Vaccine-Related. Thrombosis: A Systematic Review and Exploratory A nalysis Frontiers in Immunology, 2021; 12: 729251.*
6. ^ *Kell DB, Laubscher GJ, Pretorius E. A central role for fibrin microclots on Long Covid/PASK: origins and imp lications. Biochem J, 2022; 479, 537.*

7. ^Sankha Shubhra Chakrabarti, Shagun Gupta, Upasana Ganguly, Ankur Kaushal, et al. (2022). Effects of the SARS-CoV-2 Spike protein on in vitro aggregation of alpha synuclein- probable molecular interactions and clinical implications. Qeios. doi:10.32388/4425WE.
8. ^Kowarz E, Krutzke, L, Reis J, Bracharz, S, Kochanek S, Marschalek, R.Vaccine-induced COVID 19 Mimicry Syndrome. Res Sq, 2021; May 26.
9. ^Actis GC, Ribaldone DG, Pellicano R. Covid vaccines hot problems: erratic serious blood clotting, ill-defined prion-like reactogenicity. Min Med, 2021; 112: 695-697
10. ^Greinacher A, et al. Anti-platelet factor antibodies causing VTT do not cross-react with SARS-Cov2 Spike Protein. Blood, 2021; 384: 2092.
11. ^Komal, A., Noreen, M. & El-Kott, A.F. TLR3 agonists: RGC100, ARNAX, and poly-IC: a comparative review. Immunol Res 69, 312–322 (2021). https://doi.org/10.1007/s12026-021-09203-6
12. a, bLancet Editorial: COVID pandemia in 2023: far from over. 2023; 401: Issue 10371
13. ^Actis GC, Ribaldone DG, Pellicano R, Fagoonee S. COVID-19: a User's Guide, status of the art, and original proposal to terminate viral recurrence. Min Med 2021; 112: 144
14. ^Abrams E., The Challenges and Opportunities for shared decision making. Allergy Clin Immunol, 2020;8: 2474-80
15. ^Silva MJA, Ribeiro LR, Lima KVB and Lima LNGC (2022) Adaptive immunity to SARS-CoV-2 infection: A systematic review. Front. Immunol. 13:1001198. doi: 10.3389/fimmu.2022.1001198

Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.