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Targeting the immunology of coronavirus disease-19: synchronization creates symphony

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Currently, there is a deluge of data on coronavirus disease 2019 (COVID-19). There are proponents of different therapies to target COVID-19 including antivirals, anti-inflammatory, and immune therapies [1–3]. There is an emerging role of thrombosis in disease pathogenesis [4]. The current emphasis seems to have shifted to predominantly immunology-based strategies like advocating mass vaccination drives for BCG, pneumococcus, and influenza; neutralizing the virus with convalescent plasma or monoclonal antibodies and testing interferon-based therapies [2]. Rheumatologists have a special say in the situation since anti-inflammatory, immune, and even anti-thrombotic therapies are their forte [5]. We feel the need of the hour is to have a strategized and synchronized attack on COVID-19 on various fronts. Thus, it is pertinent for rheumatologists and immunologists to know about, and integrate, various diverse strategies in the battle against COVID-19.

The outcome of any infectious disease depends on its yin–yang relationship with the immune system. A hyperactive immune system can be as dangerous as a virulent virus. The SARS-CoV-2 has evolved into a pandemic, as it has mastered various aspects: immune evasion, high reproductive rate, spread via asymptomatic individuals, and virulence by both cytopathic effects as well as by inducing a hyperactive immune response.

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Thus, a multi-pronged attack strategy is required to combat it (Fig. 1). The first is to limit its spread via social distancing [6]. The Korean experience is exemplary in going into an early lockdown [7]. The second is to identify and isolate positive cases via different and extensive testing strategies [8]. These first two strategies will prevent the more virulent strains from passing on to new individuals. Exclusion of such strains will help in the selection of less virulent strains and hopefully, in the long run, a mildly virulent strain will remain endemic similar to other prevalent coronavirus strains.

The third strategy is to limit viral entry for which drugs like camostat, hydroxychloroquine or even heparin have been proposed [9–11]. The fourth is to limit viral replication via repurposing of various drugs developed for other viruses such as remidesivir (Ebola), lopinavir/ritonavir (Human Immunodeficiency virus), favipiravir (influenza) since there is overlap of the reverse transcriptase mechanism amongst these RNA viruses [3]. The fifth is to limit the cytopathic effects of the virus that is attempted with inhibition of the canonical renin–angiotensin–aldosterone (RAAS) pathway with angiotensin I converting enzyme (ACE) inhibitors [12] or prothrombotic disseminated intravascular coagulation with heparin [13]. The sixth is immune modulation against the virus as suggested below and also elaborated in Fig. 1.

One focus is on humoral (antibody related) aspects of immune modulation including natural defence by cross-reacting antibodies to other viruses, the effect of BCG vaccination, intravenous immunoglobulin (IvIg), convalescent serum and monoclonal antibodies [2].

The complementary aspect of immune therapy is to strengthen the cell-mediated immunity (CMI) against SARS-CoV-2. Severe COVID-19 is associated with low interferon (IFN) [14] and this might imply suppression of CMI. There is some preliminary evidence that type 1 IFN therapy may have benefit in COVID-19 [15, 16]. An

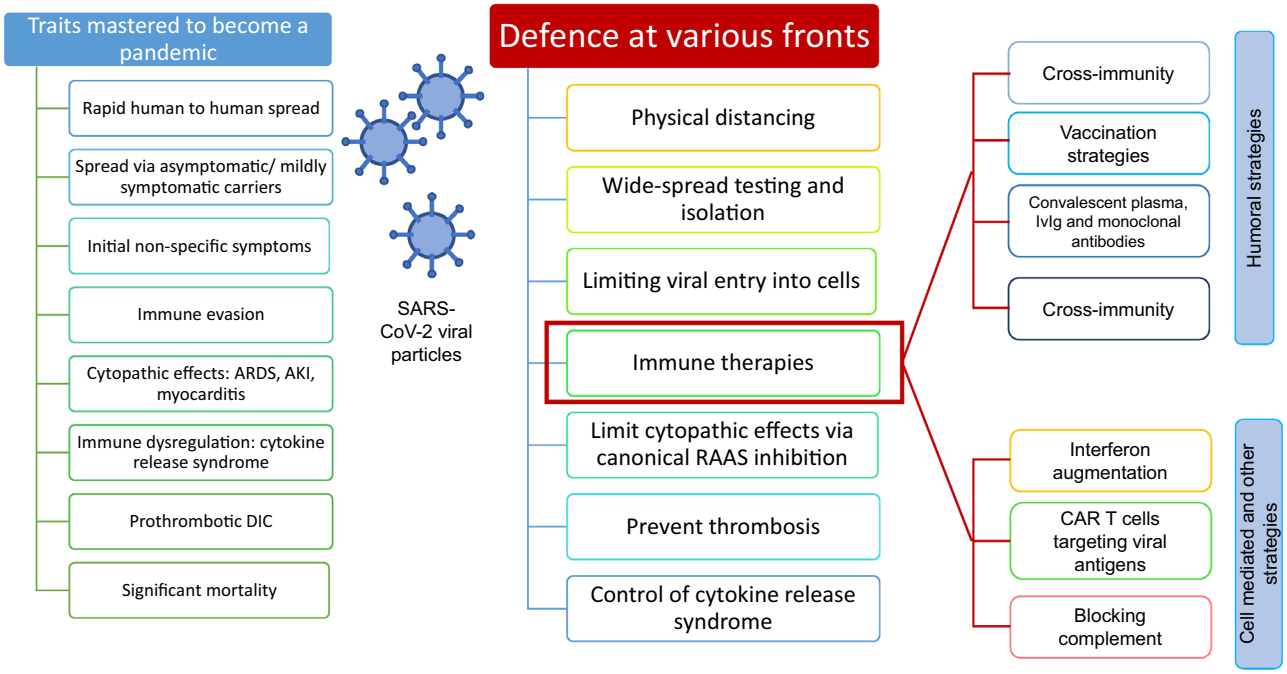

Fig. 1 Various hallmarks of Coronavirus disease 2019 (COVID-19) and multimodal strategies required to combat it. *ARDS* Acute Respiratory Distress Syndrome, *AKI* acute kidney injury, *DIC* disseminated intra-vascular coagulation, *RAAS* renin–angiotensin–aldosterone system, *IvIg* intravenous Immunoglobulin, *CAR-T cells* chimeric antigen receptor-T cells

initial in silico study has proposed the use of baricitinib in COVID-19 [17]. However, baricitinib blocks the interferon pathway and thus, this approach is not free from controversy. Another cutting edge concept is the use of chimeric antigen receptor (CAR) T cells against SARS-CoV-2 viral antigens to augment the patients' CMI. Such proof of concept studies has been carried out for HIV and cytomegalovirus [18]. There is a trial of CAR-NK (Natural killer) cells registered for COVID-19 [NCT04324996]. However, again, producing adequate numbers of CAR-T cells to battle a pandemic is not a feasible option at present.

The complement system forms an integral part of immune system. There are also proposals to target the complement system to abrogate systemic thrombosis in COVID-19 [19]. Blockade of complement component C5a has been shown to be effective in treating acute lung injury in murine models of influenza A viruses H5N1, H7N9, and severe acute respiratory syndrome (SARS) coronavirus [20].

There is emerging evidence for combining treatment strategies [21]. However with the concoction of therapies, the real challenge will be to find the optimal timing and sequencing of each. This can be considered within the confines of a large multi-therapy trial like the World Health Organization's SOLIDARITY trial [22]. Our hypothesis is that the small effects sizes from each treatment strategy can be synergistically added to obtain maximum benefit for severe COVID-19 disease.

Author contributions SA drafted the manuscript and it was critically revised by both SA and PA. Both the authors have approved the final

manuscript and take full responsibility for the integrity of the data and the contents of the manuscript.

Compliance with ethical standards

Conflict of interest Sakir Ahmed declares that he has no conflict of interest. Prajna Anirban declares that he has no conflict of interest.

Ethical approval This letter is a brief review of secondary data and does not come under the purview of an ethics review.

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