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Current Perspective

Immune checkpoint inhibitors: a physiology-driven approach to the treatment of coronavirus disease 2019

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Abstract While confirmed cases of the deadly coronavirus disease 2019 (COVID-19) have exceeded 4.7 million globally, scientists are pushing forward with efforts to develop vaccines and treatments in an attempt to slow the pandemic and lessen the disease's damage. Although no proven effective therapies for treating patients with COVID-19 or for managing their complications currently exist, the rapidly expanding knowledge regarding severe acute respiratory syndrome coronavirus 2 and its interplay with hosts provides a significant number of potential drug targets and the potential to repurpose drugs already tested in other diseases. Herein, we report the biological rationale of immune-activating drugs and a brief summary of literature data on the potential therapeutic value of immune checkpoint inhibitors that have been recently tested beyond cancer treatment for their potential to restore cellular immunocompetence.
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Coronavirus disease 2019 (COVID-19) is a pandemic infection caused by a positive-sense RNA betacoronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Acute respiratory distress syndrome (ARDS) and multiorgan dysfunction are among the leading causes of death in critically ill patients with COVID-19. Elevated concentrations of proinflammatory cytokines and chemokines including interleukin (IL)-2, IL-6, interferon gamma−induced protein 10, macrophage inflammatory protein alpha, monocyte chemotactic protein 1 and tumour necrosis factor-alpha (TNF-α) [1,2] suggest that a cytokine release syndrome may play a major role in the pathology of COVID-19.

Higher mortality has been linked to elderly subjects and those with comorbidities including pulmonary disease, cardiac disease, kidney disease, diabetes, hypertension and cancer [3]. Whether cancer *per se* increases the risk of SARS-CoV-2 infection and its complications or rather cancer-associated comorbidities and treatment remains to be clarified. A recent study showed that patients with cancer undergoing chemotherapy or surgery in the past month have an increased risk of severe complications compared with those not receiving recent treatments [4]. This risk seemed higher in the presence of additional chronic medical conditions, which is consistent with other recent reports [3,5]. Curiously, none of the patients in this study received anticancer immunotherapy including treatment with immune checkpoint inhibitors (ICIs), which are extensively used to treat many cancers. Given the limited number of cases analysed, these findings could simply be due to chance; however, it also adds to other evidence suggesting that ICIs are protective rather than harmful in patients with COVID-19. While chemotherapies are indeed known to exert a systemic immunosuppression along with a myelosuppressive state by lowering the complete blood count and/or impairing the immune regulatory response even in the face of a normal blood test, this seems not to be the case for ICIs. On the contrary, they restore cellular immunocompetence [6].

The immune checkpoint pathway is an endogenous component of the immune system that is responsible for coordinating the physiological immune response, maintaining self-tolerance and protecting tissues from damage. Several models have shown that blocking programmed cell death-1 (PD-1) or programmed death-ligand 1 (PD-L1) can prevent T-cell death, regulate cytokine production and reduce organ dysfunctions. T cells play a vital role in viral clearance, with $CD8^+$ cytotoxic T cells (CTLs) capable of secreting an array of molecules such as perforin, granzymes and interferon gamma to eradicate viruses from the host. At the same time, $CD4^+$ helper T cells (Ths) can assist CTLs and B cells and enhance their ability to clear pathogens. However, persistent stimulation by the virus may induce T-cell exhaustion, leading to a loss of cytokine production capability and reduced functions [7,8]. Many factors are involved in this process, and negative costimulatory molecules including immune checkpoints are key elements.

There is increasing recognition that a state of impaired host immunity accompanied by a significant cell degeneration in secondary lymphoid tissues follows the initial hyperinflammatory phase of COVID-19. First, critically ill high-risk patients with COVID-19 often present with lymphocytopenia: A fall in the total lymphocyte number to 0.6×10^6/mL is associated with a mortality rate of 75% [2]. Second, patients with COVID-19 have high levels of serum IL-6, IL-10 and TNF-α and express increased levels of exhaustion markers PD-1 and T-cell immunoglobulin mucin-3 on the surface of their peripheral T cells, which in turn impair T-cell effector functions and prevent functional memory [9]. Finally, compared with cases of pneumonia not caused by SARS-CoV-2, patients with COVID-19 have decreased B cell and Th counts but a comparable number of the main cytokine storm (CS) players including monocytes, neutrophils and natural killer cells [10]. These latest data suggest that viral damage is direct rather than inflammatory driven and strongly supports the use of immune-activating drugs that have been little considered to date for fear of exacerbating the inflammatory reaction and causing a CS.

Among immune-activating drugs, ICIs have been recently tested beyond cancer treatment for their potential to restore immunocompetence in the context of sepsis and influenza infection. A recent phase Ib trial reported that in patients with systemic sepsis, the anti−PD-1 monoclonal antibody nivolumab can restore lymphocyte count and function with no concern on the CS, i.e. levels of IL-6, IL-8 and TNF-α are unaffected [11]. These findings were consistent with those of the anti−PD-L1 monoclonal antibody BMS-936559 in patients with sepsis-induced immunosuppression [12]. Another intervention aimed at testing the safety of ICIs was influenza vaccination in patients with cancer treated with anti−PD-1/anti−PD-L1 antibodies. Several studies reported no increase of incidence or severity of immune-related adverse events [13,14], and as an additional finding, a lower overall rate of influenza among vaccinated patients when compared with rates of laboratory-confirmed influenza has been reported [14]. Other data show that ICI-induced pneumonitis is a very rare phenomenon, with 2.5−5% with anti−PD-1/anti−PD-L1 single-agent therapy to 7−10% with dual checkpoint blockade, and most patients experienced clinically significant, new or worsening immune-related adverse events after the first 6 months of treatment [15]. These data suggest that ICIs enhance T-cell response to viral antigens without triggering unintended immune consequences including the CS and autoimmunity.

Currently, there are no finally verified data and no antiviral drugs licensed by the US Food and Drug Administration and European Medicines Agency for treating patients with COVID-19 or for managing their complications. Since its first outbreak in China, COVID-19 was empirically treated with antiviral and respiratory supportive therapies mainly agents already used in prior SARS epidemics. Thus, this provides an opportunity for the research community to better outline the value of immune-modulating agents in the treatment of COVID-19. Current evidence revealed that a timely anti-inflammation treatment is of pivotal importance in avoiding exacerbation and preventing further injury in severe SARS-CoV-2−induced pneumonia. Although the use of some of them is still controversial, a plethora of anti-inflammatory agents have been proposed to alleviate the systemic CS. Based on the promising results from an open-label study in 21 patients with severe and critical COVID-19 [16], tocilizumab—a human monoclonal antibody that binds to both soluble and membrane-bound IL-6 receptors (IL-6Rs)—is currently being investigated to address cytokine release syndrome in patients with severe ARDS, which includes randomised, controlled trials (ChiCTR2000029765; NCT04320615) and single-arm trials (ChiCTR2000030796; NCT04317092). These studies must be considered alongside two trials assessing the safety and therapeutic efficacy of anti−PD-1 inhibitors in patients with similar eligibility criteria (NCT04268537; NCT04333914).

Regardless of the shortcomings reported in patients receiving single-agent tocilizumab, it is likely that more effective treatments targeting both overexuberant inflammation and exhausted T cells require the combination of two classes of agents because they work through in a different and complementary mechanism. PD-1 expression likely increases to prevent an uncontrolled inflammatory cascade [17]. Therefore, the use of anti−PD-1 treatment would produce satisfactory therapeutic effects in combination with an anti−IL-6R. This approach requires caution. Indeed, in the early phase of viral infection, the PD-1/PD-L1 axis is also involved in the physiological process of T-cell maturation, implying that PD-1 negatively regulates the terminal differentiation of naive CTLs into effector T cells. Thus, the blockade of the PD-1 pathway adjusts the strength and quality of cytotoxic cell attack to accelerate virus clearance with minimal collateral tissue damage [17]. However, in a later phase, the blockade of the coinhibitory receptor PD-1 can release the brake in exhausted T cells that in turn increases the antiviral T-cell responses [18].

Most importantly, the CD8$^+$ T-cell immunosurveillance of viruses is dependent on human leucocyte antigen class I (HLA-I) molecules that are expressed on the surface of all nucleated cells. Genetic differences in *HLA* alleles have been recently recognised to confer differential viral susceptibility and severity of COVID-19 [19]. Data validated in two independent cohorts of patients with cancer receiving ICIs revealed that heterozygous *HLA-I* genotypes were associated with better survival than homozygosity for one or more *HLA-I* genes, and treatment efficacy was diminished by loss of *HLA-I* heterozygosity [20]. These findings highlight that genetic variability in the immune system may affect susceptibility to (and severity of) SARS-CoV-2; therefore, strategies to boost immune responses at this stage are certainly important for individuals particularly vulnerable to COVID-19.

We believe that there is sufficient evidence to support clinical trials combining IL-6R antagonists with PD-1 inhibitors to improve outcomes in patients with COVID-19. We propose that an earlier intervention with anti−PD-1 therapy will minimise the need for intensive care support.

Author contributions

All authors listed have made a substantial, direct and intellectual contribution to the work and approved it for publication.

Conflict of interest statement

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