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UNDERSTANDING THE DISEASE

Targeted immunomodulation: a primer for intensivists

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Targeted immunomodulation is a topic that gained wide interest from translational researchers in the past decades, yet immunomodulatory drugs were not frequently administered to intensive care patients. The coronavirus disease 2019 (COVID-19) pandemic has resulted in the first widespread use of the single target immunomodulators tocilizumab, an interleukin-6 (IL-6) receptor blocking antibody, and baricitinib, an inhibitor of janus kinase (JAK), and may have opened the doors for other immunomodulatory treatments in critically ill patients [1]. In this manuscript, we provide a short introduction on targeted immunomodulation for intensivists. We will try to answer the most common questions that intensivists encountering this topic may have.

Why modulate the immune response?

Critically ill patients suffer of organ dysfunction, which is frequently attributed to dysregulation of the inflammatory host response [2]. Inflammatory processes have a central role the pathophysiology of organ dysfunction in critically ill patients. Besides the consequences of an over-stimulated innate immune response, there is increasing evidence that the susceptibility of critically ill patients to secondary infections can be linked to a failed immune response, irrespective of primary insult. Reshaping the host response can, therefore, theoretically facilitate a more rapid resolution of organ injury as well as protect against secondary infections.

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What is the difference between immunosuppression and immunomodulation?

The most prototypical example of broad immunosuppressive drugs are corticosteroids. They have broad effects through multiple genomic pathways. Therefore, they are almost always effective in suppressing both auto-inflammatory (involving the innate immune response) and auto-immune (involving the adaptive immune response) conditions [3], and may reduce organ injury[4]. Immunomodulators have much more specific effects and typically intervene in one pathway and, therefore, could be used to target exactly the over-activated pathway in the causal path towards injury (Fig. 1).

How to modulate the immune response?

In contrast to the broad and rather unselective suppression of the immune system that corticosteroids have, immunomodulators have very specific effects. The over-activated innate immune response can be targeted at multiple points: the induction of the response, signaling functions and/or effector cells. The induction effect of pathogen or damage associated molecular patterns (PAMPs/DAMPs) on the inflammatory cells can be limited by blocking toll-like receptors (TLR), such as TLR4. Co-stimulation of complement factors can be limited by selective inhibition of C5a. Essential signal molecules such as IL-6, IL-1 beta and tumor necrosis factor alpha (TNFa) can be blocked at the receptor level. Inhibition of JAK-STAT limits the effect of circulating inflammatory mediators on their target cells [5]. JAK subtypes have various effects and different drugs selectively block these receptors, calming diverging aspects of the immune response. The cross-talk of the innate immune response with other biochemical processes can also cause harm, exemplified for example by [6] inflammation-related endothelial dysfunction, which may be targetable by imatinib [6].

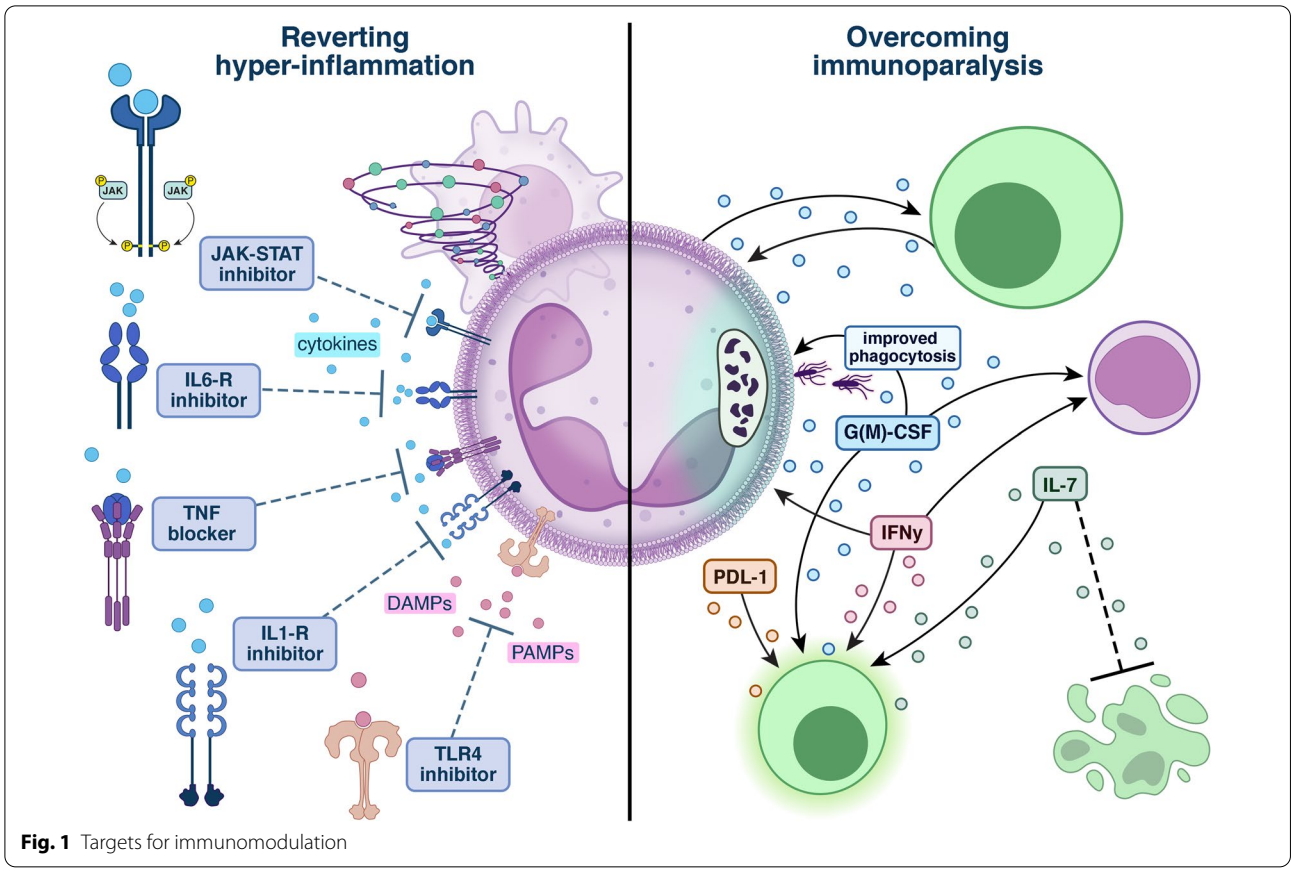

Fig. 1 Targets for immunomodulation

Besides immunomodulation towards a selective suppression of a network of inflammatory response, activation of suppressed immune cell function can be a different goal [4] in patients with suspicion of inadequate immune responses. Immunotherapy in various types of cancer via the programmed death (PD) receptor and PD-ligand 1 has resulted in markedly improved survival through the stimulation of anti-cancer lymphocytes. T cell exhaustion also plays an important role in critical illness related secondary infections and targeting these pathways may provide means to counter this disturbance and make patients more resilient to secondary infections [7]. IL-7 also stimulates the proliferation of T cells and has anti-apoptotic properties. Granulocyte-colony stimulating factor (G-CSF) and granulocyte–macrophage colony stimulating factor (GM-CSF) could help to stimulate both innate and adaptive immune responses and restore cytokine secretion and pathogen killing. Interferon gamma (IFNγ) administration can also be used to overcome immune paralysis [8].

In whom to modulate the immune response?

In chronic auto-inflammatory and auto-immune diseases, trial and error is a common clinical solution because when a patient feels better and disease related biomarkers decrease, the therapy likely works. Intensive care, however, is a time-hostile environment so we do not have the luxury of such individualized experimentation and have to rely on causal inference from randomized controlled trials to answer this question. A one-size fits all approach has failed over and over again for immunomodulators in critical illness syndromes [9], likely because applying interventions to syndromes, such as sepsis, acute respiratory distress syndrome (ARDS) or acute kidney injury does not not target specific mechanisms or pathways [10].

In recent years, subphenotypes of critical illness have been better described and we have gained more insight into the spectrum of immune dysfunction and these may provide a first step towards treatable subgroups [11]. For example, a hyper-inflammatory subphenotype, first described in ARDS, could also be identified in critically ill patients without ARDS and was associated with more organ-dysfunction [12]. Bedside testing for

cytokine biomarker is currently being developed making such approaches possible in clinical practice [13].

Other approaches, using single biomarker levels, such as lymphocyte counts, or functional assays of lymphocyte and innate immune cell function rather than subphenotypes, could be used to assign treatment strategies. This is precisely the approach taken in the PROVIDE randomized controlled trial (RCT), with administration of Anakinra to patients with signs of macrophage activation syndrome (an auto-inflammatory condition) and IFNγ in patients with immune paralysis defined by a low percentage of CD45/CD14-monocytes that express HLA-DR [14]. There is at least one study currently ongoing that uses such an approach as well (ImmunoSep; https://clinicaltrials.gov/ct2/show/NCT04990232).

The future of immunomodulation

In this article, we provide a primer of our understanding of immunomodulators in critically ill patients [9]. In the near future immune, subphenotype aware RCTs are being conducted and they may provide evidence in favor of immunomodulator treatment to overcome innate immune system activation or immune paralysis in specific subsets of the population. Beyond these novel types of RCTs, true immune-profiling and treatment personalization may be on the horizon. One could imagine a future where bedside analysis of immune cells predicts the need for specific immunomodulation.

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Declarations

Conflict of interest
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