Microbes, Infection and Chemotherapy

ORIGINAL RESEARCH

https://doi.org/10.54034/mic.e1976

New Frontiers in Immunological Therapeutics in the Critically Ill Patient: From Immunosuppression to Immunomodulation

Authors: Jorge L. Vélez-Páez[1,2,*]

Abstract

TSince the onset of the SARS-CoV-2 pandemic, there has been a significant advancement in our ability to intervene in specific immunological pathways, supported by compelling evidence. Autoinflammatory and autoimmune responses represent deregulations of innate and adaptive immunity, respectively, and are common in critically ill patients, occurring primarily or secondarily. Immunosuppression entails the global inhibition of immune responses, while immunomodulation involves the regulation or activation of specific pathways through selective activation or inhibition of molecules and their receptors. A structured search was conducted using the MeSH terms "immunomodulation," "immunosuppression," and "critical patient" in the MEDLINE, SCOPUS, and WoS databases. The objective of this review is to explore how immunomodulation offers a rational approach to counter immunoparalysis processes and modulate excessive proinflammatory responses, ultimately leading to improved clinical outcomes.

Key word: immunomodulation, immunosuppression, critical patient.

[1]Universidad Central del Ecuador, Facultad de Ciencias Médicas, Escuela de Medicina, Quito, Ecuador.

[2]Hospital Pablo Arturo Suárez, Unida de Terapia Intensiva, Centro de Investigación Clínica, Quito, Ecuador.

Corresponding author:
*Jorge Luis Vélez Páez, Universidad Central del Ecuador, Quito Ecuador.
E-mail: jlvelez@uce.edu.ec
ORCID: 0000-0002-6956-4475

Submitted: December 03, 2023
Reviewed : October 10, 2023
Approved: October 20, 2023

How to cite:
Vélez-Páez JL. New frontier in immunological therapeutics in the critically ill patient: from immunosuppression to immunomodulation. Microbes Infect Chemother. 2023; 3: e1976. https://doi.org/10.54034/mic.e1976

Introduction

To familiarize ourselves with strategies aimed at mitigating the pro-inflammatory immune response in critically ill patients, we will use acute respiratory distress syndrome (ARDS) as an illustrative example. ARDS represents a hallmark pathology that confronts intensivist physicians on a daily basis, as it shares a common pathophysiology but arises from various causes (bacterial infections, viral infections, autoimmune disorders, trauma, inflammation, and more). Regardless of the etiology, ARDS leads to a severe inflammatory reaction, resulting in acute alveolar damage, endothelial injury, disruption of endothelial cell adhesion molecules (cadherins), glycocalyx damage, increased capillary permeability, apoptosis induction, and ultimately, the development of acute non-cardiogenic pulmonary edema. (1,2)

On a molecular level, it is essential to grasp that nuclear factor kappa B is a DNA-binding protein responsible for regulating the genetic expression of various proinflammatory proteins. Glucocorticoids act by inhibiting the nuclear transcription of this factor, thereby suppressing the inflammatory cascade in the lungs. Meduri and colleagues demonstrated that the use of glucocorticoids results in a sustainable reduction in the concentration of procollagen I and III in bronchoalveolar lavage. (3,4,5)

In addition to the molecular basis, the timing of glucocorticoid use is critical. Early administration (within the first 72 hours) aims to attenuate the severity of ARDS and prevent its progression, while late administration (beyond 7 days) seeks to avert the development of pulmonary fibrosis, a common outcome in severe ARDS cases. (1,2)

Recognizing the presence of a pro-inflammatory immunological component in this syndrome, it seems both logical and tempting to explore pharmacological strategies, such as steroids, with a focus on immunosuppression and inflammation reduction. This approach aims to extinguish the immunological and inflammatory "fire," with the ultimate goal of improving clinical outcomes, including severity and mortality.

Objective and Search Strategy:

The primary objective of this review is to explore the rationale behind employing immunomodulation as a viable

approach to counteract immunoparalysis processes and modulate excessive proinflammatory responses, ultimately leading to improved clinical outcomes.

To achieve this objective, we conducted a structured search utilizing MeSH terms, specifically "immunomodulation," "immunosuppression," and "critical patient," within the MEDLINE, SCOPUS, and WoS databases.

What Results Have We Achieved When Administering Corticoids?

The evidence regarding the use of corticosteroids in the treatment of acute respiratory distress syndrome (ARDS) has been disparate, partly due to the lack of standardization of diagnostic criteria since the syndrome was initially described by Ashbaugh in 1967 (6,7). Currently, the Berlin criteria serve as the standardized diagnostic criteria, albeit with certain notable limitations. (1)

The challenges in standardizing the use of corticosteroids stem from the diversity in type (e.g., dexamethasone, hydrocortisone, methylprednisolone), dosage (high vs. low), timing of therapy initiation (early or late), duration of therapy in days, and the underlying etiology of ARDS (viral, bacterial, etc.). It's important to note that, with the exception of specific clinical scenarios, such as severe bacterial pneumonia and severe COVID-19, the results of corticoid use have not been promising. In some cases, they have even been associated with increased mortality, as observed in influenza cases, where corticoid use not only prolongs viral elimination but also facilitates superinfections.

A comprehensive meta-analysis published in 2021 provides insights into the use of corticosteroids in ARDS. This analysis considered 18 studies involving more than 2800 patients. The authors conducted a subgroup analysis for mortality based on various factors, including the type of corticosteroid used (methylprednisolone, dexamethasone, hydrocortisone), the timing of therapy initiation after ARDS diagnosis (early, 72 hours vs. late > 72 hours), duration of treatment (7 vs. > 7 days), corticosteroid dosage (below the median daily dose, < 88 mg/day in methylprednisolone equivalents), and the etiology of ARDS (COVID-19 or non-COVID-19). The study's conclusions indicate that corticosteroids reduce mortality and the duration of mechanical ventilation in all ARDS patients while being associated with few adverse effects, the most significant of which is hyperglycemia. The benefits were consistent across different types of corticosteroids, timing of treatment, and dosage, but longer treatment duration proved more effective than shorter therapy. Despite this, the level of certainty in all conclusions was considered low; nevertheless, the authors recommend that all ARDS patients be treated with corticosteroids (8). These findings align with the results of a randomized controlled trial (RCT) conducted by Villar et al., which demonstrated that early treatment with dexamethasone reduces the duration of mechanical ventilation and mortality (9).

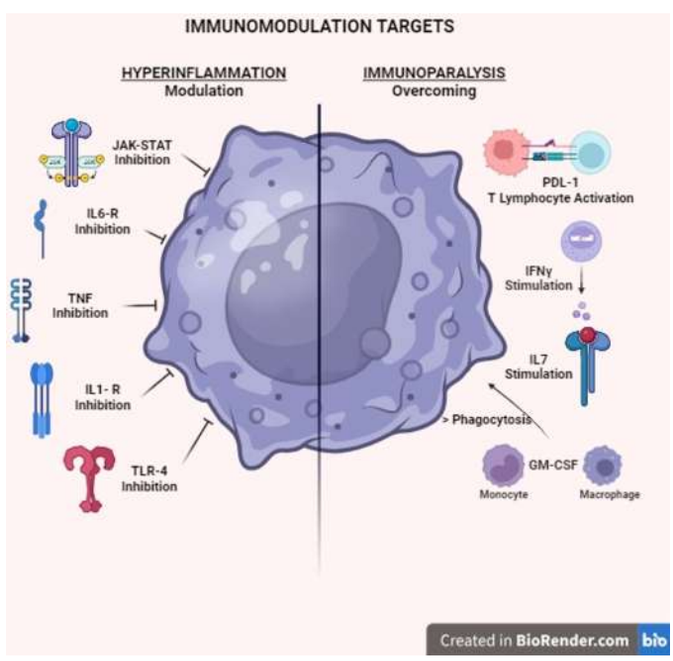
From the above discussion, it is evident that the innate and adaptive immune system, when dysregulated, can be detrimental, and their global inhibition (immunosuppression) using steroids, for instance, has a role but remains uncertain. However, an alternative approach, namely immunomodulation, involves targeting specific pathways and personalizing therapy. This approach was explored to a significant extent during the COVID-19 pandemic. The use of monoclonal antibodies designed to block specific immunological targets, such as the interleukin 6 (IL-6) receptor with Tocilizumab (10) or the JAK-STAT pathway with Baricitinib (11), yielded favorable results, including reduced mortality, in specific patients with severe clinical conditions.

Immunomodulation: Molecular Targets

The question of whether to opt for immunosuppression (e.g., steroids) or immunomodulation finds an insightful response in a 2023 letter to the editor by Janssen et al., titled "Targeted Immunomodulation: A Primer for Intensivists." In this publication, the rationale against immunosuppression and in favor of immunomodulation is elucidated with remarkable clarity. The letter proposes two fundamental targets for immunomodulation: modulating hyperinflammation and reversing immunoparalysis (immunosenescence) (as illustrated in Figure 1) (12).

Figure 1

Molecular targets for immunomodulation (Made by the author)



Abbreviations. IL1: interleukin 1, IL6: interleukin 6, TNF: tumor necrosis factor, TLR: toll-like receptor, IL7: interleukin 7, GM-CSF: granulocyte-monocyte colony stimulating factor, IFN: interferon, PDL-1: ligand PD1, PAMP: pathogen-associated molecular pattern, DAMP: damage-associated molecular pattern.

With regard to the latter point, immunoparalysis is a common occurrence in chronically critically ill patients and can give rise to an aged phenotype with altered innate immunity. This is characterized by a skewed ratio of naive cells to memory T cells, decreased thymic output, shorter lymphocyte telomeres, an increased number of functionally senescent T

cells, and fewer regulatory B lymphocytes. Clinically, this translates to an elevated risk of infections, autoimmune diseases, chronic inflammatory conditions, and poorer overall clinical outcomes (13).

Notably, critically ill patients exhibit diverse and individualized responses to the same clinical scenarios, such as sepsis or acute respiratory distress syndrome (ARDS). These responses range from deregulated autoinflammatory (innate immunity) and autoimmune (adaptive immunity) reactions to idiosyncratic responses. Consequently, a one-size-fits-all treatment approach is not applicable (12).

Table 1

Molecular targets of immunomodulation, mechanism of action and therapeutic effect. (Made by the author)

Target Molecule	Action	Effect
JAK-STAT pataway	Inhibition	It reduces the proinflammatory effect of mediators on their target cells.
IL6 receptor (IL6-R)	Inhibition	Modulation of the proinflammatory effect.
IL1 receptor (IL1-R)	Inhibition	Modulation of the proinflammatory effect.
TNF alfa	Inhibition	Modulation of the proinflammatory effect.
Tyrosine kinase (Imatinib)	Inhibition	Modulates inflammatory endothelial dysfunction.
TLR-4	Inhibition	Decrease in the production of PAMPs and DAMPs by inflammatory cells.
IL-7	Stimulation	T lymphocyte proliferation and antiapoptotic effects.
GM-CSF	Stimulation	It stimulates both innate and adaptive immune responses and restores cytokine secretion.
IFN gamma	Stimulation	Overcome immune paralysis.
PDL-1	Inhibition	Activation and increase in the half-life of lymphocytes.
CTLA-4	Inhibition	Activation and increase in the half-life of lymphocytes.

Abbreviations. IL1: interleukin 1, IL6: interleukin 6, TNF: tumor necrosis factor, TLR: toll-like receptor, IL7: interleukin 7, GM-CSF: granulocyte-monocyte colony stimulating factor, IFN: interferon, PDL-1: ligand PD1, PAMP: pathogen-associated molecular pattern, DAMP: damage-associated molecular pattern.

So, who should be candidates for immunomodulation? The answer may lie in establishing phenotypes through various approaches, including genetics, proteomics, epigenetics, clinical data, epidemiology, and biomarkers. These methods can enable the precise identification and intervention in specific pathways, facilitating the practice of precision medicine. This approach has been practically applied, as seen in the case of SARS-CoV-2 infection, where proinflammatory or prothrombotic phenotypes were defined using biomarkers like IL-6 or D-dimer, leading to individualized treatment strategies (12,14). An elegant clinical trial, PROVIDE, provided valuable insights by demonstrating that in patients with macrophage activation syndrome (autoinflammatory dysregulation) and immunoparalysis (identified by a low percentage of CD45-CD14 monocytes expressing HLA-DR), therapies targeting the IL-1 receptor with Anakinra and interferon gamma stimulation, respectively, yielded encouraging clinical results (12,15).

Finally, the key to effective immunomodulation does not entail the global suppression of defense mechanisms (immunosuppression). Instead, it involves the identification of specific pathways within innate immunity, adaptive immunity, and factors specific to pathogens (as outlined in Table 1). By regulating cell signaling and modulating effector responses, this approach aims to prevent chaotic systemic inflammatory activation, particularly through key inflammatory cells like macrophages activated by pathogen-associated molecular patterns (12).

Conclusion

Autoinflammatory and autoimmune responses, which signify dysregulations of innate and adaptive immunity, are prevalent among critically ill patients. These responses can manifest as primary conditions or secondary reactions to various pathological triggers.

Immunosuppression, characterized by the broad inhibition of immune responses, stands in contrast to immunomodulation. The latter approach involves the precise regulation or activation of specific immunological pathways through the selective targeting of molecules or their receptors.

In light of the evidence, immunomodulation emerges as a compelling and rational objective. It offers the potential to effectively counteract immunoparalysis processes and modulate the exaggerated proinflammatory responses frequently observed in critical illnesses. Such an approach holds promise for improving clinical outcomes and patient care.

Conflict of interest

The author declares no conflict of interest.

Source of Funding

None.

Author Contribution Statement

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

Ethics statement

The authors declare that the published work reflects an investigation and analysis carried out truthfully and completely.

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