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Precision immunotherapy treatment for sepsis

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Abstract. **In intensive care units, sepsis has traditionally been the disease with the highest mortality rate and the highest cost of care. Now, the attention to sepsis is not only the initial systemic inflammatory response, but also the immune disorders which lead to the weakened clearance of septic infection foci, the activation of secondary infection and latent infection, and ultimately organ dysfunction. The research of sepsis immunotherapy is in full swing. However, there are not any fully approved clinically effective drugs on the market now, and we do not fully understand the immunological microenvironment in sepsis. This article intends to inspire future clinical practice by providing a thorough analysis of sepsis immunotherapy from the perspectives of immune status evaluation, potential immunotherapy drugs, defects in immunotherapy, and future research prospects.**

Key Words:
Sepsis, Immune disorders, Immunotherapy, Precision medicine.

Introduction

Sepsis is a widespread issue with potentially fatal organ failure and high mortality brought on by a dysregulated host response to infection[1,2]. At the moment antibiotics, source control, resuscitation, and organ support are the main treatments for sepsis. Therefore, the requirement for efficient adjuvant therapy is critical to ending the impasse. Sepsis is no longer thought to be merely an infection brought on by an inflammatory response. Additionally, the majority of recent studies[3,4] on sepsis have concentrated on preventing the cytokine-mediated stage of inflammation; nevertheless, recent investigations[5] have suggested that both an inflammatory response and immunosuppression have occurred in the early stages of sepsis. Subsequently, the concept of sepsis as persistent inflammation, immunosuppression, and metabolic failure syndrome (PICS) is suggested. The Third International Consensus Definition for Sepsis and Septic Shock states that patients suffering from sepsis should pay attention to the immune stability of the body in addition to infection, hemodynamics, tissue perfusion, organ function, etc.

A persistent inflammatory state caused by defective innate immunity and repressed adaptive immunity, which ultimately results in persistent organ damage, was shown by genomic analysis of tissue samples from individuals with sepsis and severe trauma in past studies[6,7]. Then, sepsis was discovered to be engaged in a series of immune regulation processes, such as delayed apoptosis of neutrophils, decreased capacity of monocytes to release pro-inflammatory cytokines, induced expression of NK cells, improved function and number of dendritic cells and so on. On the surface of these immune cells are numerous checkpoints, which are crucial components of the immune regulatory system. These include programmed cell death (PD-1) and its ligand receptor (PD-L1), cytotoxic T cell antigen (CTLA-4) and other negative costimulatory molecules. A variety of immune cells' activities can be shut down by the activation of the cell signaling pathway, controlling how strong the autoimmune response will be. Despite the fact that prior research has not supported the efficacy of immunosuppressants such as the Fc component of immunoglobulin G 1 (IgG1), E5 murine monoclonal antiendotoxin antibody, interleukin-1 receptor antagonist, and human monoclonal antibody HA-1A in the treatment of sepsis, we are of the opinion that the results may be impacted by the level of treatment that was used before. The following is a review of the recent progress of immunotherapy for sepsis.

How to Assess the Immune Status?

Numerous factors, such as: 1) lymphocyte exhaustion and depletion, 2) expansion of anti-inflammatory immune cells, 3) altered expression

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of human leukocyte antigen DR (HLA-DR) and PD1/PD-L1, 4) metabolic and epigenetic changes that lead to the reprogramming of immune cells in sepsis patients, resulting in a highly complex immunosuppressive environment.

Because unclassified sepsis patients were included in many clinical trials in recent years, many of them failed. Equitable research object selection will be essential to raise the standard of clinical studies. Therefore, it is crucial for immunotherapy to identify sepsis patients who have immunosuppression utilizing biological and immunological approaches.

First of all, immune function is impacted by fundamental conditions including immunological senescence brought on by aging, immune insufficiency brought on by starvation, and immunoparalysis brought on by chronic illnesses and malignancies. Secondly, the types, virulence and drug resistance of pathogenic microorganisms in sepsis are all factors affecting immune function. Thirdly, the reactivation of cytomegalovirus, Epstein Barr viruses, herpes simplex viruses and latent virus, as well as secondary hospital infections and opportunistic fungal infections, are all manifestations of decreased immune function. Additionally, sepsis has a very complicated immunosuppressive environment, in addition to the complex immune system composition, genomic changes in individual differences, complex intracellular signaling pathway network. The body immune function also changes dynamically with the development of sepsis. As a result, the immunoparalysis of sepsis has no apparent pathophysiology. Only by distinguishing the immune status of patients according to the corresponding biomarkers can sepsis be treated accurately.

Currently, detecting inflammatory markers and changes in the cycle of immune cells is the main method used to assess immunological levels clinically. And a lot of clinical research[8,9] have been looking for markers to precisely assess immunization status.

mHLA-DR

One of the most often utilized markers for immunoparalysis and illness development in sepsis is monocytes human leukocyte antigen DR (mHLA-DR), which is essential for antigen presentation. Studies[10,11] have shown that mHLA-DR expression is persistently low, which not only predicts a poor clinical result but also makes one more vulnerable to subsequent infection. The mHLA-DR not only increase expression on T-cells in peripheral blood circulation of non-surgical septic patients, but also in the Gram-positive bacterial infection group compared to the Gram-negative infection group[12]. And a recent retrospective study[13] found that the procalcitonin/mHLA-DR ratio on day 7 was more sensitive than mHLA-DR to improve the prediction accuracy of 28-day mortality in patients with sepsis.

PD-1/PD-L1

By binding to programmed cell death 1-ligand 1 (PD-L1), programmed cell death 1 (PD-1) promotes immunosuppression by negatively regulating T cell function, preventing T cell proliferation and the activity of cytotoxic T lymphocytes, and suppressing the production of cytokines like leukocyte interleukin-2 and interferon-γ. PD-1 and PD-L1 are most highly expressed in CD4+/CD8+T cells and monocytes respectively in sepsis[14,15]. Preclinical and clinical researches[16,17] find that PD-1/PD-L1 not only can reduce apoptosis and improve overall immune function to reduce multiple organ dysfunction[12], but also may be the valuable tool for the prediction of high mortality in sepsis people[17]. Overexpression of PD-1/PD-L1 has been shown to impair T cell proliferation and increase secondary hospital infections. It is also linked to a decreased count of mHLA-DR expression and circulating CD4+T cells[18].

Cytokines

It was not until the 1960s that immune cells were first found to produce and release potential cytokines due to the anti-tumor effects of "lymphotoxins" produced by lymphocytes. Interleukins, chemokines, tumor necrosis factors, interferons, and growth factors are examples of cytokines. A complex immunological milieu is created by the cascaded interactions between several cytokines. For instance, IL-1β can regulate the expression of IL-6 and IL-8 as well as other inflammatory genes. And then the elevated levels of IL-6 and IL-1β are associated with severity of sepsis and poor prognosis[19,20]. Tumor necrosis factor-α (TNF-α) is reported to down-regulation of CXCR2 in neutrophils, then reduce the neutrophil recruitment to the inflammatory site and bone marrow or spleen release immune cells, causing significant organ damage[20,21]. In

addition, a study[22] has also found that lipid polysaccharides combined with interferon-γ (IFN-γ) can inhibit macrophage autophagy, boosting macrophage activation, which is helpful for sterilizing and improve survival. However, the production of IFN-γ in the blood of sepsis patients and autophagy of macrophages were inhibited. And the increased interleukin-10 (IL-10) levels and IL-10/TNF-α ratio are also considered to be significant indicators of the degree of inflammation in sepsis and are linked to immunoparalysis and high mortality rates in sepsis[23,24].

In summary, there is currently no single indicator available for clinical diagnosis of immunoparalysis. These indicators are basically found in animal or *in vitro* investigations, on the immune cell surface, or in circulation tests. Therefore, the validity of these signs should be considered during the clinical assessment of the patient's immunological status, and then joint assessment and dynamic assessment, rather than blindly draw to conclusions.

Potential Immunomodulation Drugs

The majority treatments of sepsis currently available are supportive, and there is still no one medication that may sustainably save the lives of people with sepsis. Since immunosuppression is the core driving force for the development of sepsis, and immunotherapy has made remarkable achievements in the field of tumors, immunotherapy for sepsis is highly anticipated.

For the time being, immunotherapy of sepsis mainly focuses on cytokine regulators (promoting pro-inflammatory factors, inhibiting anti-inflammatory factors), immuno-checkpoint inhibitors and anti-apoptosis, promoting immunocell hyperplism. And with the continuous exploration, there are numerous *in vivo* and *in vitro* studies[25-27] using immunomodulation drugs for the condition of immunoparalysis associated with sepsis patients. These treatments include the popular PD-1/PD-L1 blockade, granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF), and INF-γ. These drugs are summarized in Table I.

Immune Checkpoint Inhibitor

The immune checkpoint inhibitors, such as inhibition of PD-1/PD-L1, cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and Indoleamine 2,3-dioxygenase, have been matured for anti-tumor immunotherapy, but clinical trials on sepsis have not been widely conducted. However, the potential is enormous.

Previous *in vitro* experiments[28,29] have shown that PD-1, highly expressed in neutrophils, monocytes, may ultimately facilitate the development of sepsis. However, PD-1/PD-L1 blockade can restore the function of neutrophils, monocytes, T cells, and natural killer (NK) cells in sepsis immunosuppression. All of them point to the possibility that PD-1/PD-L1 blockage functions as a single immunomodulator to control a range of abnormalities. Additionally, a Phase 1 randomized clinical trial[23] (RCT) enrolled 38 patients with sepsis to evaluate the safety and toxicity of BMS-936558 (Nivolumab). The result[30] showed no safety issues and no cytokine storm with nivolumab administration. And then a Phase 1/2 clinical trial[31] (JapicCTI-173600) using Nivolumab in patients with sepsis-induced immunosuppression in Japan has been completed, with results showing good resistance to 960 mg single-drug dosage. Follow-up phase 3 trials are needed to further demonstrate the efficacy of PD-1/PD-L1 blockade.

Other immune checkpoints like CTLA-4, CD80, CD86, CD40 and CD40L, OX40 and OX40L, 4-1BB and 4-1BBL, BTLA and TIM family have been found to play corresponding roles in immune paralysis in sepsis *in vitro* studies[32]. CTLA-4 pathway was found to be involved in neutrophil-mediated T lymphocyte dysfunction in sepsis, and that CTLA-4 antibodies[33] could improve survival in septic mice and the function of T lymphocytes. Further clinical trials are needed to assess the effectiveness of CTLA-4 inhibitor.

Thymosin α1

Thymosin α1 is implied in the reduction of the duration of mechanical ventilation, organ damage and mortality for more than a decade in people with severe sepsis. And latest data[34,35] also demonstrated that thymosin α1 might boost the number of lymphocytes in severe COVID-19 patients, reverse T lymphocyte depletion, induce immune reconstruction, and enhance thymus output. In addition, thymosin α1 was found to inhibit the activation of CD8-T cells, thereby suppressing inflammatory storms. Additionally, it was discovered[36,37] that thymosin α1 treatment, either alone or in combination, for sepsis increased the level of HLA-DR expression in monocytes, inhibited inflammatory cytokines, and controlled immune stability. The ETASS study[38], a large RCT that included 361 septic patients, showed a

Table I. Summary of potential immunomodulation drugs in immunoparalysis.

Drugs	Trial number	Phase	Status	Study Title
GM-CSF	NCT00252915	2	Completed	Reconstruction of Monocytic Immunocompetence by Granulocyte-macrophage-colony Stimulating Factor (GM-CSF) in Patients with Severe Sepsis and Septic Shock.
GM-CSF	NCT02361528	2	Completed	A Double-Blind, Randomized, Placebo-controlled Multicenter Trial of Granulocyte-Macrophage Colony-stimulating Factor Administration to Decrease ICU Acquired Infections in Sepsis-induced Immunodepression.
rh-GCSF	NCT01479114	4	Completed	Effect of Recombinant Human Granulocyte Colony-Stimulating Factor on CD11b in Septic Neonates.
GM-CSF/ INF-γ	NCT01374711	Not Applicable	Completed	The Effects of Immunostimulation With GM-CSF or IFN-y on Immunoparalysis Following Human Endotoxemia.
INF-γ	NCT01649921	3	Completed	The Effects of Interferon-gamma on Sepsis-induced Immunoparalysis.
INF-γ or Anakinra	NCT03332225	2	Completed	A Trial of Validation and Restoration of Immune Dysfunction in Severe Infections and Sepsis.
Anakinra or rhIFNγ	NCT04990232	2	Recruiting	Personalized Immunotherapy in Sepsis.
PD-1/PD-L1 blockade	NCT01161745	Not Applicable	Completed	PD-1/PD-L1 Pathway Study on Septic Patients.
PD-1/PD-L1 blockade (bms-936559)	NCT02576457	1	Terminated	Safety, Pharmacokinetics and Pharmacodynamics of BMS-936559 in Severe Sepsis.
PD-1/PD-L1 blockade (Nivolumab)	NCT02960854	1	Completed	A Study of Nivolumab Safety and Pharmacokinetics in Patients with Severe Sepsis or Septic Shock.
PD-1/PD-L1 blockade (Nivolumab)	JapicCTI-173600	1/2	Completed	Pharmacokinetics, Pharmacodynamics, and Safety of Nivolumab in Patients with Sepsis-Induced Immunosuppression: A Multicenter, Open-Label Phase 1/2 Study.
IL-7 (CYT107)	NCT02640807	2	Completed	A Study of IL-7 to Restore Absolute Lymphocyte Counts in Sepsis Patients.
Mw Vaccine	NCT02025660	2/3	Completed	Efficacy of Mw Vaccine in Treatment of Severe Sepsis.
Thymosin α1	NCT02867267	3	Completed	The Efficacy and Safety of T α1 for Sepsis.
Thymosin α1	NCT04901104	Not Applicable	Not yet recruiting	Long-term Prognosis of Patients with Sepsis After Immunotherapy.
TNF-α (AZD9773)	NCT01144624	2	Completed	A Study to Assess Safety, and Tolerability of 2 Doses of AZD9773 (CytoFab™) in Japanese with Severe Sepsis/Septic Shock.
TNF-α (AZD9773)	NCT01145560	2	Completed	A Study to Compare the Efficacy and Safety of 2 Dosing Regimens of IV Infusions of AZD9773 (CytoFab™) With Placebo in Adult Patients with Severe Sepsis and/or Septic Shock.
Aspirin	NCT02922673	Not Applicable	Completed	The Effects of Acetylsalicylic Acid on Immunoparalysis Following Human Endotoxemia.
β-glucan	NCT01727895	Not Applicable	Completed	Effects of Orally Administered Beta-glucan on Leukocyte Function in Humans.

decrease in all-cause mortality for 28 days (26.0% *vs.* 35.0%) in the thymosin α1 group compared to the conventional treatment group. However, the secondary analysis of the ETASS study[39] showed that early immunoparalysis is an independent risk factor for poor prognosis in older patients, but not for non-older patients. This serves as a reminder that subgroup analysis may be required in the future for patients of various ages. In addition, two sizable multicenter clinical trials (NCT02867267,

NCT04901104) on the use of thymosin α1 in sepsis have just completed. And they sought to assess the efficacy and safety of thymosin α1, with 28-day all-cause mortality and 3-year mortality as the primary outcome, respectively.

IFN-γ

The expression of mHLA-DR increased in the IFN-group while IL-10 significantly decreased, according to an *in vivo* RCT study[40] in 2012 that included 18 patients with Escherichia coli endotoxin-induced immunoparalysis and randomized treatment with IFN-γ, GM-CSF and placebo. And then the Radboud University sponsored a RCT (NCT01649921) of IFN-γ in sepsis-induced immunoparalysis patients. However, only 4 patients were included, and the outcomes have not yet been released. Another recently concluding RCT (NCT03332225) compared the effects of IFN-γ, anakinra, and placebo in 36 septic patients. The trial used 28-day mortality as the main outcome indicator, and the results would be released in the near future.

GM-CSF/G-CSF

The active site of GM-CSF is higher, mainly in neutrophils and bone marrow precursor cells, which can promote the production of granulocytes and macrophages. While the G-CSF active site is in neutrophils, monocytes, eosinophils, etc., it primarily increases granulocyte formation and activity. GM-CSF has a stronger anti-infection effect than G-CSF.

GM-CSF and G-CSF were all found to have the function of inhibiting cytokine storms and maintaining normal physiological function of lung, and both are very promising immunomodulators in sepsis with immunoparalysis currently[41]. More than ten years ago, a small sample RCT[42] that included patients with abdominal sepsis found that GM-CSF could reduce the number of infectious complications, shorten hospital stays, cut down on antibiotic use, and lower hospital expenses. A phase 3 RCT (NCT02361528) included 166 participants to measure whether GM-CSF (sargramostim) could reduce the incidence of intensive care unit (ICU)-acquired infections in sepsis-induced immunoparalysis. And the primary endpoint is the number of patients presenting at least one ICU-acquired infection at 28 d or ICU discharge, and the findings are currently awaited. Future clinical trials with larger samples are needed to confirm the efficacy of GM-CSF/G-CSF.

IL-7

Previous *in vitro* studies[43,44] have found that IL-7 can induce IFN-γ secretion as well as promoting T-cell proliferation and inhibiting apoptosis. IRIS-7-B[45] was the first RCT for adaptive immunomodulatory therapy for sepsis and included a total of 27 patients. The results showed that absolute lymphocyte count, circulating CD4+ and CD8+ T lymphocyte count were significantly increased and sustained for several weeks after IL-7 treatment compared with baseline.

IL-15

The IL-15 was found to prevent apoptosis and immunoparalysis and improve survival in sepsis. In mice models of sepsis, IL-15 has also been shown to improve the number of T cell and NK cell and ameliorate age-induced T cell depletion in mouse models of sepsis[46,47]. However, there are not clinical trials running right now to evaluate whether IL-15 improves survival outcomes in patients with sepsis.

β-glucan and aspirin, two widely used and affordable medications, also took part in two research trials[48] to evaluate whether they can improve the immunoparalysis state of patients with sepsis. And the results did not find the effectiveness of β-glucan[48], while the results of aspirin were not available. Once aspirin results are favorable, prehospital aspirin use can be further evaluated to prevent immunosuppression and improve outcomes.

Deficiencies in Immunotherapy for Sepsis

We should pay attention to the flaws in immunoregulatory therapy as it quickly develops into sepsis. First of all, immunotherapy for tumor patients resulted in significant immunotoxicity, including skin reactions, endocrine disorders, liver and kidney damage, gastrointestinal toxicity, pneumonia, and other uncommon neurotoxicity and cardiotoxicity. Patients who already suffered from sepsis will suffer even more severe adverse effects once they start to appear. Secondly, since antibiotics must be used to treat sepsis, they are likely to reduce the effectiveness of immune modulators. Furthermore, a recent study[49] has discovered for the first time that the degree of PD-1 expression affects how well cancer patients respond to immunotherapy when taking antibiotics. Therefore, more research is required to determine whether there are associated variables in the immunoparalysis-microenvironment of sepsis that predict the antagonistic effect of antibiotics and

immune modulators. These issues should also be taken into account in sepsis immunotherapy, and pertinent research should be initiated to create suitable therapeutic strategies.

Conclusions

In conclusion, a plethora of fundamental studies and clinical trial outcomes in recent years have demonstrated that sepsis immunotherapy is moving in the correct direction, has enormous potential, and might even become the sepsis terminator. There will be more immunotherapy medications available as a result of the quick advancement of immunotherapy research. Seizing the opportunity to increase the advantages of immunotherapy is what needs to be done right away. For example, what is the best time for immunotherapy applications? Is it more effective to combine different immunomodulators, and how would it work? Considering the highly heterogeneous characteristics of sepsis itself, not everyone can benefit from immunotherapy. We must also distinguish between patients' various needs. Immunotherapy is anticipated to reshape the way sepsis is treated by enabling personalized and exact treatment.

Ethics Approval
There are no ethical issues involved.

Availability of Data and Materials
All relevant data and material are presented within the manuscript.

Conflict of Interest
There is no conflict of interest.

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Authors' Contributions
J. Wang searched relevant literature, extracted data, and drafted the manuscript. J. Wang and G. Zhang conceived the idea, participated in manuscript revision. All the co-authors have approved this version of the manuscript.

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