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Review Article

Polyclonal intravenous immunoglobulin: An important additional strategy in sepsis?

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ABSTRACT

Sepsis syndrome is characterized by a systemic inflammatory response to infection potentially leading to acute organ failure and rapid decline to death. Polyclonal intravenous immune globulin, a blood product derived from human donor blood, in addition to antiinfective activities, also exerts a broad antiinflammatory and immunomodulating effect.

Intravenous immunoglobulin (IVIg) has been proposed as adjuvant therapy for sepsis even though the clinical studies demonstrating their efficacy and safety are relatively small. Several systematic reviews and meta-analyses of intravenous immunoglobulin treatment in sepsis have been performed. As a result of heterogeneity across studies and inconsistencies in results, the majority have concluded that more evidence, coming from large, well-conducted randomized controlled trials (RCTs), is required. Moreover the appropriate timing of administration and the identification of specific clinical settings represent a key factor to maximizing their beneficial effect. The authors, in this revision, review the basic mechanisms of action of IVIg, the rationale for their use, and their clinical applications.

1. Introduction

Intravenous immunoglobulin (IVIg) is therapeutic preparation mainly including human IgG collected from a large number of healthy donors, that is largely used for replacement therapy in patients with primary or secondary antibody deficiencies; in these patients, IVIg is administered in order to maintain normal trough IgG level (level observed immediately before the next IVIg infusion) and reduce the number and severity of acute infectious complications [1].

In the last three decades IVIg has been also increasingly used for the treatment of various autoimmune and systemic inflammatory diseases, and currently the immune modulating indication is largely prevalent, mainly in off label use [2,3].

Sepsis, that is a systemic inflammatory response syndrome (SIRS) arising from an infection, is a life-threatening condition with high mortality. Sepsis with acute organ dysfunction (severe sepsis) and septic shock are major healthcare problems, affecting millions of individuals around the world each year, with a mortality rate of 22% and 76% [4] respectively. The number of cases of severe sepsis in the United States exceeds 750,000 per year [5] and was recently reported to be rising [6]; moreover, 229,044 deaths from severe sepsis have been estimated in 2009 [7], which would place severe sepsis as the third most common cause of death in the United States, after heart disease and malignant neoplasms [8]. The incidence increased exponentially with age, suggesting that the number of cases will increase in coming years.

The development of sepsis results from a complex interaction between the infecting microorganism and the host response and represents the harmful consequences of dysregulated immune response: severe sepsis, in fact, is associated with altered homeostasis characterized by activation of inflammation, resulting in high levels of proinflammatory mediators, enhancement of coagulation, and impairment of fibrinolysis. These pathophysiological abnormalities contribute to impaired tissue perfusion and organ failure. For several years, the increased inflammatory response, defined as systemic inflammatory response syndrome (SIRS), has been the focus in the pathogenesis of sepsis; more recently, attention has highlighted secondary immune suppression, defined as compensative anti-inflammatory response syndrome (CARS), equally capable to contribute to organ damage and lead patients to exitus. The proinflammatory and the anti-inflammatory responses are sequential events during sepsis development with a first proinflammatory phase, characterized by an uncontrolled increase in the production of cytokines with inflammatory profiles, such as tumor necrosis factor (TNF), interleukin 1 (IL-1) and IL-6, able to induce a real cytokine storm [9]. The sepsis, going on, involves anti-inflammatory mechanisms leading to a damage of the adaptive and innate immune system, with a loss of CD4 and CD8 T lymphocytes, B cells and dendritic cells induced by apoptotic events [10–12]; further mechanisms of immunosuppression include down-regulation of activating cell-surface molecules, such as HLA-DR, T cell "exhaustion," and increased suppressor cells (T regulatory cells and myeloid-derived suppressor cells) [13–19]. Although production of both proinflammatory

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and anti-inflammatory cytokines is observed from the very first hours during sepsis, the respective relevance between the two opposite phases is conditioned by the characteristics of the patient, such as genetic asset, age, comorbidities, and nutritional status. The hyperergic phase is potentially the leading cause of exitus in young subjects, in the presence of pathogens such as *Neisseria meningitidis*. In contrast, the immunosuppressive phase determines the greatest risk of prolonged hospitalization, emergence of opportunistic infections or death in the elderly subjects.

Despite recent advances in the management, such as the evolution of support therapy and the use of new anti-infective agents, sepsis continues to pose a challenge in critical care. With the increasing understanding of the pathophysiology of sepsis, the attention has focused on new therapeutic approaches targeting dysregulated host response rather than the microorganism that elicited it [20]. In addition to the administration of antibiotics and the eradication of septic foci when indicated, several adjuvant therapies, aimed at modulating the immune system, have been considered. To date, despite a large number of clinical trials, no recently developed specific therapies for sepsis have proven effective [21]. Only recombinant human activated protein C (rhAPC), with its antithrombotic, anti-inflammatory, and profibrinolytic properties was approved for use following the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial in 2001. rhAPC gave appreciable results in patients with severe sepsis or septic shock with a 6.1% absolute reduction and a 19.4% reduction in the relative risk of 28 day mortality due to all causes in patients with severe sepsis ($p = 0.005$) [22]. These results have been confirmed in a limited number of clinical studies, also reporting that the drug is expensive and carries an elevated risk of bleeding. In late 2011 the PROWESS SHOCK trial was released, and showed no benefit of rhAPC in patients with septic shock [23]. Accordingly, the drug was withdrawn from the market and in recent international guidelines on sepsis published in 2012 [24] there is no mention for such an indication.

2. Mechanism of IVIg activity

IVIg exerts its immune modulating effect on the innate and adaptive immune systems (Table 1). Many immune regulatory mechanisms, although not completely elucidated, have been proposed to explain its beneficial effects in these settings.

These factors cooperate in synergistic way and can exert a potential benefit in patients with severe inflammatory diseases.

It has been recently described that a small, sialylated fraction of IgG is responsible for the anti-inflammatory activity and that the removal of glycosylated residues abrogates IVIg activity to a level comparable with that of aglycosylated IVIg. Moreover, experimental data lead to the hypothesis of a specific macrophage receptor able to recognize sialic acid-rich IgG linked to the IgG Fc fragment, suggesting that both sialic acid residues and the IgG Fc fragment are crucial for an anti-inflammatory effect [25]. Further studies should examine the impact of engineered IVIg in the optimization of its clinical efficacy: for instance the potential role of sialylated Fc raises the hypothesis to modify immunomodulatory activities through increasing glycosialylated Fc amount of native IVIg preparations.

Table 1
Hypothesized main mechanisms of action of IVIg in immune modulating function.

$F(ab)^2$-mediated activities	Fc-dependent activities
Suppression or neutralization of cytokines	Blockade of the FcRn
Neutralization of activated complement components	Modulation of activating FcγRs
Restoration of idiotypic/anti-idiotypic networks	Up-regulation of inhibitory FcγRIIB
Blockade of leukocyte-adhesion-molecule binding	Immunomodulation by sialylated IgG
Targeting of specific immune cell-surface receptors	Increase proliferation and immunosuppressive effect of Tregs
Modulation of maturation and function of dendritic cells	
Hindrance of natural-killer cell activity	

$F(ab)^2$: fragment antigen binding; Fc: fragment crystallizable; FcRn: neonatal Fc receptor for IgG; FcγRs: receptors for Fc-IgG; FcγRIIB: receptor for Fc-IgG with inhibitory activity; Tregs: Regulatory T cells.

Fifteen percent of the off-label use of IVIg in the United States is to treat a broad range of infectious diseases [26] and among these, IVIg are still being evaluated for adjunctive treatment of suspected or proven sepsis.

In experimental studies, it has also been shown that polyvalent IVIg can improve opsonization, prevent nonspecific complement activation, protect against the antibiotic-induced endotoxin release, and neutralize endotoxin as well as a wide variety of superantigens [27]. As a result of the broad range of anti-infective specificities and of immune regulatory properties, polyclonal IVIg has been proposed as an adjunctive therapy for sepsis and septic shock. IVIg, in fact, operates differently accordingly to the specific clinical situation; in sepsis its regulatory effect might restore the balance between host immune response and pathogen virulence factors [28]. Recently additional immune regulatory pathways have been hypothesized. Asakura et al. [29] showed a protective effect of IVIg administration in animal models of disseminated intravascular coagulation (DIC) and organ failure after infusion of lipopolysaccharide (LPS). This beneficial effect might be due to attenuation of the overshooting pro-inflammatory state with decreased plasma levels of TNF and IL-6 in the IVIg group. It has been reported also that the damage of the microcirculatory flow induced by LPS could benefit from treatment with IVIg [30].

Recent studies underline the possibility that IVIg administration can modulate different T cell subsets, in particular Th-17 and regulatory T cells (Treg). *In vitro* it has been observed that IVIg inhibits the proliferation and maturation of human Th17 cells, as well as their cytokine profile (decreased production of IL-17A, IL-17F, IL-21, and CCL20) [31]. Kessel et al. [32] showed the suppressive effect of $CD4^+CD25^+$ T cells presented as the decrease of TNF-α production by stimulated $CD4^+CD25^-$ T cells was further increased by adding IVIg to cell culture and additional studies show that the use of IVIg can establish an increase of the proliferation of Treg cells [33,34]. This mechanism explains one additional therapeutic advantage of IVIg in autoimmune and allergic disease and suggests a possible beneficial effect also in other clinical conditions characterized by a sustained and dysregulated inflammatory response, such as severe sepsis. The effects of treatment with IVIg on the blood–brain barrier in animal models suffering from sepsis were also analyzed, showing that polyclonal IVIg and especially those enriched with IgA and IgM improve the integrity of the blood–brain barrier [35].

In addition it has been investigated the role of catalytic antibodies that are immunoglobulins endowed with a capacity to hydrolyze an antigenic substrate. Catalytic antibodies of the IgG and IgM isotypes are part of naturally occurring antibodies [36,37] and seem to participate in the removal of metabolic wastes and protect from bacterial infections through their intrinsic ability to convert molecular oxygen into hydrogen peroxide and ozone [38,39].

Whether catalytic antibodies could also regulate the inflammatory response and participate in the control of disseminated microvascular thrombosis remains to be defined. Lacroix-Desmazes et al. [40] assessed IgG catalytic activity from 34 consecutive patients diagnosed with severe sepsis or septic shock. The cumulative rate of survival was higher among patients with high catalytic rates of IgG as compared with patients with low catalytic rates ($p < 0.05$).

IgG enriched in catalytic antibodies could, therefore, represent an attractive therapeutic approach in sepsis.

However, several clinical trials have been performed on the prophylactic and therapeutic effect of IVIg in patients with sepsis; most of them include few patients and the results have been conflicting, so that evidence supporting its use is inconclusive.