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Editorial

Immunoglobulins for Prophylaxis and Treatment of Sepsis: New Experience with a Natural Immunomodulatory Compound

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Innate and adaptive immunity are characterized by Späth in this issue as the main pillars of the host response against bacterial invasion. While phagocyte receptors are not able to adapt to the changing diversity of antigens, immunoglobulins (biochemical transducer) may bridge this gap [1]. The interaction of complement and immunoglobulins is very complex. Initiation of the classical pathway requires immunoglobulins G and M, the alternative pathway does not require immunoglobulins but is rapidly activated in the presence of antibodies [2–4]. It is the cooperation between immunoglobulins and complement which leads to immune complexes which can bind to phagocytes, if the receptors are expressed on the corresponding cells. There are five classes of immunoglobulins (IgA, IgG, IgM, IgD, IgE); however, only IgG, IgM, and IgA are available in commercial preparations. The polyspecific IgM is especially suited for the primary immune response; it can bind to multiple diverse antigens. Pre-existing IgM may have a low affinity to antigens, but this may be compensated by high valency and cross-reactivity. There are only two immunoglobulin preparations containing more than 6% of IgM available. A small fraction of immunoglobulin may undergo structural changes which may activate the complement cascade in the absence of binding to an antigen upon infusion. Chemical modification may prevent spontaneous complement activation: β-propiolactone/UV light treatment or limited S-sulfonation. However, the effect of limited sulfitolysis on effector function of IgM remains to be elucidated [5–7]. Several studies with preparations containing IgG, IgM, and IgA were performed in patients to support the host defense against bacterial infection. Problems are the rather low content of IgM in these preparations. Can IgM function without IgG or IgA? Is IgM superior to IgG in treating bacterial infections? There are efforts to produce IgM preparations with an IgM content above 60%. Heating of a highly enriched IgM preparation may prevent the spontaneous complement activation without loss of the effector function. Heating of IgG preparations is known for the induction of complement activation [8–11]. Secretory IgA binds to enteropathic bacteria and viruses, reduces colonization, prevents translocation and enhances exclusion of mucosal pathogens. However, the interaction of IgA and complement is not yet clear [12,13].

There is an anti-inflammatory response of high-dose IVIgG treatment. We demonstrated that plasma IL-4 levels were markedly and significantly increased in IgG treated trauma patients, whereas IL-6 was decreased compared to the patients in the placebo group [14]. However, we do not understand all aspects of this effect. The role of naturally occurring autoantibodies is not settled. IVIgG may induce alteration of in vitro production and release of cytokines, a short phase with release of pro-inflammatory cytokines followed by a prolonged phase with the release of anti-inflammatory cytokines. IVIgG may be a potent downregulator of pro-inflammatory IL-1 and may alter the IL-1 stimulation of PBMC. Plasma-derived preparations enriched in IgM and IgA could downregulate TNF-α and IL-6 and increase the release of IL-1ra and upregulate FcαR (CD89). In mixed lymphocyte reaction (MLR) experiment with Pentaglobin it was demonstrated there was a modulation of IL-2 and IFNγ production with subsequent impact on TNFα and IL-6 release [15–23].

It has to be recognized that all effects of immunoglobulins may act simultaneously during and after infusion. The immune status of the recipient may decide which effect is prevailing. Double hit, e.g., trauma and sepsis, leading to multiple organ failure may induce macrophage hypoactivation and hyperactivation with decreased and increased production of cytokines, respectively [24]. There is also evidence that patients only profit from the anti-inflammatory effect of immunoglobulins when given in high doses.

The concept of local immunity was developed several decades ago and has been recently supported by several clinical investigations in sepsis [25]. Rüssmann and co-authors describe the functions of local immunity with regard to IgA/IgM secretory immunity in bronchus associated lymphoid tissue (BALT) and gut associated lymphoid tissue (GALT). Membranous epithelial cells called M cells (microfold cells) produce MHC class II molecules which can present antigens to the local T-cells. Polyreactive sIgA antibodies are produced by B-1 cells which belong to the natural antibody reper-

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toire. Specific antibodies are produced by B-2 cells after these were in contact with antigens. These antibodies prevent adhesion of microbial products and pathogens to the bowel mucosa. Most antibodies are locally produced, the intestinal mucosa contains more than 80% of all immunoglobulin producing cells in the human body; however, transformation in hepatocytes and transport to the bowel have been reported. There is evidence that the titer of specific sIgA antibodies correlates with the resistance to infection. It has been demonstrated that therapeutic IgM and IgA containing immunoglobulin concentrates can modify mucosal immunity and may provide protection against sepsis [26].

Change in immunoglobulin synthesis has been observed after trauma. Shatney and Benner observed in trauma patients with sepsis reduced IgG, IgA and IgM levels [27]. The antibody response after trauma can be measured in the immune reaction to T-cell dependent Tetanus Toxoid (TT). Trauma is associated with a diminished ability to propagate and maintain a normal IgG antibody response, despite the presence of increased numbers of antigen-specific B-cells [28]. In anergic patients the IgG antibody reaction to a protein antigen (TT) is reduced [29]. Patients with delayed type hypersensitivity are associated with increased mortality. There is also a correlation between reduced TT response and IL-2 secretion [30]. Burn injury induces a reduced TNP specific Ig2a antibody isotyp (Th 1 dependent) whereas the TNP specific Ig1 and IgE (Th 2 dependent) response was not affected. The IgG2a response was restored by anti-IL-10 Mab and not by IgG administration. This leads to a normalization of IL-2 and IFN-γ production of mouse splenocytes. Burn injury causes a reduction in the antigen specific Th1 cell function and IL-10 functions as trigger for the reduction of Th1 activity [31]. According to Rodrick the problem of reduced immunoglobulin synthesis is caused by dysfunction of T-cells (T cell help) or by failure in the antigen presentation.

The rationale for immunoprophylaxis against sepsis consists of the increasing incidence of sepsis [32], the progressive development of microbial resistance [33] and limited options to treat sepsis with the possibility to induce unwanted side effects [34]. There is a wide variety of invasive microbial pathogens and mediators which means that only a multi-component therapy may be successful. Targets for vaccines according to Opal are endotoxin, bacterial superantigen, peptidoglycan, lipoteichoic acid, bacterial DNA. In his report Opal focus on endotoxin and bacterial superantigen vaccine strategies. Vaccines have certain advantages: they are directed against microbial mediators of sepsis and not the endogenous inflammatory mediators, prior to the onset of sepsis protective antibodies are generated already in the early phase of SIRS, and vaccines may serve as complementary treatment to immunotherapy and standard treatment. However, until now they lack protective antibody levels against all microbial components, and there is uncertainty of the duration of immune protection and the level of antibodies necessary for protection. Furthermore the existence of poor vaccine responders and the need to define a patient population which is most likely to benefit from vaccines cannot be ignored.

The anti-endotoxin approach is based on the hypothesis that endotoxin is a key mediator in Gram-negative sepsis. Lipid A which is in principal responsible for the endotoxic properties is not available to immunoglobulins. Several studies with antibodies against Lipid A (HA-1A and E5) failed to improve survival. The detection of Toll-like receptors, transmembrane activator for endotoxin signaling may have opened up a new area for potential LPS modifying agents [35]. Oligosaccharide epitopes are now a major focus of vaccine development. Core glycolipid structures may crossreact to other LPS serotypes and may thus be a potential vaccine [36]. A prerequisite for a safe and well tolerated vaccine is the removal of reactogenicity while the immunogenicity is preserved. First steps with detoxified OMP (outer membrane protein)/ de acylated J5 LPS showed crossreaction and protection in Gram-negative sepsis (Opal 1996 ICAAC Meeting). However, the mechanism by which these antibodies induce protection remains to be clarified. O-specific polysaccharide antigens of LPS are serospecific and can generate a protective immune response but no cross protection. Hyperimmune serum of the 23 most common capsular polysaccharides (Klebsiella, E. coli, Pseudomonas aeruginosa) failed to demonstrate an overall improvement in survival in sepsis [37].

Bacterial superantigens have gained more interest in the search for vaccines. Streptococcal pyrogenic exotoxin and staphylococcal enterotoxin are known to stimulate CD 4+, CD 8+, and $\gamma\delta$ T-cells. Crosslinking of TCR and MHC class II molecules by superantigens result in release of pro-inflammatory cytokines from both T lymphocyte and monocyte populations. Costimulatory molecules, e.g. CD 28, B7, LFA-1/ICAM-1, VLA-4/VCAM-1, play a significant role in the response of immune cells to superantigens [38–40]. Active vaccine against one streptococcal superantigen (SPEA), however, increased the mortality rate [41]. Specific immunoglobulins directed against conserved regions of the SE/SPE toxins may be protective [42]. There is experimental and clinical evidence to support the use of IVIG in superantigenic shock [43].

Cardiopulmonary bypass is known to induce the activation of inflammatory mediators and dysregulation of cell-mediated immunity [44]. The production of cytokines, e.g., TNF-alpha, IL-1, IL-6, and IL-8 may be induced by endotoxin [45]. With regard to immunoprophylaxis Sablotzki and co-workers summarize how different cytokines are expressed during cardiopulmonary bypass, how the cytokines correlate to pathophysiologic changes during cardiopulmonary bypass, e.g., ischemia, duration of CPB, cardiac index, systemic vascular resistance, catecholamin-support. The Th1/Th2 response has also been demonstrated in CPB.

There is a decrease in IL-2 production, whereas IL-6 and other Th2 cytokines are increased [46]. Furthermore anti-inflammatory cytokines IL-10 and TGF-β were elevated following CPB [47]. This dys-regulation of the immune response may lead to Systemic Inflammatory Response Syndrome (SIRS), multiple organ dysfunction syndrome (MODS) and exitus, in case the patient is not able to balance the immune response. The balanced immune response may be characterized by concomitant increase in pro- and anti-inflammatory cytokines [48]. The prophylaxis with immunoglobulins may interfere with cytokines, leukocytes and serum bactericidal activity, complement activation. There is evidence for toxin inactivation and a synergistic action with acylureidopenicillins [49]. Recently it has been demonstrated that a commercial immunoglobulin IgA- and IgM-enriched immunoglobulin preparation containing high antibody titers against various human pathogens was successful in the prevention of postoperative infections in anergic patients undergoing cardiac surgery [50]. The authors emphasized that at present it is not clear how the prophylactic administration of immunoglobulins contributes to the reduction in infectious complications. The effect of immunoglobulin administration on the prevention of excessive macrophage stimulation via neutralization of circulating endotoxin, short-term downregulation of inflammatory macrophages and neutrophils, and the restoration of cell-mediated immune response has been the objective of another clinical study in patients with CPB in our immunoglobulin study group.

Werdan summarizes the results of published trials with immunoglobulin preparations in sepsis treatment. Certainly many studies with IVIG have problems in design and small numbers of patients; some studies report extremely high mortality rates in septic surgical patients (almost 70%) in the placebo group. According to Werdan it is unlikely to reduce the mortality in the total group of patients with sepsis or septic shock. However, in patients with a sepsis severity score above 17 [51], septic shock and endotoxemial [52], neutropenic leukemia and sepsis syndrome [53] and in children with fulminant meningococcal sepsis [54] immunoglobulin treatment has been successful. Moderate improvement in the degree of sepsis and in the severity of disease by immunoglobulins was demonstrated in a large clinical study [55]. Certainly immunoglobulins are not the "magic bullet" but they are important partners for a combined therapeutic approach in future clinical trials.

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