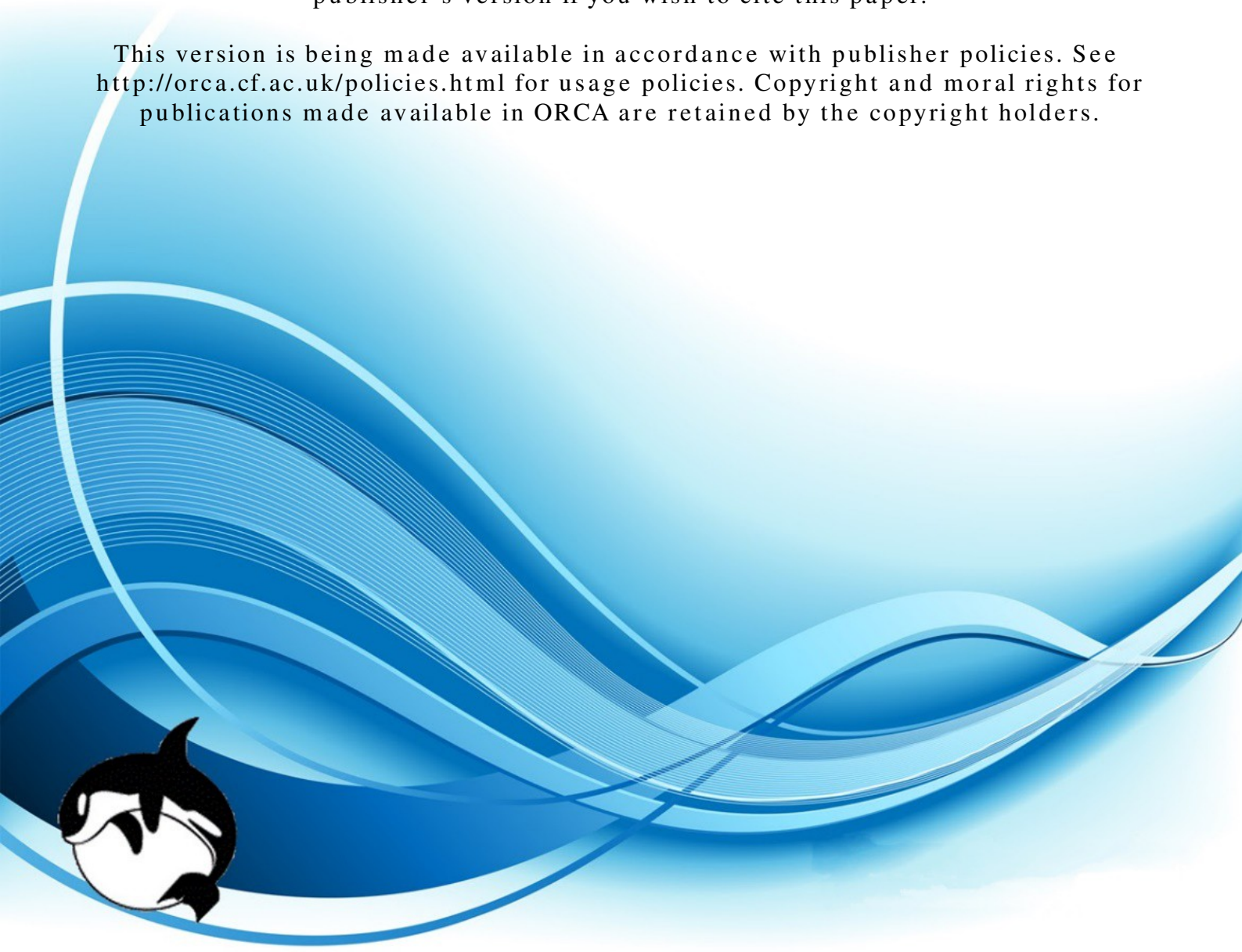

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Immunomodulation in sepsis-why blunting the response doesn't work?

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Up to 25 million patients undergo high-risk surgical procedures each year worldwide, of whom 3 million do not survive until hospital discharge (1). A large proportion of these patients will have emergency laparotomy to gain access to the abdominal cavity. This procedure carries a high risk of death, often in the region of 20-30% mortality, many times due to sepsis (2)(3)(4).

Intravenous immunoglobulin use has been proposed as an adjunctive treatment of postoperative sepsis not only to neutralize bacterial toxins (endotoxin and exotoxin) and to increase serum bactericidal action but also for modulation of cytokine release and its immunomodulatory effect (5). Immunomodulatory and anti-inflammatory mechanisms of immunoglobulins may reflect the involvement of several biological pathways, including a) decrease in the production of proinflammatory cytokines, b) suppression or neutralization of autoantibodies, c) down-regulation of adhesion molecules and chemokines, d) neutralization of superantigens and e) activated complement components and f) modulation of maturation and function of dendritic cells (6).

Intravenous immunoglobulins have been used with mixed results in postoperative sepsis and in this issue of the Journal Tagami et al. (2015) provide another important jigsaw to the picture (7). In their propensity-matched analysis of 2161 patients from the Japanese Diagnosis Procedure Combination database, they failed to show any beneficial effect of intravenous immunoglobulin therapy started on the first postoperative day, following emergency gastrointestinal surgery complicated with severe sepsis.

Whilst their results are in line with recent clinical effectiveness analyses on the field, their efforts are laudable to evaluate current clinical practice in Japan (8). The meticulous clinical description of the patients in both the immunoglobulin and placebo treated group shows that the use of polyvalent immunoglobulin preparations in the current setting is ineffective and costly, however it also highlights the importance of the unknown and unmeasured immunological variability of their un-stratified population, which could be attributable for the negative results (7).

It has been shown that immunoglobulin levels decrease in severe sepsis. In a recent study by Giamarellos-Bourboulis et al. (2013) all patients produced much lower IgM than healthy volunteers; this defect was exaggerated in septic shock (9). In our own observations, including patients with abdominal sepsis after emergency surgery, we observed similar decrease in plasma immunoglobulin levels, particularly IgM, whereas patients without infection did not show a significant decrease as compared to healthy individuals (courtesy of Heurich-Sevcenco, unpublished data, personal communication).

Considering the key role of the immune system in sepsis, immunomodulation, for instance replacing immunoglobulins to blunt the hyperinflammatory response and enhance bacterial clearence, could be effective in postoperative sepsis, however the clinical trials, including the current analysis of Tagami et al. have been

unconvincing (7)(10)(11).

Until recently, immunomodulatory approaches have focused on suppressing the immune system, based on the assumption that an overwhelming inflammatory response was the primary cause of death in sepsis (12-14). Interestingly, careful examination of recent investigations outline that both pro-inflammatory and anti-inflammatory responses occur early and parallel in sepsis, although the net initial effect of these competing processes is typically manifested by an early, hyperinflammatory phase characterized by vasodilatation resulting in shock, elevated core temperature and increased metabolism (15). Results of studies of circulating cytokines in patients showed that, in addition to pro-inflammatory cytokines, concentrations of potent anti-inflammatory cytokines such as interleukin-10 were increased early on (15)(16).

In a very elegant longitudinal observation, Gomez et al. (2014) showed that in patients admitted to the ICU with severe sepsis, both pro- and anti-inflammatory responses (such as IL-6, TNF-alpha rise, monocyte HLA-DR expression reduction and IL-10 rise) were observed simultaneously during the course of the disease (16). These findings provide further evidence against the argument that the inflammatory response comes in waves, with a pro-inflammatory response preceding the anti-inflammatory response. The immune system probably evolved to activate both activities at the same time to assure that the pro-inflammatory response is attenuated in a timely manner to avoid secondary detrimental consequences. However, both activities, which may be simultaneous at the transcriptional level, are potentially different at the translational level by displaying various cytokine and chemokine kinetics, different affinity constants for receptors, and an interaction with co-factors. Thus, their biological activities may be different, and prediction exclusively based on the transcriptome may not be completely translated to the functional level (17).

Indeed, in our own recent observations we found that patients with early onset severe sepsis were profoundly immunosuppressed on the day of ICU admission on the basis of monocyte HLA-DR expression and also on chemokine response (i.e. IL8/CXCL8, a typical neutrophil chemoattractant; and MCP1/CCL1, a monocyte and neutrophil chemoattractant) (18). The extent of the immunosuppression varied with the microbial component and chemokine tested and, critically, also varied between patients (18). This functional immunosuppressed state was observed despite measuring the normal hyperexpressed proinflammatory cytokine levels (e.g. IL-6 and IL-8) from the same samples (18).

Major surgery is known to result in a transient suppression of various immune functions, including T-cell cytokine production and monocyte expression of HLA class II antigens (19). It therefore appears conceivable that postoperative immunosuppression may contribute to defective monocyte functions in patients with sepsis. Indeed, Weighardt and colleagues (2000) shown that postoperative sepsis was associated with defects in production of both pro- inflammatory and

anti-inflammatory cytokines. Interestingly, in their study survival correlated with recovery of inflammatory but not anti-inflammatory responses (19).

Based on the properties and mechanism of action of the immunoglobulins discussed above, it is therefore not surprising that Tagami et al. (2015) could not show any beneficial effect of the treatment, even when it was started very early in the septic process (7). The failure to show the benefits of immunoglobulin therapy in this study, and other high-profile trials aimed at blocking inflammatory mediators or pathogen recognition, demonstrates the need for a re-evaluation of the immunomodulatory approaches to sepsis (7)(12)(13). The focus of recent research has shifted to reflect this: therapies aimed at enhancing immune responsiveness in immunosuppressed sepsis patients are now being evaluated (e.g., GM-CSF, IFNγ) in animal models and in small scale clinical trials (20)(21). We have recently reported a novel strategy to boost the immune response by using Toll-like receptor (TLR)-derived peptides that target the TLR co-receptor CD14, enhancing its activity (18). This strategy is based on the fact that optimal TLR-mediated responses to most microbial components require engagement of CD14, which is expressed at the cell surface (mainly monocytes, macrophages and neutrophils) and as a soluble co-receptor (sCD14) in plasma and other biological fluids (18). The therapeutic potential of targeting CD14 with TLR2-derived peptides was highlighted by the peptides' ability to rescue the pro-inflammatory response and restoring at least in part the pre-morbid responsiveness of immune cells to microorganisms of immunosuppressed sepsis patients' whole blood in vitro (18).

Notably, our data points to the existence of inter-subject variations in the immune response to infection, which may reflect differing susceptibility to secondary infections among the immunosuppressed sepsis patients. It also shows variations among patients in their sensitivity to the novel therapeutic strategy (18).

This also highlights one flaw in the Tagami study: the decision to administer immunoglobulins was based solely on clinical parameters such as diagnosis of septic shock by the treating physician, which have repeatedly been shown to be inadequate stratification tools (7)(22). Indeed, previous clinical trials on the field were, for the most part, designed without stratification of patients (11).

A prerequisite for the application of immunotherapy, either against the proinflammatory response or to reverse immunoparalysis in sepsis, is the appropriate stratification of patients (23). Various biomarkers should help in deciphering whether an individual is in the hyperinflammatory versus the hypoinflammatory phase of the disorder. Indeed, immunotherapy could worsen the outcome by causing an over-exuberant inflammatory response if applied during the wrong phase (23).

Since biomarkers of compromised immune functions in sepsis, often are related to one mechanism of immunoparalysis, it is not plausible that a single marker can act as a completely reliable biological tool to guide immunotherapy. It has been

shown that single biomarkers' effectiveness is in many instances limited, by a lack of specificity and sensitivity to distinguish the presence of an infection and to stratify patients into homogenous groups for targeted treatment. Biomarker panel based models offer a tool to facilitate early diagnosis, in identifying patient populations at high risk of complications, and in monitoring progression of the disease, which are critical assessments for appropriate therapy and improvement in patient outcomes. Wong et al (2014) recently described a multi-biomarker panel which improved outcome stratification in septic shock (22). The use of such panel amongst the patients investigated by Tagami et al (2015) and others could exclude the lowest risk patients who are likely to survive without experimental intervention and also exclude the highest risk patients unlikely to survive with any therapy.

Whilst the evidence is tilting towards to the use of immunostimulants, rather than anti-inflammatory therapies like the immunoglobulins, in further clinical trials, an appropriate stratification is mandatory to enhance the potential for measurable risk reduction among moderate or high-risk patients with modifiable outcomes.

References

1. Pearse RM, Moreno RP, Bauer P, Pelosi P, Metnitz P, Spies C, et al. Mortality after surgery in Europe: a 7 day cohort study. Lancet 2012; 380: 1059–65. doi: 10.1016/S0140-6736(12)61148-9

2. Cook TM, Day CJ. Hospital mortality after urgent and emergency laparotomy in patients aged 65 yr and over. Risk and prediction of risk using multiple logistic regression analysis. Br J Anaesth 1998; 80: 776–81.

3. Vester-Andersen M, Lundstrom LH, Moller MH, Waldau T, Rosenberg J, Moller AM, et al. Mortality and postoperative care pathways after emergency gastrointestinal surgery in 2904 patients: a population-based cohort study. Br J Anaesth 2014; 112: 860–70. doi:10.1093/bja/aet487

4. Nakagoe T, Miyata H, Gotoh M, Anazawa T, Baba H, Kimura W, et al. Surgical risk model for acute diffuse peritonitis based on a Japanese nationwide database: an initial report on the surgical and 30-day mortality. Surg Today 2014 Sep 18. [Epub ahed of print] DOI: 10.1007/s00595-014-1026-x

5. Shankar-Hari M, Spencer J, Sewell WA, Rowan KM, Singer M. Bench-to-bedside review: Immunoglobulin therapy for sepsis - biological plausibility from a critical care perspective. Crit Care. 2012;

16: 206. doi: 10.1186/cc10597

6. Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. N Engl J Med 2012; 367: 2015–25. doi: 10.1056/NEJMra1009433

7. Tagami T, Matsui H, Fushimi K, Yasunaga H. Intravenous immunoglobulin use in septic shock patients after emergency laparotomy. Journal of Infection. 2015; in press

8. Soares MO, Welton NJ, Harrison DA, Peura P, Shankar-Hari M, Harvey SE, et al. Intravenous immunoglobulin for severe sepsis and septic shock: clinical effectiveness, cost effectiveness and value of a further randomised controlled trial. Crit Care 2014; 18: 649. doi: 10.1186/s13054-014-0649-z

9. Giamarellos-Bourboulis EJ, Apostolidou E, Lada M, Perdios I, Gatselis NK, Tsangaris I, et al. Kinetics of circulating immunoglobulin M in sepsis: relationship with final outcome. Crit Care 2013; 17: R247. doi: 10.1186/cc13073

10. Alejandria MM, Lansang MAD, Dans LF, Mantaring JB. Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock. Alejandria MM, editor. Cochrane Database Syst Rev 2013; 9: CD001090. doi: 10.1002/14651858.CD001090.pub2

11. Kreymann KG, de Heer G, Nierhaus A, Kluge S. Use of polyclonal immunoglobulins as adjunctive therapy for sepsis or septic shock. Crit Care Med 2007; 35: 2677–85. doi:10.1097/01.CCM.0000295263.12774.97

12. Opal SM, Laterre P-F, Francois B, LaRosa SP, Angus DC, Mira J-P, et al. Effect of eritoran, an antagonist of MD2-TLR4, on mortality in patients with severe sepsis: the ACCESS randomized trial. JAMA 2013; 309: 1154–62. doi: 10.1001/jama.2013.2194

13. Ranieri VM, Thompson BT, Barie PS, Dhainaut J-F, Douglas IS, Finfer S, et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med 2012; 366: 2055–64. doi: 10.1056/NEJMoa1202290

14. Toth I, Mikor A, Leiner T, Molnar Z, Bogar L, Szakmany T. Effects of IgM-Enriched Immunoglobulin Therapy in Septic-Shock-Induced Multiple Organ Failure: Pilot Study. J Anesth 2013; 27: 618–22. doi: 10.1007/s00540-012-1553-9

15. Munford RS, Pugin J. Normal responses to injury prevent systemic inflammation and can be immunosuppressive. Am J Respir Crit Care Med 2001; 163: 316–21. doi: 10.1164/ajrccm.163.2.2007102

16. Gomez HG, Gonzalez SM, Londoño JM, Hoyos NA, Niño CD, Leon AL, et al. Immunological characterization of compensatory anti-inflammatory response syndrome in patients with severe sepsis: a longitudinal study. Crit Care Med 2014; 42: 771–80. doi:10.1097/CCM.0000000000000100

17. Hamers L, Kox M, Pickkers P. Sepsis-induced immunoparalysis: mechanisms, markers, and treatment options. Minerva Anestesiol 2015; 81: 426–39.

18. Raby A-C, Holst B, Le Bouder E, Diaz C, Ferran E, Conraux L, et al. Targeting the TLR co-receptor CD14 with TLR2-derived peptides modulates immune responses to pathogens. Sci Transl Med 2013; 5: 185ra64. doi: 10.1126/scitranslmed.3005544.

19. Weighardt H, Heidecke CD, Emmanuilidis K, Maier S, Bartels H, Siewert JR, et al. Sepsis after major visceral surgery is associated with sustained and interferon-gamma-resistant defects of monocyte cytokine production. Surgery 2000; 127: 309–15. doi: 10.1067/msy.2000.104118

20. Meisel C, Schefold JC, Pschowski R, Baumann T, Hetzger K, Gregor J, et al. Granulocyte–Macrophage Colony-stimulating Factor to Reverse Sepsis-associated Immunosuppression. Am J Respir Crit Care Med 2009; 180: 640–8. doi:10.1164/rccm.200903-0363OC

21. Leentjens J, Kox M, Koch RM, Preijers F, Joosten LAB, van der Hoeven JG, et al. Reversal of immunoparalysis in humans in vivo: a double-blind, placebo-controlled, randomized pilot study. Am J Respir Crit Care Med 2012; 186: 838–45. doi: 10.1164/rccm.201204-0645OC

22. Wong HR, Lindsell CJ, Pettilä V, Meyer NJ, Thair SA, Karlsson S, et al. A multibiomarker-based outcome risk stratification model for adult septic shock. Crit Care Med 2014; 42: 781–9. doi:10.1097/CCM.0000000000000106

23. Cohen J, Opal S, Calandra T. Sepsis studies need new direction. Lancet Infect Dis. 2012; 12: 503–5.