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Intravenous immunoglobulin in sepsis: can we find the right dose?

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Intravenous immunoglobulin (IVIG) administration in sepsis has been surrounded with controversies since the publication of the first international consensus meeting on this potential therapy almost 40 years ago ¹. Researchers called for evaluation of different treatment doses and durations of IVIG treatment in sepsis, when one of the earliest randomised controlled trials (RCTs) showed no effect and higher rate of significant complications in the IVIG group, using 150 mg/kg bolus dose for three consecutive days ². Recent clinical trials used a wide variety of dosing regimes ranging from 200 mg/kg/day to 1000 mg/kg/day, with similarly disappointing results ³⁻⁵. The study presented in the current

issue of the Journal by *Nakamura et al.* is the first step in the right direction ⁶. They found that single administration of 15g IVIG versus 5g IVIG boluses administered over a three-day period resulted in similar clinical outcomes in a cohort of propensity matched sepsis patients from a single Japanese centre. This equates to around 200-220 mg/kg in the single dose and 70-80 mg/kg in the divided dose groups, although the weight of their patients is not reported. The dose in the Nakamura study was confined to the approved dose used in Japan and as the IVIG administration for the indication of sepsis is not routinely reimbursed in other healthcare systems, we have to commend their pragmatic approach investigating whether a larger single dose has similar effects to a smaller, divided dose ⁶. The last RCT to report on the use of IVIG in sepsis caused by severe community acquired pneumonia, a condition which also presented in half of the patients in the Nakamura study, used similar dose (approximately 200mg/kg/day) ⁴. However, the CIGMA investigators used this higher dose for three days and still reported no significant difference in the important clinical outcome measures such as ventilator-free days and mortality ⁴. In their exploratory analysis, they have shown that IVIG might confer benefit in patients with high C-reactive protein (CRP) and low IgM levels as well as for patients with high procalcitonin levels, with significantly more patients surviving with less organ dysfunction in the IVIG group ⁴. It is important to note that in the Nakamura study, the single 15g IVIG dose has resulted in faster resolution of inflammatory markers, than the lower divided dose and their patients shared similar biochemical characteristics with the high CRP and high procalcitonin subgroup of the CIGMA trial ^{4,6}. These important findings point towards the efficacy and potential clinical utility of higher dose IVIG. As the proposed biological effect of IVIG therapy in sepsis is immunomodulation, it is accepted that the highest dose tolerated with the most pronounced response should be used ⁷. The currently tested mean dose of ~200mg/kg is

only sufficient to replace the reduced level of IVIG in the serum, whereas for immunomodulatory effects doses of greater than 500mg/kg for more than 2 days are needed ⁷. For instance, Tagami et al. have investigated the effect of 5g IVIG (70-80mg/kg) the dose for three days on the outcome of patients suffering from septic shock due to pneumonia in a propensity matched analysis ⁸. They found no beneficial effect on the rate of ventilator-of shock-free days and 28-day mortality. Based on the data reported in these earlier studies, a Phase II dose finding trial can safely discount the use of 5g/day or 70-80mg/kg regime, which otherwise could be seen as an important potential comparator based on current clinical practice.

It appears from the recent publications of the different Japanese groups that they have an opportunity to combine forces and use the national database for IVIG administration to further explore the questions of dose and patient stratification ^{3,8,9}.

Stratification of patients to groups which might have benefit from an experimental therapy have been advocated for more than a decade, with little effect on trial design to date.

Recent discoveries from the group of Shankar-hari et al. help us to understand the biological processes of immunoglobulin deficiency and also point towards better diagnostic tools for stratification of critically ill patients with sepsis ⁹. They demonstrated, that increased light chain levels with low immunoglobulin levels suggest impaired immunoglobulin assembly ¹⁰.

These low immunoglobulin levels could also be a consequence of changes in the relative proportions of B-cell subsets. B-cell apoptosis appears to be greater in memory cells when compared with naive B cells. This suggests that B-cell depletion is not a consequence of impaired bone marrow production ¹¹. Similarly to the CIGMA investigators and others, we have also found that the combined presence of low levels of the endogenous immunoglobulins IgG1, IgM and IgA in plasma is associated with reduced survival in patients

with sepsis and multi-organ failure and the low IgM levels correlated with the high CRP values (courtesy of Dr Heurich-Sevchenko, unpublished data) ^{4,12}. It is plausible, that to achieve maximum effect of immunomodulation, targeting certain subgroups of sepsis patients, such as those at highest risk of pro-inflammatory overdrive and impaired immunoglobulin homeostasis, could benefit more from the higher doses of IVIG replacement.

Historically, IVIGs were used to target Gram-positive infections, especially infections caused by *Streptococcus* and *Staphylococcus* species ¹. New markers, such as soluble-TLR2 levels, which appear to be increasing in response to Gram-positive bacterial insult, could highlight those patients who are at highest risk of developing the dysregulated response to severe infection ¹³. Combined with more conventional infectious markers, such as CRP and PCT, it could be used for identifying subpopulations (such as patients with exaggerated inflammation) who benefit the most in future trials.

The international critical care community has spent 40 years on exploring a biologically plausible treatment option for severe infection, with countless failed multicentre trials, whilst failing to acknowledge and address the lack of fundamental knowledge of immunoglobulin homeostasis. Reading carefully the detailed information and placing one jigsaw on the table at a time, the smaller studies such as Nakamura et al. presented, can help us to design better, less harmful and more cost-effective dose finding Phase II studies to evaluate the effect of IVIG treatment in sepsis.

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