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BIOTEST SYMPOSIUM
THE INCREDIBLES 2 – IMMUNOGLOBULINS IN TRANSPLANTATION

The Biotest symposium at this year's European Society for Organ Transplantation (ESOT) Congress 2021 was chaired by Martina Sester and aimed to discuss immunoglobulins in transplantation. Martina introduced the session with an overview of the topics to follow and stressed that cytomegalovirus (CMV) immunoglobulins (CMVIg) may represent an additional tool in the treatment of CMV infections. She then introduced her fellow speakers with a brief agenda on what was to follow.

Following the initial introductions, Martina commenced the session with a talk titled 'Mission Impossible' to convey how CMVIg could tip the balance towards patient benefit. She opened by discussing the clinical evidence for the beneficial role of immunoglobulins in preventing CMV infections and how this has been demonstrated in various clinical studies. Three studies mentioned by Martina included the use of CMVIg as an adjunct prophylaxis with ganciclovir, in patients with hypogammaglobinaemia and as an adjunct in patients with antiviral drug resistance. Using the first study as an example, Martina explained how patients who received additional doses of CMVIg had less CMV infection compared with the ganciclovir prophylaxis group by around 36%. In another study, in which 38 CMV heart transplant recipients were enrolled, the results demonstrated that patients with CMV infections had lower levels of CMV antibodies and T cells. Martina highlighted how antibodies and T cells make a reasonable contribution to controlling CMV load, which she stressed to delegates was an important finding. To conclude this section of her talk, Martina highlighted that the role of immunoglobulins in hypogammaglobinaemia has been investigated in multiple studies, with results demonstrating that hypogammaglobulinaema is associated with a higher incidence of CMV infections, and that IgG replacement can prevent CMV in disease in some patients. Martina then discussed her involvement as part of a consensus team, specifically on CMV management guidelines, to highlight the current recommendations of IgG replacement therapy. She emphasised the controversy within this field and combined it with the desire for future research in this area.

Martina then went on to discuss the mechanistic principles and modes of action of CMVIg, including neutralisation and opsonising activity, antibody-dependent cytotoxicity (ADCC), interaction with γδ T cells and indirectly improving T-cell response. Martina explored each of the potential modes individually, providing delegates with more detailed information, starting with neutralising and opsonising activity. She explained the key mechanism of CMVIg is to prevent the virus from infecting target cells and facilitating the uptake of phagocytotic cells. Martina then explained the mechanism of ADCC, highlighting that natural killer cell receptors recognise CMV antibodies to kill CMV-infected target cells. In terms of γδ T cells, Martina discussed the proposed mechanism that γδ T cells express CD16 to allow the recognition of antibodies that are coated with CMV antigens. She explained that the recognition of immunocomplexes can activate γδ T cells to secrete interferon-γ. By utilising the supernatant of γδ T cells and placing it on CMV-infected fibroblasts, the *in vitro* inhibition of viral replication can be achieved. Finally, to improve T-cell responses, the proposed mechanistic contribution of CMVIg may be related to increased antigen presentation and the ability to increase cytokine induction and increased proliferation.

To conclude her presentation, Martina reminded the audience that there is evolving evidence towards the clinical benefit of CMVIg in prophylaxis in lung and heart transplant recipients and its potential benefit as an adjunct in drug-resistant CMV strains. Finally, she advised that more precise knowledge on the mode of action may facilitate targeted use to help tip the balance towards preventing CMV infection.

Following Martina's talk, the next speaker, Quirino Lai, spoke about viral reactivations following liver transplantation – more specifically, the use of immunoglobulins in hepatitis B virus (HBV) and CMV prophylaxis. He began with a focus on HBV, diving into the data and history of the topic and pointing out that HBV infection is the most common chronic viral infection worldwide. Quirino discussed the evolution of prophylaxis against HBV recurrence alongside important advances in the management of HBV and changes in prophylactic concepts. He also highlighted that there has been a recent increase in the use of new drugs and a decrease in the use of immunoglobulins due to the reduced risk of resistance to newly introduced drugs.

Quirino then went into a meta-analysis that he had performed to discuss the use of hepatitis B immunoglobulins (HBIg) in combination with antiviral drugs (as a class, followed by specific antiviral medicines) in comparison with the agents alone. He took delegates through the results of his meta-analysis and summarised the results; these demonstrated that HBIg in combination with certain antiviral drugs, namely lamivudine (LAM), is superior to the use of either of the two agents alone in the setting of prophylaxis against HBV reoccurrence. However, he stressed that

in combination with newer antiviral drugs, the results provided no definitive data, and no statistical significance was found due to the lack of available literature and small study group sizes.

Quirino continued by speaking about the cost of HBIg. He referred to a study reporting the use of LAM as a prophylactic for post-liver transplant BV recurrence with adefovir (ADV) as a rescue therapy, compared with using LAM and HBIg. The data revealed higher costs for LAM and HBIg compared with the costs for rescue therapy with ADV, but recurrence and death were found to be high at 15-year follow-up. Consequently, the authors suggested to investigate and use a more tailored approach to optimise cost–benefit. Quirino emphasised how, in his opinion, we need to run new cost analyses to observe the current situation across several different geographical locations and unique settings. He continued his presentation by discussing whether HBV can really be eliminated due to the presence of covalently closed circulating DNA, which prevents complete clearance, highlighting that it's an unanswered question and that we need to be cautious.

Quirino then moved on to talk about CMV in prophylaxis, emphasising that it is usually treated with antiviral drugs as several guidelines recommend their use, even with the risk of side effects. He discussed data demonstrating that patients receiving prophylaxis had improved survival compared with those patients who weren't. He also referred specifically to data on CMVIg in critically ill liver transplant patients, highlighting that where immunoglobulins were used, survival was superior to that in patients who received no prophylaxis.

Quirino summarised his talk by reiterating that antivirals are typically recommended for prophylaxis and CMV disease; however, he reminded delegates that we must consider their well-known safety profile, particularly in severe clinical conditions.

The final speaker, Paolo Solidoro, concluded the session by giving a talk on how to tackle viral pathogens post-lung transplantation, focusing on the numerous studies available. Paolo began his presentation by talking about the nature of viral infections, sharing data that suggest the prevalence of herpesvirus is greater in those who have had lung transplantation than those who have not. He explained that this could be related to either undiagnosed pneumonia or due to physiological replication in the alveolar site.

Paolo also discussed the advantages and disadvantages of prophylaxis compared with pre-emptive therapy, emphasising that antiviral prophylaxis allows clinicians to reduce immunobiological control; however, this is associated with the delayed priming of T-cell immune reconstitution and a higher incidence of late-onset CMV disease. By contrast, pre-emptive therapy requires strict control of CMV reactivation, without univocal agreement regarding the monitoring of specimens and cut-off. Paolo then talked about a study on acute rejection and infection, comparing the two types of therapy. He presented efficacy data demonstrating prophylaxis to be beneficial in preventing rejection and infection as well as reducing the trend towards CMV pneumonia and Epstein-Barr virus (EBV) infections.

Paolo then presented data confirming the efficacy of CMVIg prophylaxis on CMV pneumonia post-lung transplantation. He summarised this section of his talk by reminding the group that the data confirm a pivotal role of CMV on rejection and appear to show that prophylaxis has a strong efficacy, not only on the reduction of infections, but also on acute graft rejection and risk factors for chronic rejection. Paolo stressed that there is such a thing as 'too much antiviral therapy'. He explained that trials are needed to evaluate the benefits of combined CMV prophylaxis (CMVIg + antiviral drug) compared with the prolonged application of antiviral agents to elaborate the most effective and cost-saving protocol for sufficient CMV prevention and long-term survival.

Paolo went on to talk about the cellular immune response in EBV, herpes simplex virus, and specifically CMV, where the temporal profile of infection, duration of infection and occurrence of CMV organ disease in lung transplantation recipients were evaluated. He shared a schematic from a paper authored by himself and colleagues on the tailored management of CMV in lung transplant recipients, pointing out some of the major conclusions. Paolo highlighted that everolimus-based (EVR) immunosuppressive regimens in lung transplantation settings appear to be associated with a lower incidence of clinically relevant CMV episodes at pulmonary levels, meaning that there is a possibility of extending the use of EVR to such a group of transplant recipients. Paolo then summarised the results at follow-up, emphasising that low-drug load combined prophylaxis resulted in a small number of CMV pneumonia cases and that prophylaxis allowed the development of natural immunity due to the low continuous exposure to CMV. Finally, Paulo explained that the enzyme-linked immune absorbent spot (ELISPOT) CMV assay is an essential tool for making the correct therapeutic choice against CMV infection.

All three speakers participated in a question-and-answer session before Martina closed the session by summarising the conclusions of each of the three presentations. She finished by thanking her fellow speakers and delegates, both in person and online, for their participation, and thanked Biotest for the opportunity and a pedestal to raise awareness on immunoglobulins.

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