The Role of Intravenous Immunoglobulins in Post-Transplant Patients

Since its discovery, the use of intravenous immunoglobulin (IVIg) preparations has been extended and established in a wide range of various clinical situations. For example, the introduction of specific immunoglobulin (hyperimmunoglobulin) represented an important milestone in the reduction of the frequency of hepatitis B virus (HBV) re-infection following liver transplantation in patients with end-stage HBV-related liver diseases. Among solid-organ transplant recipients, the cytomegalovirus (CMV) continues to have a major impact on patient and allograft recipient survival, based on a variety of direct and indirect effects. One of the issues currently under discussion and evaluation is the use of CMV-specific immunoglobulin to prevent CMV disease in patients at risk, such as heart transplant recipients and intensive care unit patients.

IVIg is a therapeutic preparation of concentrated antibodies (immunoglobulins) extracted from pooled human plasma from healthy blood donors or individuals with high titres of antibodies against certain viruses (hyper-Ig). IVIg was first introduced in the middle of the 20th century as a replacement therapy for patients with primary immunodeficiency disorders [1]. Hepatitis B hyperimmunoglobulin (HBIG) was the first agent to be included in the molecular and cellular pathways that may at least partially explain IVIg-related effects include the activation of the recently discovered IL-33-Th2 receptor axis [7]. According to a recent work of Tjon et al. [7], IVIg therapy in 29 patients with either immunodeficiency or autoimmune disease resulted in a down-regulation of the IgG receptor FcγRIIa and the interferon-γ receptor 2 (IFN-γR2) on circulating myeloid dendritic cells and the stimulation of IL-33 production by macrophages. In addition, IVIg-inhibited T cell proliferation by direct activation of Tregs was comparable to the effect of calcineurin inhibitors [9, 10]. Against this scientific background, Metselaar concluded that HBIG may not only protect against the HBV reinfecion but also against acute graft rejection by modulating the key immune cells involved in allograft rejection (Fig. 1).

**Fig. 1.** Effects of IVIg on the immune system; schematic picture modified according to Prof. Metselaar’s presentation.

Direct and Indirect Effects of Cytomegalovirus Infection

Cytomegalovirus (CMV) is another viral pathogen affecting solid-organ recipients and is one of the most common risk factors for transplantation outcome [11]. Human CMV is a ubiquitous virus with a worldwide distribution, usually acquired early in life through contact with infected body fluids such as saliva. Once acquired, the infection persists for life and may undergo periodic reactivation. Following solid-organ transplantation, which requires accompanying suppression of the immune system, CMV infection can be reactivated, as specific immune cells are down-regulated by the immune-suppressive medication. CMV can lead to direct or indirect effects of infection [12, 13]. Direct effects include CMV syndrome (encapsulating fever, myelo-suppression, myalgia and arthralgia), tissue-invasive CMV disease leading to hepatitis, gastroenteritis, and pneumonitis, and increased mortality [14]. Furthermore, there are also so-called indirect effects, both general and transplant specific, which can significantly affect outcomes (Table 1). For example, CMV infection has been associated with higher rates of cardiovascular events [15]. First data of an animal model have shown that CMV infection alone may cause a significant increase in arterial blood pressure and can be seen as a co-factor in aortic atherosclerosis [16]. The increased arterial blood pressure was independent of atherosclerotic plaque formation in the aorta. In addition, CMV infection was associated with an increase in renin expression in mouse and human cells, which depended on the infectious dose [16].

**Diagnosis in At-Risk Populations**

While most CMV infections in immunocompetent individuals are benign and self-limited, CMV is an important cause of morbidity and mortality in individuals with compromised immune function. In lung, heart and heart-lung transplant recipients, the CMV disease risk seems to be highest when the primary CMV infection occurs in a graft recipient with no pre-existing CMV-specific immunity, such as the seronegative recipients of organs from CMV-seropositive donors (D+/R−) [11]. There are several available methods for diagnosing CMV, including CMV serology, antigenemia, and quantitative PCR assays. The role of serology in the post-transplant period is limited because a positive IgG/IgM test can neither determine when a person was infected nor be used to diagnose a primary
CMV infection. The PCR assays have been considered as «gold standard», given their high sensitivity and rapid turnover time, although these are not fully standardised [17].

Main CMV Prevention Strategies

Strategies to prevent CMV have been associated with a decrease of CMV disease and toxicities [15]. However, there is significant variation in clinical application of these strategies among centres and the best strategy for preventing CMV infection has not been definitively identified [11]. The updated International CMV Consensus Guidelines indicate that the centres should develop and validate their protocols when a pre-emptive strategy is used [15].

Pre-Emptive Approach in Intensive Care Unit Patients

It has also been increasingly recognised that not only transplant recipients are «at risk» of CMV infection and disease, but also «critical ill» patients who were traditionally considered to be immunocompetent (approx. 25%), as stressed by Dr. Uwe Schulz, Heart and Diabetes Centre NRW (HDZ NRW), Bad Oeynhausen. According to a descriptive review of 13 studies of CMV infection, those at particular risk were intensive care unit (ICU) patients with mechanical ventilation at admission, with sepsis, where corticosteroids were used (in one study) or where there was a longer ICU stay (33–69 days vs. 22–48 days amongst patients with CMV). CMV infection was assessed at least weekly, the mean (or median) time to onset of CMV infection ranged from 4 to 28 days. In addition, a PCR assay seemed to help diagnose CMV infection 2–4 days earlier than the antigenemia assay.

In clinical practice, the PCR assay should be used at least weekly to monitor CMV infection in ICU patients, as Dr. Schulz summed up, meaning that blood samples of at-risk patients should be tested weekly with the CMV quantitative PCR to detect virus activation. Actually, there is no established viral load threshold to guide pre-emptive treatment. But according to clinical experience, once viremia (>500,000 copies/ml) in blood and/or other organs is detected, pre-emptive antiviral treatment (10–28 days) should be started in asymptomatic ICU patients, followed by close virological monitoring. Dr. Schulz also mentioned that CMV-specific IVIg should alternately be considered if the use of antiviral agents is limited (e.g. impaired renal function, leukenopenia). In addition, for recurrent CMV disease in thoracic organ transplant recipients, the updated International CMV Consensus Guidelines recommend considering IVIG or CMVIG as adjunctive therapy in cases of hypogammaglobulinaemia [15].

CMV Prophylaxis in the Heart Transplant Setting

Dr. Schulz presented results of a first pilot study in the heart transplant (HTx) setting where recipients were treated with a valganciclovir-free strategy. HTx patients with asymptomatic infection who had been tested positive in the CMV-DNA PCR (n = 15) initially received 1 dose of CMV IVIg (Cytotec®, ≤75 kg: 50 ml; >75 kg: 100 ml). More than half of the HTx patients (60%) were CMV-DNA PCR negative after a single CMV IVIg dose (9/15), as Dr. Schulz reported. Five patients (33%) experienced a relapse following successful single-dose treatment, and only 1 patient (7%) required more than 2 infusions of CMV IVIg within 2 weeks. The follow-up was between 3 and 10 months. Dr. Schulz concluded that, in this retrospective case study, CMV IVIg was not only shown to have been highly effective, but also to be safe and generally well tolerated: Only 1 case was reported with a hypersensitivity reaction for unknown reasons. Overall, the current clinical experience indicated that the use of CMV IVIg is addressing unmet medical needs in patients at risk (e.g. ICU patients) who show low copy numbers of CMV-DNA, impaired renal function and/or neutropenia.

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