Infections and allograft rejection – intertwined complications of organ transplantation

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The practice of organ transplantation is associated with two cross-linked and often-interdependent clinical outcomes – allograft rejection and infection. The allogeneic stimulation triggered by the exposure to foreign antigen (ie, allograft) and the immunosuppressive drugs used to prevent and treat allograft rejection predispose the transplant recipient to a wide variety of bacterial, viral, fungal, and parasitic infections. Interestingly, certain infections are believed to influence the occurrence of acute and chronic allograft rejection. Hence the question, "*Which comes first, infection or allograft rejection?*" can be answered with "yes" or "either." Indeed, the bidirectional interplay between these two clinical events could lead into a vicious cycle that presents a conundrum in the transplantation field.

In this issue of *Swiss Medical Weekly*, Garbino and colleagues highlights the multifaceted relationship among allograft rejection, immunosuppressive therapy, and infection [1]. Using a cohort of 98 patients who underwent liver transplantation during a ten-year period from 1987 to 1997, Garbino and colleagues demonstrate that infections and allograft rejection are a very common occurrence after liver transplantation. Eighty percent of patients developed at least one infectious complication, often during the first month after liver transplantation, while 70% of patients had at least one episode of biopsy-proven allograft rejection. Garbino and colleagues further observed that infections occur more commonly in liver transplant patients who had at least one episode of allograft rejection. Moreover, infections (especially viral infections) were commonly observed during 30 days following allograft rejection and its treatment.

These observations concur with well-established knowledge that allograft rejection and infections are interrelated outcomes of organ transplantation [2]. Identifying and understanding the underlying mechanism that binds these clinical events together could lead to better prevention and treatment. Commonsense dictates that the use of intensified immunosuppressive drugs to treat an allograft rejection episode markedly increases the risk of subsequent infections and therefore represents the common link between these two processes. The classic example is the increased predisposition to cytomegalovirus (CMV) disease following treatment with OKT3 [3]. It is believed that the intensified immunosuppression that results from treatment leads to a profound and often global suppression of pathogen-specific immunity. This leads to the reactivation of latent infections and the inability to control newly acquired and reactivated infections. Importantly, it is believed that a "cross-talk" between allograft rejection and infection exists and this is likely mediated by the bidirectional trafficking of cytokines and other chemical mediators.

Indeed, allograft rejection *per se* could trigger the occurrence of certain infections [4]. The cellular and immune activation events that occur during episodes of allograft rejection could initiate reactivation of latent pathogens. For example, the interdependent association between allograft rejection and CMV infection has been suggested to be mediated by elevated levels of tumour necrosis factor (TNF)-α [5, 6] – a key cytokine that serves as a potent inducer of CMV IE gene transcriptional reactivation [7]. The high intragraft level of TNF-α during acute cellular rejection [5] could lead to a localised or disseminated CMV infection. Hence, it is not surprising that allograft rejection is one of the most important predisposing factors for late-onset CMV disease in liver and other solid organ transplant recipients [2].

Conversely, it is believed that infection *per se* triggers the occurrence of allograft rejection. In this study by Garbino and colleagues, infections were more common following allograft rejection and its treatment. However, certain infections were also observed prior to allograft rejection. Although we may never know for certain if there is a cause (infection)-and-effect (rejection) association, it is important to emphasise the many experimental and clinical studies that have proposed that certain infections could influence acute and chronic allograft rejection [8]. Viral triggers of allograft rejection have gained much interest and debate in the field for more than a decade [9]. Clinical associations between viruses and acute and chronic allograft nephropathy, vanishing bile duct syndrome, bronchiolitis obliterans, transplant coronary vasculopathy have been reported by

numerous investigators [10]. Even subclinical CMV infection, when prolonged, has been associated with allograft loss and mortality in liver recipients [11, 12]. Furthermore, anti-CMV treatment has been associated with a reduction in allograft rejection [13]. Collectively, these observations identify a potential important role for infections in the pathogenesis of allograft rejection after transplantation.

What can we derive from these clinical studies and how will the information translate into better care of our most vulnerable transplant patients? By reporting clinical observations, such as this study by Garbino and colleagues, we highlight the importance of a clinical problem that needs to be addressed urgently. Currently, some centres have responded by adapting a strategy of heightened clinical and laboratory infection surveillance during and after episodes of allograft rejection and its treatment. In our centre, the practice of administering "targeted antiviral treatment" during and after OKT3 treatment of an allograft rejection episode emanated from clinical studies similar to the report by Garbino and colleagues [1, 3].

At this point, we emphasise that the ultimate goal should always be the creation of a balance in the so-called "net state of immunosuppression" so that allograft function is maintained without engendering significant infectious risks. We believe that this is an attainable undertaking, which will require significant efforts of multidisciplinary collaborative teams of clinicians and scientists. Some of the ongoing efforts to this end include the development and optimisation of diagnostic assays to detect potential pathogens, the development of assays that accurately measures the functional level of immunosuppression [14], the advancement in pharmacogenomics that will allow customisation of immunosuppressive treatments that will match the drug to the individual's genomic make up [15], among others. Such a practice, when it becomes implemented in the clinical arena, could potentially increase the efficacy of immunosuppressive drugs, while at the same time, it could avoid or reduce side effects such as infections.

The emerging practice of immunominimisation and the development of novel immunosuppressive drugs with inherent antimicrobial activity could also lead to reduction in infectious complications. In recent years, the goal of developing immunosuppressive drugs has shifted from controlling allograft rejection to reducing the many associated side effects. Whether these newer drugs are associated with reduced overall incidence of infections after transplantation remains to be seen. In this context, mycophenolate mofetil possesses anti-*Pneumocystis jirovecii* activity *in vitro* and could lead to a reduced incidence of pneumocystosis [16]. Mycophenolate mofetil also potentiates the anti-herpes activity of ganciclovir [17]. However, higher rates of tissue-invasive CMV disease, varicella zoster and other herpes infections have been reported with its use [18]. Two novel anti-CD25 monoclonal antibodies – Daclizumab and Basiliximab – have been associated with lower incidence of CMV and herpes simplex infections [19, 20]. A lower incidence of CMV infections has also been reported with use of everolimus [21]. Interestingly, this low incidence could have resulted from the lower incidence of allograft rejection [9]. Rapamycin has potent *in vitro* activity against various fungi including *Cryptococcus neoformans*, *Candida albicans* and *Aspergillus fumigatus* [22], although clinical data to support this benefit has yet to be reported.

The immunosuppressive drug regimens have changed considerably since this study was conducted. Hence, the results of this study by Garbino and colleagues may not reflect contemporary clinical practice. Nonetheless, this study highlights the important risks associated with intensified immunosuppression and the complex interplay between allograft rejection and infection. The result of this study should therefore serve as a reminder and a catalyst in our ongoing search for the optimal method of practicing transplantation medicine. Finding the right balance – minimised allograft rejection, optimised immunosuppression, and without entailing the risk of infection – is a very desirable cause that everyone in the transplantation field should strive for.

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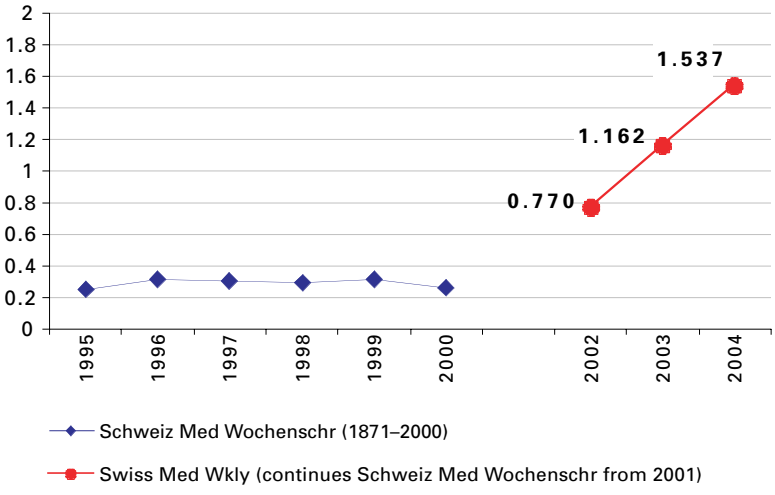

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