Understanding Risk and Enhancing Safety in Immunotherapy Trials

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(See the Major Article by Loechelt et al, on pages 248–54.)

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In the past decade, there has been major progress in the development of novel immunosuppressive therapies. In addition, there have been advances in the clinical applications of these therapies to suppress both alloimmunity and autoimmunity. In some situations, however, the toxicity of the therapies, including infections, can limit their use. In this issue of Clinical Infectious Diseases, Loechelt and colleagues performed monitoring for herpesviruses in 126 patients with type 1 diabetes mellitus (DM) [1]. These patients were enrolled in a randomized controlled trial of daclizumab and mycophenolate mofetil (MMF). The original trial did not find a significant protective effect of daclizumab and MMF on the loss of insulin-producing β cells in patients with new-onset type 1 diabetes [2]; Loechelt et al concluded that daclizumab and MMF did not increase morbidity from herpesviruses. Nevertheless, the monitoring of these patients for herpesvirus infections has provided novel insights into the effects of common viral infections with the use of potent exogenous immunosuppression in the nontransplant setting.

In the current study, the authors performed careful laboratory and clinical monitoring for Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), and varicella zoster virus (VZV). Both primary infections and reactivations were observed but significantly increased morbidity was not seen in patients receiving either one or both immunosuppressive drugs compared with placebo. There was a trend toward greater EBV viral burden ($P = .06$) in patients receiving both daclizumab and MMF compared to those on no immunosuppression. However, most patients were either asymptomatic or had a self-limited mononucleosis-like syndrome. EBV is an important herpesvirus in transplantation; pediatric transplant patients especially are at greater risk of posttransplant lymphoproliferative disease (PTLD), primarily because they are often EBV-seronegative prior to transplantation and may receive a seropositive organ. In this study, EBV viral loads were reportedly not significantly different from viral loads measured in transplant patients at the same lab. In the transplant setting, high EBV viral loads have been correlated with an increased risk of PTLD [3]; however, other than mononucleosis-like syndrome in 3 patients, there was no development of lymphoproliferative disease in the current study. This may have been due partly to the discontinuation of immunosuppression when 2 sequential positive viral loads were obtained. Viral load monitoring and subsequent reduction of immunosuppression has been shown to decrease progression to PTLD in the transplant setting [4]. In contrast to the transplant setting, the subjects in Loechelt et al’s study were also on fewer immunosuppressive agents than would typically be used and had not received a T-cell–depleting agent such as antilymphocyte globulin (a known risk factor for PTLD) [5]. Transplanted patients are often also on immunosuppressive regimens that include a calcineurin inhibitor and/or corticosteroids, in addition to MMF. There are various other contrasts between the type 1 DM setting and transplant setting. In a seronegative individual who has undergone transplant, there is an allogeneic stimulus and transfer of cells harboring latent virus (if the donor is seropositive). Also, ischemic injury to the graft and major histocompatibility complex mismatch could all promote local viral replication,
leading to greater risk of severe sequelae such as lymphoproliferative disease.

Rates of other herpesviruses such as CMV, HSV, and VZV were low. This is in contrast to transplant patients, in whom CMV is one of the most common viral opportunistic infections and is associated with significant morbidity and occasional mortality. Similarly, reactivation of VZV and either localized or disseminated zoster are significant problems in the transplant population. In particular, primary infections with herpesviruses (occurring when the donor is seropositive pretransplant and the recipient is seronegative, or due to primary acquisition from community exposure) are usually of the greatest severity in transplant patients and necessitate prompt antiviral therapy to prevent severe disease. In contrast, several patients in the current study had primary infections, many of which were not treated with antiviral therapy, and yet this did not result in severe disease. This is reassuring for future trials of immunotherapy in this patient population. Many patients with new-onset type 1 diabetes are young and are therefore often seronegative for herpesviruses. This means there is an increased likelihood of primary infections during follow-up.

The mechanism of action of the immunosuppression agents used is important to understand in this setting. Daclizumab is a humanized monoclonal antibody against the interleukin 2 receptor present on T lymphocytes and primarily affects T-cell function. Daclizumab was withdrawn from the market in 2008; however, drugs with a similar mechanism of action such as basiliximab are widely used in transplantation. Mycophenolate mofetil inhibits the purine pathway enzyme, inosine monophosphate dehydrogenase; therefore, it is a potent inhibitor of both B-cell and T-cell proliferation. Both immunosuppression agents are routinely used in the transplant setting to prevent allograft rejection. CD4⁺ and CD8⁺ T-cell responses play a critical role in both the response to primary infection and to control reactivation of herpesviruses. High doses of MMF have been associated with both increased CMV disease rates posttransplant and delayed response to therapy [6]. For BK viremia, studies show that a cessation of MMF results in clearance of viremia and prevents progression to BK virus–associated nephropathy [7]. In addition, the use of high doses of MMF is also implicated in poor response to influenza vaccine suggestive of an inability to respond to new antigens [8].

Perhaps one of the most important lessons learned from this study is that there is a critical need for careful and prospective infectious disease monitoring in clinical trials of immunosuppressive agents. Monitoring should be performed using standardized clinical and laboratory definitions for infectious diseases as this can allow for comparisons across studies. Building in comprehensive monitoring protocols within the framework of these trials serves several important functions: (1) it provides accurate epidemiological data about the infectious risks associated with given immunosuppressive agents; (2) it allows the trial to be conducted in a safer manner (eg, in the current trial, patients with persistent viremia had the drug discontinued); and (3) it informs the clinician about the need for monitoring patients receiving these medications once approved for a given indication. Similar monitoring protocols have been proposed by the American Society of Transplantation for use in trials of immunosuppressive agents for organ transplantation [9]. However, this practice is variable across studies. Often in multicenter trials, specimens are batch tested at the end of the study and testing does not provide real-time results. Also, many trials may not be powered to detect differences in infection rates and smaller trials such as that presented by Loechelt et al will only detect major differences; however, trends seen in smaller studies may serve as preliminary results or cautionary notes that pave the way for larger studies or provide clinical guidance for use of these drugs. For example, a recent 3-year follow-up of a phase III study of belatacept vs cyclosporine in kidney transplantation showed a higher incidence of central nervous system PTLD in the belatacept arm [10]. Although the numbers of patients developing this complication was small, the drug is currently not recommended for use in EBV mismatched transplant patients (ie, donor seropositive/recipient seronegative).

Although it is important to monitor for common viruses, there are also several examples where immunosuppressive therapies for various nontransplant indications have led to unusual or unexpected infectious complications. One example is the use of natalizumab, a monoclonal antibody against α-integrin, for multiple sclerosis. Although natalizumab is highly effective for multiple sclerosis, it can lead to reactivation of JC virus and progressive multifocal leukoencephalopathy with an estimated incidence of 11.1 per 1000 persons [11]. Another example is the use of infliximab, a chimeric antibody to tumor necrosis factor α, which has been useful for a variety of inflammatory conditions but has been associated with an increased risk of tuberculosis reactivation [12]. Eculizumab, a terminal complement inhibitor, is authorized for the treatment of paroxysmal nocturnal hemoglobinuria; although not entirely unexpected, severe meningococcal sepsis has been reported with this medication, prompting guidelines to vaccinate and/or prophylax against meningococcus with the use of this medication [13]. This highlights the importance of clinical vigilance in the use of these therapies.

In summary, it is important to include prospective clinical and laboratory monitoring for specific infectious complications in trials of immunotherapy regardless of disease or clinical

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indication being evaluated. This will help inform risk and improve patient safety.

**Note**

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**References**