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Minireview

Management of Epstein–Barr Virus-induced Post-transplant Lymphoproliferative Disease in Recipients of Solid Organ Transplantation

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The optimal management of Epstein–Barr virus (EBV)-induced post-transplant lymphoproliferative diseases (PTLD) remains controversial. While withdrawal or reduction of immunosuppression is widely accepted as the strategy for the treatment of EBV/PTLD, the role of additional therapeutic interventions remains less clear. Newer strategies, including anti-B-cell monoclonal antibodies and adoptive immunotherapy offer the promise of impaired efficacy and outcome against EBV disease, but lack data demonstrating how and when to use these approaches. The current review provides an overview of potential strategies and presents guidelines for the management of EBV/PTLD in solid-organ transplant recipients.

Key words: Epstein–Barr virus (EBV), post-transplant lymphoproliferative disease (PTLD), organ transplantation

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Introduction

Despite an increasing understanding of Epstein–Barr virus (EBV) disease in solid organ transplant recipients, the optimal management of this important complication in these patients remains controversial. Mortality rates as high as 60% have been reported among organ transplant recipients diagnosed with post-transplant lymphoproliferative disease (PTLD). A large proportion of the PTLD-associated deaths appear to be due to chronic rejection resulting from withdrawal of immune suppression in an effort to treat the PTLD. In contrast to these dismal results, we have achieved long-term survival rates ranging from 60 to 100% for EBV-associated PTLD diagnosed in children undergoing solid organ transplantation at our institution, with death or graft loss due to chronic rejection an infrequent problem in these patients. These differences in outcome may be explained, in part, by center-to-center differences in case definitions of EBV disease. Alternatively, variability in the management approach to PTLD may be the explanation. Currently, there is a lack of comparative data evaluating potential therapeutic strategies and no clear consensus for their use in the management of PTLD in organ transplant recipients. The purpose of this review is to provide an overview of potential therapies and to present guidelines developed at the Children's Hospital of Pittsburgh for the management of EBV/PTLD in solid-organ transplant recipients. Emphasis will be placed on reviewing traditional therapeutic options and on discussing the potential role of newer strategies for the management of EBV-associated disease of B-cell origin. While EBV-associated PTLD of T- and NK-cell origin occurs (as does EBV-negative PTLD), management of these complications is beyond the scope of this review.

At-Risk Population

Primary infection with EBV following organ transplantation is the major risk factor for the development of EBV disease and PTLD in organ transplant recipients. While EBV disease occurs uncommonly (< 1%) in patients who are EBV-seropositive before organ transplant, EBV-associated disease develops in more than 20% of patients experiencing primary infection following transplantation. Accordingly, the index of suspicion for the diagnosis of EBV disease and PTLD should be much higher in those patients who were known to be EBV-seronegative before transplant. An exception to this rule appears to be the intestinal transplant recipient. Experience from our center suggests that EBV disease may occur at least as frequently in intestinal transplant recipients who were EBV-seropositive before transplant compared with those who were EBV-seronegative. Thus, a high index of suspicion should be maintained for any intestinal transplant recipient with a clinical syndrome compatible with EBV/PTLD. Finally, additional risk factors associated with an increased risk of developing EBV/PTLD include the development of CMV disease (especially in the D+/R-– CMV serogroup) and the use of antilymphocyte antibodies.

Classification and Diagnosis

Epstein–Barr virus is increasingly recognized to be associated with a wide range of disease manifestations. The recognized

spectrum of EBV disease has expanded with the evolution of immunosuppressive agents, the expanding types of organ transplant procedures and the availability of increasingly sensitive diagnostic tools. At present, a variety of descriptive histological classifications are used to define PTLD. A recent consensus conference of the American Society for Transplantation suggested that the term 'PTLD' be used to encompass a large spectrum of lymphoproliferative processes. The conference recommended that while the term 'PTLD' should be applied to post-transplant infectious mononucleosis and plasma cell hyperplasia, these entities should be segregated out as reactive hyperplasias. The conference further recommended that, when the term PTLD was not further qualified, it should refer to neoplastic forms of PTLD. These would include polymorphic PTLD (including polymorphic lymphoma and polymorphic B-cell hyperplasia, which can be a monoclonal lesion) or lymphomatous PTLD (including so-called monomorphic PTLD). Histologic review of neoplastic PTLD should reveal disruption of underlying architecture by a lymphoproliferative process, presence of monoclonal or oligoclonal cell populations and evidence of EBV in many of the cells. While the finding of all three of these features would be desirable, the clear demonstration of a lymphoid tumor exhibiting any two of these features is sufficient to establish the diagnosis of neoplastic PTLD.

A potential limitation of this or any of the previously published clinicopathologic classifications of EBV/PTLD is that they do not encompass patients who present with non-specific viral syndromes due to EBV. Patients may present with febrile illnesses very similar to the classic 'CMV syndrome' (e.g. fever, malaise, anorexia, abdominal pain and/or diarrhea) which do not fall within the classic definitions of EBV/PTLD. A widening spectrum of EBV-associated diseases appears to be increasingly recognized as clinicians look more carefully for EBV disease using more sensitive tests. Thus, we favor including EBV-associated non-specific viral syndromes in the spectrum of EBV-associated diseases. In general, our initial approach to the management of most patients with EBV-associated disease is similar regardless of whether they have a viral syndrome, reactive hyperplasia or neoplastic PTLD.

The diagnosis of EBV disease in solid organ transplant recipients is based on clinical history and physical examination findings in combination with laboratory confirmation. A high index of suspicion must be maintained at all times. The diagnosis of EBV/PTLD should be considered in at-risk transplant recipients with fever for more than 3 d without an identified source. Patients may present with a history of lethargy or malaise, which may only be evident during the time periods that the patient is febrile. A history of diarrhea (which may be guiaic positive) is suggestive of gastrointestinal involvement. Patients typically present with evidence of peripheral adenopathy, hepatosplenomegaly and/or exudative tonsillitis. Many patients will have the same signs and symptoms as immunocompetent patients with mononucleosis. Uncommonly, patients may have neurologic symptoms suggestive of central nervous system involvement with PTLD. In addition to performing a careful history and examination, we recommend routinely obtaining CT scans of the chest and abdomen to document occult foci of EBV disease and establish the full extent of disease.

In general, histologic evaluation is required to confirm the diagnosis of PTLD. The finding of characteristic histologic features in combination with immunohistologic staining confirms the diagnosis of EBV disease. Currently, *in situ* hybridization with the EBER-1 probe (which labels EBV-encoded RNA in infected cells) is the most reliable histologic stain and its use is recommended in all cases of suspected EBV disease. More recently, measurement of EBV viral load in the peripheral blood with polymerase chain reaction (PCR) has been evaluated as a diagnostic tool for patients with symptomatic disease. Growing experience suggests that elevated EBV viral loads will be present in the vast majority of patients with EBV/PTLD. It is important to note that the height of the EBV viral load is comparable among patients with EBV-associated viral syndromes and those with PTLD. While the measurement of the EBV viral load is a promising new diagnostic test, it has several limitations. Concerns with these assays include the fact that they are not standardized and that it is not clear that all patients with EBV/PTLD will have elevated viral loads. In addition, viral loads may be elevated in the absence of evidence of active disease. Thus, while measurement of the EBV viral load is a useful screening procedure for suspected EBV disease, the test lacks specificity and it cannot replace histologic examination of suspected sites of involvement when the diagnosis of PTLD is contemplated. Finally, clinicians should not rely on serologic tests to make the diagnosis of EBV/PTLD, as many patients will have positive EBV titers on the basis of passive immunization from blood products and others may seroconvert without manifesting any clinical symptoms. In addition, the immunosuppressive agents used in transplant recipients might result in some patients having falsely negative serologic results.

Management

Reduction of immune suppression

It is now widely accepted that EBV-driven lymphoproliferation, and the subsequent development of EBV/PTLD, occurs as a consequence of the immune suppression necessary to prevent rejection. Starzl and colleagues first suggested reduction or withdrawal of immune suppression as a strategy for the treatment of PTLD in the 1980s. This approach has been widely accepted as the initial strategy for the treatment of most categories of EBV disease. The goal of this approach is to allow the host to recover natural immune surveillance and subsequently gain control over the proliferation of EBV-infected cells. Regression of polyclonal and monoclonal EBV-associated PTLD lesions, by reduction of immune suppression alone, or in combination with other strategies, has been reported to occur in 23–86% of patients. The wide variation in response may be explained by differences in the definitions of PTLD, but also by the amount and duration of reduction used by individual centers. In our experience, the vast majority of nonmalignant

lesions will respond. In general, most patients show evidence of clinical response within 2–4 weeks of reduction of immune suppression, although a belated response has been observed as long as several months in some patients.

Antiviral chemotherapy

Initial interest in the role of antiviral chemotherapy for treatment of EBV/PTLD arose in 1982 when Hanto described a patient whose EBV-associated PTLD lesion appeared to wax and wane in association with starting and stopping acyclovir. Both acyclovir and ganciclovir inhibit lytic EBV DNA replication *in vitro* and may be of value in treating the lytic phase of EBV infections. Ganciclovir is ≈10-fold more potent than acyclovir at inhibiting lytic EBV replication *in vitro*, and has the additional advantage of inhibiting CMV that may be present as a copathogen in some cases of EBV/PTLD. Based on Hanto's report and the *in vitro* activity of these agents, use of acyclovir or ganciclovir for the treatment of EBV/PTLD has become routine. However, their efficacy has not been established in prospective, comparative clinical trials, and many investigators have questioned their role in the treatment of EBV/PTLD. The vast majority of EBV-infected cells within PTLD lesions have been shown to be transformed B cells that are not undergoing lytic infection. Neither acyclovir nor ganciclovir suppresses EBV-driven proliferation of B cells *in vitro*, nor are they active against B cells that are latently infected with EBV. Furthermore, EBV viral loads in the peripheral blood can climb to very high levels and PTLD may develop while patients are receiving intravenous acyclovir or ganciclovir. In addition, results from our laboratory using reverse transcriptase PCR confirm that the bulk of the viral load in the peripheral blood appears to be associated with proliferation of EBV-immortalized cells and not with lytic infection. The only biologically plausible role for these agents is to prevent the minority of lytically infected cells within PTLD lesions from spreading EBV to new clones of previously uninfected B cells.

Interferon

The use of interferon has been anecdotally described as a therapeutic option for PTLD. In support of this strategy is the fact that EBV-infected B cells produce an interleukin-10 homologue that interferes with interferon-gamma synthesis, a substance believed to inhibit the growth of EBV-transformed B cells. In addition, interferon may function both as a proinflammatory mediator and as a natural antiviral agent. However, prospective, controlled clinical trials establishing the therapeutic role of interferon have not been performed. In the tacrolimus era, we have treated six of 48 pediatric liver and cardiothoracic transplant recipients diagnosed with EBV/PTLD with interferon. Five of these patients received alpha-interferon 2b; one was treated with gamma-interferon. Three of the six patients appeared to respond to the interferon therapy without significant side-effects, although each developed rejection. Each of these patients also had their immune suppression reduced or withdrawn. Two of the patients died of widespread disease that may have been too extensive for this agent to make an impact. The remaining thoracic transplant recipient was taken off interferon because of the development of severe rejection. On the basis of our observations, along with other reports in the literature, we conclude that the role of interferon in the treatment of EBV/PTLD has not been clarified and that rejection occurs frequently in patients receiving this therapy.

Intravenous immune globulin

A potential role for the use of intravenous immune globulin (IVIG) for the treatment of EBV/PTLD has also been suggested. Several reports have documented an association between loss or absence of antibody against at least one of the Epstein–Barr nuclear antigens (EBNAs) in EBV-infected organ recipients and the subsequent development of PTLD. In addition, a correlation between an increasing level of anti-EBNA antibodies (including those introduced through transfusions) with a decrease in EBV viral load has been demonstrated. Taken together, these reports may provide a rationale for considering the use of antibodies in the prevention and/or treatment of EBV disease and PTLD. IVIG has been used in combination with interferon-alpha as a treatment for PTLD. Based on our experience with the use of high-titer CMV IVIG (CytoGam^{R}, MedImmune, Inc.) as pre-emptive therapy for intestinal bowel transplant recipients with elevated EBV viral loads, we have incorporated CytoGam in our treatment of some pediatric and adult solid organ transplant recipients with EBV/PTLD. As with the use of antiviral agents and interferon, there are no comparative trials evaluating the role of IVIG in general, or CytoGam in particular, in the treatment of EBV/PTLD.

Anti-B-cell antibodies

The use of anti-CD21 and anti-CD24 monoclonal antibodies has been reported for the treatment of PTLD in recipients of solid organ and bone marrow transplantation (BMT). Although these reports were of a limited and noncomparative nature, the results were promising for polyclonal but not monoclonal disease. These two monoclonal products are no longer available, but rituximab, a new anti-CD20 monoclonal antibody, has recently been approved for the treatment of certain CD20-positive B-cell non-Hodgkin's lymphomas. This product may provide similar results among patients with PTLD expressing the CD20 antigen to those seen with the anti-CD21 and anti-CD24 products. Clinical investigators in France published a retrospective analysis of the use of rituximab in 32 patients with PTLD. Most of the patients developed PTLD after solid organ transplantation. Rituximab was initiated a median of 14 d after the diagnosis of PTLD as primary therapy in the majority of patients (although it followed reduction of immunosuppression in 27 of 30). The overall response rate was 65% in solid organ transplant recipients, most of whom experienced a long-term cure at a median follow-up of 8 months. However, relapsed PTLD developed in ≈20% of responders a median of 7 months after completing their therapeutic course of rituximab.

There are several important questions regarding the use of rituximab. Its usefulness in B-cell lymphoproliferative lesions that do not express CD20 has not been reported and would not be expected. Will the prolonged elimination of resting B cells by this agent result in additional opportunistic infections

or sequelae in patients treated for PTLD with rituximab? If safety is reasonable, should rituximab be used in all patients or only those who fail an initial period of observation on reduced immunosuppression? If relapse occurs after the use of rituximab, how should management proceed?

Cellular therapy

Cytotoxic T-lymphocytes (CTLs) directed against EBV-specific antigens are thought to be the major source of control over EBV infection in immunocompetent individuals. Withdrawal of immune suppression reverses the nonspecific suppression of T cells used to prevent rejection and allows the development and expansion of these EBV-specific CTLs in patients with symptomatic EBV disease. The use of EBV-specific CTL therapy has been used for the management of EBV/PTLD in BMT recipients. Unfortunately, several problems currently limit the applicability of this strategy to solid organ transplant recipients. PTLD lesions in BMT recipients are of donor origin. Thus, the EBV-specific CTLs obtained from the original bone marrow donor are capable of recognizing and destroying EBV-infected B cells in the BMT recipient. In contrast, PTLD lesions developing after solid organ transplantation are typically of recipient origin. Accordingly, there is a need to raise EBV-specific CTLs of recipient origin for a comparable strategy to be effective. Because EBV-associated PTLD occurs much more frequently in patients who were EBV-seronegative before transplant, pre-existing immunity specific to EBV does not exist. Thus, to obtain functional EBV-specific CTLs, one would need to 'immunize' and/or stimulate recipient T cells against EBV *ex vivo*. Although efforts to do just this are being developed, this therapy is not yet available. Finally, PTLD of donor origin has been reported. Thus, if and when cellular therapy becomes a viable option for solid organ transplant recipients, determination of the origin of the cells making up the tumor (donor vs. recipient) would seem prudent in order to determine the appropriate source for EBV-specific CTLs.

Cytotoxic chemotherapy

In general, the need for the use of chemotherapy appears to be more frequent in adult than in pediatric organ transplant recipients with PTLD. A recent series of 39 pediatric liver transplant recipients with biopsy-proven PTLD identified only three children who failed more conservative therapeutic strategies based on decreasing immunosuppression. Similarly, only two out of 36 pediatric liver transplant recipients who developed PTLD at our center under tacrolimus-based immunosuppression were treated with chemotherapy. The survival rate in this series was 78%, with only 14% of the mortality felt to be directly associated with PTLD. Because of historically high mortality rates associated with the use of chemotherapy for PTLD, as well as the likelihood that PTLD in children will respond to more conservative measures, we recommend restricting the use of chemotherapy to patients who have malignant large B-cell lymphoma or Burkitt's lymphoma, or who fail to respond to lowering of immune suppression. Decisions regarding the initiation of chemotherapy for patients with lymphoma are complicated by the fact that some centers use the term 'lymphoma' for tumors that are still likely to be responsive to reduction in immunosuppression. Identification of oncogene expression and tumor suppressor genes may also identify a subgroup of patients requiring cytotoxic chemotherapy. While most patients deserve a trial of reduced immune suppression, the optimal duration of this trial before opting to start chemotherapy has not been determined. It is worth noting that children presenting late (>2 years) after transplant are less likely to respond to withdrawal of immune suppression. Accordingly, clinicians may appropriately have a lower threshold for initiation of chemotherapy in these patients. Finally, the availability of rituximab offers a second-line strategy that may allow avoidance of chemotherapy in many cases.

In contrast to the experience in pediatric transplant recipients, PTLD in adult patients appears to be much less likely to respond to withdrawal of immune suppression. This is particularly true for patients presenting late (>2 years) after transplant. Accordingly, while a brief trial of reduced immune suppression is still recommended in adult organ transplant recipients with PTLD, some investigators strongly support the early use of chemotherapy in these patients. The appropriate duration of the trial of decreased immune suppression and potential role of rituximab as an alternative to chemotherapy remain to be determined. Furthermore, the optimal, chemotherapeutic regimen for EBV-associated PTLDs has not been designed. Recognizing the absence of definitive data in this area, treatment trials of EBV/PTLD based on a sequential approach (reduced immune suppression followed by alpha-interferon and PRO-MACE-CytaBOM with GM-CSF) are currently underway.

Radiation and surgery

Current understanding of EBV/PTLD strongly suggests that it is best thought of as a systemic process, even when only a solitary lesion is identified. However, anecdotal experience with the use of localized radiation therapy or surgical resection indicates that these approaches may be effective in the management of isolated lesions. Accordingly, some experts favor this approach when PTLD is limited to a solitary lesion. Despite these published examples, we believe that the evidence defining EBV/PTLD as a systemic illness supports the limitation of the use of surgery and radiation to the management of local complications (e.g. gastrointestinal hemorrhage or local compression of a critical structure). A potential exception to this is PTLD involving the central nervous system (CNS). A recent consensus report on EBV-associated PTLD suggested that the most effective treatment of CNS PTLD is field radiation therapy. The report also suggested a possible role for surgical excision for anatomically limited CNS disease.

EBV Viral Load Monitoring and the Management of PTLD

Although evidence supports measuring the EBV viral load in the peripheral blood as an adjunct to making the diagnosis

of EBV/PTLD, fewer data are available regarding the potential use of serial measurements of the EBV viral load as part of the management of this disease. Based on our experience, we believe that this test provides clinically relevant information regarding a patient's response to therapy. Accordingly, we recommend weekly monitoring of the EBV viral load in the peripheral blood for patients diagnosed with EBV/PTLD. A decline in viral load both suggests that the patient is responding and may identify the time when the patient is at risk for developing rejection. A viral load that remains high for more than 4 weeks, particularly if the patient is not showing evidence of a clinical response, should warrant consideration of a modification in both the child's specific PTLD therapy and immunosuppressive management.

The role of ongoing monitoring after a patient has appeared to respond to treatment is unclear. In our experience, most patients develop rebound elevations in their viral load during serial monitoring after recovery from PTLD. Some, but not all, of the rebounds appeared to correlate with the reintroduction or augmentation of immune suppression. To date, viral load rebounds have only rarely been associated with symptoms or evidence of recurrence of EBV/PTLD in our patients. Since the frequency of rebound is extremely high and the rate of recurrent PTLD appears to be less than 10%, the interpretation of elevated EBV viral loads for patients with a past history of PTLD is unclear. Accordingly, we do not routinely recommend following of this assay for patients who have recovered from PTLD.

Current Recommendations

An overview of the initial management approach to EBV/PTLD at the Children's Hospital of Pittsburgh is shown in Table 1. Initial therapy for all episodes of EBV/PTLD other than those identified histologically as 'malignant' lymphomas consists of reduction or withdrawal of immunosuppression. The extent of this reduction varies according to the type of organ transplant that the patient has received. An effort is made to maintain these reductions until patients develop evidence of rejection and/or resolution of their EBV/PTLD. Patients identified by histologic criteria as having 'malignant lymphomas' are referred for chemotherapy. As noted earlier, this is more likely to occur in adult transplant recipients.

In addition to reduction of immune suppression, most patients are also begun on intravenous ganciclovir. The use of this drug has become standard in our management, despite the concerns noted earlier in this review. IVIG is also used on some, but not all, patients diagnosed with EBV/PTLD. We use the commercially available, high-titer anti-CMV antibody (CytoGam) as our agent of choice. In general, ganciclovir and CytoGam are continued until there is clinical and virologic (e.g. falling EBV viral load) evidence of resolution of EBV/PTLD.

After implementation of initial therapy, patients are watched carefully for evidence of improvement or progression of their

Table 1: Initial approach to pediatric transplant recipient with non-malignant EBV/PTLD at the Children's Hospital of Pittsburgh

	Liver	Kidney	Heart	Lung	Intestine
Immune suppression	Stop tacrolimus/CyA[a], AZA[b], MMF[c] Steroids at maintenance	Stop tacrolimus/CyA, AZA, MMF Steroids at maintenance	Stop tacrolimus/CyA, AZA, MMF Restart tacrolimus/CyA after level falls to achieve FK level ~5 ng/mL or CyA[d] level 75–100 Steroids at maintenance	Stop tacrolimus/CyA, AZA, MMF Restart tacrolimus/CyA after level falls to achieve FK level ~7–8 ng/ml or CyA level 100–125 Steroids to maintenance	Stop tacrolimus/ CyA, AZA, MMF Restart tacrolimus/ CyA after level falls to achieve FK level ~7–8 ng/ml or CyA level 100–150 Steroids to maintenance
Antiviral therapy	Ganciclovir i.v. CytoGam i.v.	Ganciclovir i.v. CytoGam i.v.	Ganciclovir i.v.	Ganciclovir i.v.	Ganciclovir i.v. CytoGam i.v.
Clinical F/U, rejection surveillance	Monitor LFTs Weekly EBV PCR Daily examination Liver biopsy for suspected ACR	Monitor renal function Weekly EBV PCR Daily examination Renal biopsy for suspected ACR	Echocardiograms (2–3 times /week) Surveillance Bx @1 wk then every 1–2 weeks Weekly EBV PCR Daily examination	TBB 7–10 d into Rx, then PRN based on status Weekly EBV PCR Daily examination Frequent pulmonary function tests and CXR	Endoscopy with Biopsy every 1–2 weeks Weekly EBV PCR Daily examination

EBV, Epstein–Barr virus; PCR, polymerase chain reaction; LFT, liver function test; CXR, chest X-ray; ACR, acute cellular rejection; TBB, transbronchial biopsy; Rx, treatment; PRN, as needed.
[a]Cyclosporine. [b]Azathioprine. [c]Mycophenalate mofetil. [d]Cyclosporine level obtained by monoclonal assay.

EBV/PTLD. Careful monitoring is also performed for evidence of rejection. For clinically responding patients who develop evidence of rejection, we typically reinstitute therapy with low doses of their primary immunosuppressant. In our experience, the majority of pediatric transplant recipients with EBV/PTLD will respond to this initial approach within 2–4 weeks. Decisions need to be made for those patients who are not responding. If a patient has persistent EBV/PTLD without evidence of either clinical or virologic response or deterioration, we would typically continue our initial therapy with ongoing, close surveillance for subsequent clinical changes. If a child has not responded and appears to be worsening (rising EBV viral load, new or enlarging PTLD lesions), we would probably introduce a rituximab as second-line therapy at this time for patients whose PTLD lesions are CD20-positive by immunostaining. Patients who continue to progress despite the use of our first- and second-line therapies are strongly considered for chemotherapy.

Prevention

The increased recognition of the importance of EBV/PTLD has prompted interest and investigation into the prevention of these complications. While a thorough discussion of these approaches is beyond the scope of this review, it is worth summarizing current efforts in this area. In contrast to CMV, the routine use of antiviral chemoprophylaxis does not appear to be effective in preventing EBV disease or PTLD. Currently, immunoprophylaxis with intravenous immunoglobulin (IVIG) and serial monitoring of EBV viral loads as a guide to pre-emptive therapy are potential viable options for the prevention of EBV-associated complications in solid organ transplantation. Data from a severe combined immunodeficiency disease (SCID) mouse model as well as anecdotal human experience support the potential role of IVIG and this strategy is currently under evaluation in a multicenter, randomized, controlled trial. Several centers have reported their results using serial monitoring of the EBV PCR to identify patients with subclinical EBV infection and have proposed strategies to prevent progression of EBV infection to disease, including reduction of immune suppression, addition of antiviral agents and/or infusion of IVIG. Although these center reports are generally uncontrolled, they provide useful experiences that may serve as the basis for formal trials to confirm the efficacy of pre-emptive strategies against EBV.

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