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Review

Rabbit antithymocyte globulin induction and risk of post-transplant lymphoproliferative disease in adult and pediatric solid organ transplantation: An update

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ABSTRACT

The most modifiable risk factor for post-transplant lymphoproliferative disease (PTLD) is the type and dose of induction and maintenance immunosuppressive therapy. It is challenging to identify the contribution of a single agent such as rabbit antithymocyte globulin (rATG) in the setting of multidrug therapy. Registry analyses can be helpful but are limited by methodological restrictions and inclusion of historical patient cohorts. These are typically from eras when rATG dosing was markedly higher than current dosing (e.g. total dose 14 mg/kg versus 6 mg/kg now), accompanied by higher exposure to maintenance therapies, and often an absence of antiviral prophylaxis. The largest registry analysis to assess rATG specifically found no risk of PTLD after kidney transplantation, but conflicting results have been reported, highlighting the difficulty of interpreting this type of analysis. The relative rarity of PTLD means that individually controlled trials are underpowered to assess its occurrence, but the available data do not suggest an effect of rATG. A pooled analysis of data from studies of rATG induction in kidney and heart transplantation found the incidence of PTLD to be comparable to published reports in the overall transplant population. Data on the effect of rATG dose are inconclusive, but in patients receiving antiviral prophylaxis it does not appear to be influential. Nevertheless, it would seem reasonable to employ the lowest dose of rATG compatible with effective induction, particularly in EBV-seronegative recipients and other high-risk groups such as heart–lung transplant recipients. Overall, the risk of PTLD following rATG induction therapy with modern dosing regimens and under current management conditions appears unlikely to make an important contribution to the risk:benefit balance.

Contents

Abbreviations: AHR, adjusted hazard ratio; ALG, antilymphocyte globulin; ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; aRR, adjusted relative risk; ATG, antithymocyte globulin; ATGAM, equine thymocyte globulin; ATS, antithymocyte serum; CI, confidence interval; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CTS, Collaborative Transplant Study; DSA, donor-specific antibodies; EBV, Epstein–Barr virus; HR, hazard ratio; IL-2RA, interleukin-2 receptor alpha; IRR, incidence rate ratio; ISHLT, International Society for Heart and Lung Transplantation; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; NHL, non-Hodgkin lymphoma; NK, natural killer; OPTN, Organ Procurement and Transplantation Network; PTLD, post-transplant lymphoproliferative disorder; rATG, rabbit antithymocyte globulin; RR, relative risk; SRTR, Scientific Registry for Transplant Recipients; UNOS, United Network of Organ Sharing; USRDS, United States Renal Data System.

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1. PTLD after solid organ transplantation

1.1. Epidemiology and risk factors

Post-transplant lymphoproliferative disorder (PTLD) remains a rare but important complication of solid organ transplantation. While it can remain a benign lymphoid hyperplasia in some cases, in others the B-cells mutate and can progress to high-grade, life-threatening lymphomas such as non-Hodgkin lymphoma (NHL). Although improved management has helped to improve outcomes [1], mortality rates remain substantially higher after the diagnosis of PTLD [2–5].

Various risk factors for PTLD have been proposed, of which recipient seronegativity for Epstein–Barr virus (EBV) with engraftment from an EBV-positive donor is the most important and well-documented, conferring more than a 20-fold increase in risk [6]. Up to 50% of PTLD cases are EBV-related [7]. The risk of developing PTLD is organ-specific, with higher rates of both PTLD [8] and NHL [9] following heart, lung and intestinal transplantation where higher doses of immunosuppression are required. An analysis of over 100,000 patients receiving a primary kidney transplant during 2000–2009 found the five-year incidence of PTLD to be 0.84% [10], compared to >1.0% in heart transplant patients [11]. Recipients of a lung or heart–lung transplant are at the highest risk due to the lymphoid-rich nature of lung tissue and importation of high levels of EBV from the donor. Age is also important: children are more likely to develop PTLD than adults [12–15] due to higher rates of seronegativity for EBV. Other possible risk factors include recent infection with cytomegalovirus (CMV) or CMV-seronegativity at time of transplant [16–18]. Clinical studies have provided robust evidence that CMV prophylaxis with virostatic agents and/or CMV immunoglobulin therapy can substantially reduce the risk of EBV-associated PTLD [19–21].

1.2. The role of immunosuppressive therapies

One of the most modifiable risk factors for PTLD is the type and dose of immunosuppressive therapy [22]. Although transplant recipients usually maintain some level of EBV-specific cytotoxic $CD8^+$ T-cells, this can vary and regimens which more intensively suppress T-cell count or function would be expected to increase the risk of PTLD. Widespread adoption of calcineurin inhibitor (CNI) therapy was associated with a significant increase in risk of NHL [23,24]. CNI agents are almost universally prescribed, at least in the immediate post-transplant period, with some evidence suggesting a higher risk for PTLD under tacrolimus versus cyclosporine [10,25]. Mycophenolate mofetil (MMF) does not appear to affect risk for PTLD [24,26]. Mammalian target of rapamycin (mTOR) inhibitors may be risk-neutral or potentially reduce risk by inhibiting growth signals in PTLD-associated EBV + B-cell lymphomas [27]. There is evidence that mTOR inhibition blocks the replication of EBV-positive B-cells, T-cells and natural killer (NK) cells [28,29]. Treatment of rejection with high-dose steroids can adversely affect risk for PTLD [30]. For the costimulation blocker belatacept, an inhibitor of T-cell proliferation, PTLD risk appears similar to that seen under CNI therapy [31] but, of note, belatacept is contraindicated in EBV-seronegative recipients. Against this complex background, the contribution of a single element in the multidrug induction-maintenance regimen cannot be accurately identified with confidence.

Particular interest has focused on the effect of lymphocyte-depleting induction therapies. The International Society for Heart and Lung Transplantation (ISHLT) guidelines state that polyclonal induction agents may be beneficial to delay CNI introduction in patients at high risk of renal dysfunction and that antithymocyte globulin (ATG) induction may be beneficial in thoracic organ recipients at high risk for acute rejection [32], based on analyses comparing rabbit ATG (rATG, Thymoglobulin®) versus basiliximab induction [33,34]. The efficacy of rATG versus IL-2RA induction in facilitating delayed CNI therapy after kidney transplantation has also been demonstrated [35], although it is uncertain whether this strategy affects the risk of delayed graft function [36].

The ISHLT guidelines also comment that routine use of induction therapy with polyclonal preparations is indicated when complete steroid avoidance is planned. Lymphocyte-depleting agents such as muromonab -CD3 [OKT3], antithymocyte antibodies and antilymphocyte preparations can induce a profound decrease in T-cell counts. During the 1980s and early 1990s, when muromonab OKT3 and non-rATG preparations were becoming more widely used [37,38], a marked increase in the incidence of PTLD was observed [13,39]. From the late 1990s onwards, however, rATG became the most commonly used polyclonal agent in the US, with equine antithymocyte globulin (ATGAM) and OKT3 becoming virtually obsolete [37,38]. Today, rATG is the most frequently administered lymphocyte-depleting agent worldwide [40]. In addition to its effect on T-cells, rATG also exerts a wide spectrum of immunomodulatory effects, targeting B-cells, plasma cells, monocytes and dendritic cells [41].

The question of whether rATG is associated with an increased risk for PTLD after solid organ transplantation is considered here in the context of contemporary management practices.

2. Evidence from registry analyses

2.1. Interpreting registry data

The relative rarity of PTLD means that randomized trials cannot include adequate patient numbers to provide meaningful data on relative risk according to immunosuppressive regimen. Moreover, the time to onset of PTLD – a median of up to seven years post-transplant in adult kidney transplant patients [42] and three years in children [43] – means that the duration of controlled trials is often inadequate. Single-center retrospective studies can offer larger numbers, with longer follow-up, but the most substantial data are derived from analyses of transplant registry databases. Registry data, however, must be considered carefully due to a number of potential weaknesses (Table 1). Data from patients transplanted from the 1980s onwards are frequently included to provide sufficient numbers and follow-up, but must be regarded cautiously since rATG dosing was markedly higher than now [44]. Since higher rATG dosing is associated with a higher risk for PTLD [11], this is an important consideration. Transplant registries do not record rATG dosing, so it cannot be established whether analyzed cohorts received doses compatible with contemporary regimens but this seems unlikely. Opelz et al. have shown a trend to lower rates of NHL in kidney and heart transplant patients receiving ATG induction from the period 1985–1989 to 1995–2001, based on data from the Collaborative Transplant (CTS) study database [9]. While dosing information is not available, this may have been due to lower doses over time.