Drugs 2006; 66 (4): 429-438
0012-6667/06/0004-0429/$44.95/0

Post-Transplant Lymphoproliferative Disease

Association with Induction Therapy?

Vikas R. Dharnidharka

University of Florida College of Medicine, Gainesville, Florida, USA

Abstract

In the last 2 decades, several polyclonal and monoclonal antibodies have been developed for induction therapy in the early post solid-organ transplantation period. The use of these antibodies has been associated, for the most part, with a decrease in early acute rejection rates. However, there has been a simultaneous rise in infectious complications, particularly in the incidence of post-transplant lymphoproliferative disease (PTLD). Determinations of adjusted odds ratios or relative risk have yielded conflicting information regarding whether these antibody agents increase the risk for PTLD. In order to interpret the results of the different studies, the reader requires a detailed knowledge of the types of analyses performed and the characteristics of the populations studied. This article analyses the available data on PTLD risk after the use of induction antibody agents. While some studies suggest an increased risk of PTLD after induction antibody use, other studies do not; the available data are not conclusive either way at this time.

Post-transplant lymphoproliferative disease (PTLD) has emerged over the last 2 decades as a major complication of solid-organ transplantation.[1] As its name suggests, PTLD is typically characterised by B-cell proliferation and lymph node masses in a solid-organ transplant recipient who is receiving immunosuppressive therapy to prevent organ rejection.[2,3] Although the cellular proliferation is uncontrolled, PTLD differs somewhat from true malignancies. Unlike in true malignancies, the immune system may still regain control of B-cell proliferation if the amount of external immunosuppression is decreased. The most severe cases of PTLD, in which the ability to regain control of proliferation is lost, are classified as frank lymphomas.[4,5] Many cases of PTLD are causally related to infections with the Epstein-Barr virus (EBV).[6] Thus, this disease entity straddles the fields of infectious disease, immunology and malignant disease.

PTLD most typically presents as a lymph node mass, either externally or with mass effects due to internal nodal enlargements. The diagnosis is suspected in the appropriate clinical setting and confirmed by biopsy and tissue analysis. Initial treatment, in most patients, is reduction of post-transplant immunosuppression. Other treatments can include anti-B-cell antibody, interferon α or chemotherapy. The prognosis is variable; polyclonal and polymorphic PTLDs have a more favourable prognosis, while monoclonal lesions or those affecting the CNS have a less favourable prognosis.[7]

Patient and graft survival after solid-organ transplantation are now markedly superior than they were in the initial days of transplantation. Acute rejection rates have also fallen dramatically, particularly in

the last 2 decades. The last 2 decades have also seen a dramatic emergence, in succession, of post-transplant viral infections such as cytomegalovirus (CMV), EBV (and associated PTLD) and BK virus nephropathy.[8] This temporal relationship between the fall in acute rejection rates and the emergence of newer infections is probably not a coincidence. The fall in acute rejections is largely due to the development of newer and more potent immunosuppressive medications. However, these medications are non-selective in nature and can also suppress components of the immune system that protect against infectious organisms, such as EBV-directed CD8+ T cells. These medications may then increase the 'net state of immunosuppression' and subsequently lead to infectious complications.[9] Among the newer medications that have been developed are antibody preparations that are administered in the early post-transplantation period to reduce the acute rejection rate during the period of highest risk. This review discusses whether these antibodies are also associated with a higher risk for PTLD development. However, it does not address the relative efficacies of the various antibody agents in preventing acute rejection. A literature search was conducted in MEDLINE for the years 1996–2005 for the terms 'lymphoproliferative disease', 'post-transplant lymphoproliferative disease', 'OKT3', 'daclizumab', 'basiliximab', 'antithymocytic globulin', 'ATGAM', 'antilymphocytic globulin', 'thymoglobulin', 'campath' and 'belatacept.' Additionally, the journal conducted a search using the above terms at my request.

1. General Risk Factors for Post-Transplant Lymphoproliferative Disease (PTLD)

Several studies have studied multiple host, recipient, transplant and immunosuppressive risk factors for PTLD. Since prospective studies use acute rejection rates or graft survival as typical endpoints, most studies that are focused on infectious complications such as EBV-associated PTLD will use retrospective single-centre or registry data. Single-centre data typically involve smaller numbers of patients but more detailed data on each patient. Transplant registries typically have larger numbers but the data are not as detailed. Transplant registry databases that have been used for PTLD risk analysis include UNOS (United Network of Organ Sharing), USRDS (United States Renal Data System) and NAPRTCS (North American Pediatric Renal Transplant Cooperative Study) in the US and CTS (Collaborative Transplant Study) in Europe. Each registry has a different primary purpose and collects different types of data. As yet, the separate data within each registry cannot be merged for analyses.

The most important risk factor is EBV seromismatch at the time of transplant. Recipients who are EBV seronegative and who receive a solid-organ transplant from an EBV-seropositive donor are at 20- to 25-fold higher risk for PTLD.[6] In such cases, the transplanted organ carries EBV into the recipient, who then develops a primary infection with this virus while on external immunosuppression. These data highlight the central role of EBV in this process of B-cell transformation and the relative importance of a primary infection versus a secondary infection or reactivation. Nevertheless, some PTLD lesions are not associated with EBV; these lesions may have alternate aetiologies that have not been ascertained as yet. Early studies from heart and liver transplant recipients also revealed a relatively higher risk with CMV co-infection, which imparts a 6-fold higher risk for PTLD.[10]

Host factors that are directly related to EBV seromatching include paediatric age (adjusted relative risk [RR] = 2.81; 95% CI 2.51, 3.12; $p < 0.0001$), since paediatric recipients are much more likely to be EBV seronegative.[11] In contrast, most immunocompetent adults have been exposed to EBV at some point. These adult donors harbour latent but CD8+ T cell-controlled virus present inside organs that are possible to transplant, such as heart, liver and kidney. Other host factors that are associated with a higher risk for PTLD include Caucasian race (adjusted RR = 2.22, 95% CI 2.00, 2.48 and $p < 0.001$ in UNOS; adjusted RR = 2.20, 95% CI 1.42, 3.30 in NAPRTCS) and male sex (adjusted RR = 1.41, 95% CI 1.29, 1.53 and

$p < 0.001$ in UNOS but not statistically significant in NAPRTCS).[11] Intestinal and thoracic organ transplants have been associated with higher rates of PTLD than kidney transplants.[11]

2. Immunosuppression Risk Factors and PTLD

Many papers have evaluated immunosuppressive medications as potential risk factors for PTLD; these papers have considered both induction antibodies and oral maintenance immunosuppressive agents. It is worth noting that most of the immunosuppressive agents, if associated with a higher risk, have RR ratios in the 1- to 3-fold range (i.e. much lower than the RR for EBV seromismatch). This finding can be interpreted in two ways: (i) the effect of immunosuppressive medications may not be as strong as that of EBV seromismatch in those cases where the tumour is EBV associated; or (ii) looking at any one agent in isolation may not reflect the 'totality' of immunosuppression, which may be a better indicator of risk for PTLD.[12,13] Importantly, none of the large registries used to date to analyse PTLD risk have reliable or complete EBV serology data. Additionally, most studies of PTLD risk have difficulty analysing oral maintenance drug use as a risk factor. Large retrospective databases, used in many of these studies, do not have adequate drug dose-administration data in longitudinal fashion. Thus, most of these studies look at oral maintenance drugs in an 'intent-to-treat' fashion (i.e. which drug the patient was listed as receiving at the time of initial post-transplant discharge). In contrast, large database studies looking at the risk for PTLD are able to account for induction antibody drug usage more accurately, since these drugs are typically administered at the time of transplant. Dosages of the antibodies used are typically not available in large registry studies, which can be a limitation if an antibody has several possible dose-administration regimens. In contrast to large multicentre databases, single-centre studies of PTLD risk are able to define drug dose administration and total immunosuppression usage with much greater accuracy, but often lack a large enough sample size to elucidate some risk factors.

3. Induction Antibodies

There are several different antibody preparations available commercially for organ transplantation rejection prophylaxis or 'induction'.[14] These agents are typically used in the immediate post-transplant period, when the risk for acute rejection is the highest. This review does not focus on the use of antibodies as 'rejection rescue drugs' at later timepoints. In general, all the agents block T-cell activation and proliferation, one of the central processes in the immune response to an allograft. These anti-T-cell agents either competitively occupy an activating receptor or initiate a lytic/inactivating signal to the T cell. Table I lists the different agents available, their targeted receptors and the adjusted RR for PTLD. Induction antibody agents can be classified as

Table I. Published adjusted relative risk (RR) for post-transplant lymphoproliferative disease (PTLD) with the use of different commercially available induction antibody agents[a,b]

Induction antibody agent	Ligand	RR for PTLD
Muromonab CD3	CD3	9.5[17] 6.0[10] 1.71[18] 1.72[19] 1.16*[16]
Equine-derived antithymocyte globulin	Multiple	1.50*[18] 1.61[20]
Antilymphocytic globulin	Multiple	1.35[20]
Rabbit-derived antithymocyte globulin	Multiple	3.00[18] 1.17*[20]
Basiliximab	Interleukin-2 receptor	1.83[18] 1.14*[19]
Daclizumab	Interleukin-2 receptor	1.92[18] 1.14*[19]
Alemtuzumab	CD52	Not known

a Opelz and Dohler[15] compared RR of lymphoma after muromonab CD3 and interleukin-2 receptor antibody use with a general population incidence of lymphoma and thus represent their RR values (not shown) differently.

b Caillard et al.[16] analysed for risk of PTLD after use of any polyclonal antithymocyte globulin induction (i.e. inclusive of equine-derived antithymocyte globulin, antilymphocytic globulin and rabbit-derived antithymocyte globulin) as one group. In this study, the adjusted RR was significantly elevated at 1.55.

* not significant.

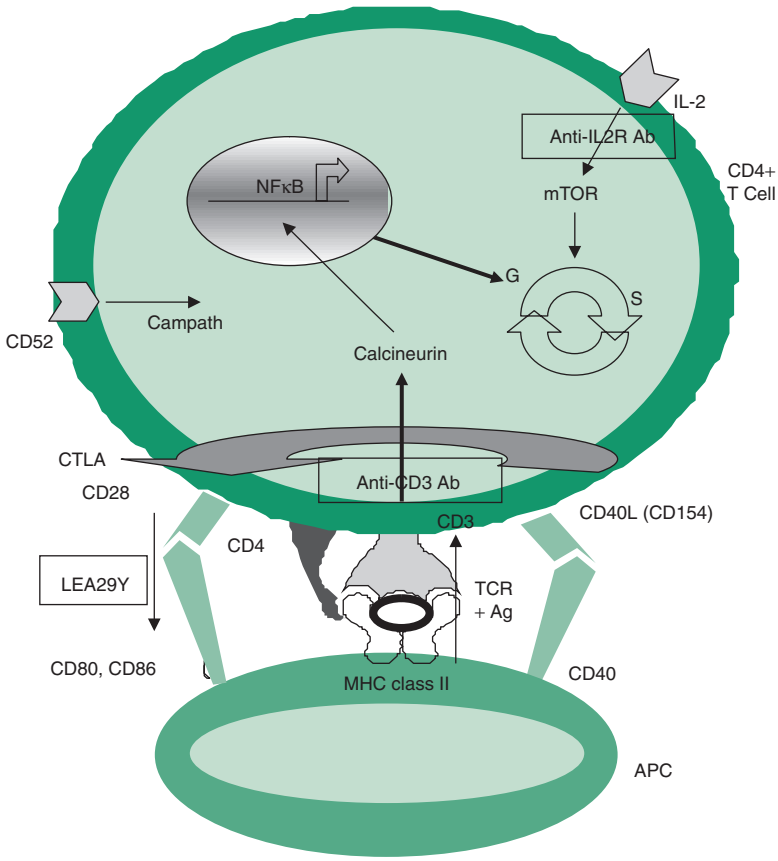

Fig. 1. Sites of action of monoclonal immunosuppressive antibodies. After binding to a specific T-cell surface receptor, the antibodies block T-cell activation and proliferation by different means, as discussed in the text. **G** and **S** indicate phases of the cell cycle. **Ab** = antibody; **Ag** = antigen; **APC** = antigen-presenting cell; **CTLA** = common T lymphocyte antigen; **IL-2** = interleukin-2; **MHC** = major histocompatibility complex; **mTOR** = mammalian target of rapamycin (silrolimus); **NF-κB** = nuclear factor-κB; **TCR** = T-cell receptor.

polyclonal (with specificity against multiple receptor targets on either T cells or antigen-presenting cells) or monoclonal (specificity to a single receptor, usually on the T-cell surface). Figure 1 lists the sites of action of the monoclonal agents. Polyclonal agents have several potential targets and their exact mechanisms of action are not yet fully elucidated.

3.1 Muromonab CD3 and PTLD

Muromonab CD3 (also known as OKT3) is a murine monoclonal antibody against the CD3 epitope expressed on T cells (figure 1).[21] The first published association between PTLD and an induction antibody was the seminal report by Swinnen et al.[17] in 1990; in a single-centre cohort of heart transplant recipients, a cumulative muromonab CD3 dose of ≥75mg was associated with a 9-fold higher risk for development of PTLD. In a retrospective single-centre analysis of heart transplant recipients by Walker et al.,[10] the use of muromonab CD3 increased the risk of PTLD by 6-fold and was synergistic with EBV seromismatch and CMV co-infection. More recently, other studies have conducted analyses of large retrospective national transplant databases within the US to evaluate risk for PTLD with muromonab CD3 use. Bustami et al.[18] analysed Scientific Registry of Transplant Recipients (SRTR; an organisation responsible for analysing data collected by the UNOS transplant registry)

data for induction-only use of muromonab CD3 compared with no induction and found an adjusted RR of 1.71 (95% CI 1.12, 2.63; p = 0.014) for PTLD. In another study of the UNOS database, Cherikh et al.[19] analysed for the risk of PTLD after monoclonal antibody use (muromonab CD3 was the only monoclonal antibody in use clinically during the time interval of this study), separating induction from anti-rejection use. In this study, induction use of muromonab CD3 was associated with an adjusted RR for PTLD of 1.72 (95% CI 1.04, 2.83; p = 0.03). In contrast, anti-rejection use of muromonab CD3 was not associated with increased risk of PTLD (adjusted RR = 0.90; 95% CI 0.37, 3.69; p = 0.78).

However, other studies have contradicted these findings of increased PTLD risk after muromonab CD3 induction use. Caillard et al.[16] analysed data from USRDS for kidney transplants performed between 1996 and 2001. The use of muromonab CD3 as induction only was not associated with a increased risk for PTLD (p = 0.6). In contrast, the use of muromonab CD3 as an anti-rejection agent was associated with a increased risk for PTLD (adjusted RR = 1.37, 95% CI 1.1, 1.76; p = 0.01). Our group[11] recently published a single-centre retrospective analysis in which we re-examined all old cases of PTLD with newer techniques. We also found no change in the incidence of PTLD in the pre-and post-muromonab CD3 era (p = 0.61). During the period of muromonab CD3 usage, the incidence of PTLD was not statistically different in patients receiving this drug and in those who did not (p = 0.34). In a randomised controlled trial of muromonab CD3 induction versus ciclosporin (cyclosporin) induction in 287 paediatric kidney transplant recipients, the number of PTLD cases in the muromonab CD3 group was not significantly increased.[22] In another recent paper, Peraira et al.[23] used low-dose muromonab CD3 (from 7.5 to 35mg cumulative dose) and reported a PTLD incidence of only 1%.

3.2 Anti-Interleukin-2 Receptor Antibodies and PTLD

By far the most controversial data regarding the RR for PTLD exist in relation to the anti-interleukin (IL)-2 receptor monoclonal antibodies, basiliximab and daclizumab, which block the CD25 receptor on the activated T cell (i.e. the ligand for the growth factor IL-2; figure 1).[24] Basiliximab is a chimeric antibody, whereas daclizumab is humanised.[25-28] Several studies,[29-33] including meta-analyses,[34,35] suggest that the addition of IL-2 receptor antibodies improves acute rejection rates.

Bustami et al.[18] analysed SRTR data and found a significant increase in adjusted RR for PTLD with use of either basiliximab (1.83; 95% CI 1.05, 3.18; p = 0.032) or daclizumab (1.92; 95% CI 1.08, 3.41; p = 0.027). In contrast, another analysis of UNOS data by Cherikh et al.,[19] which was published at nearly the same time, revealed only a 14% non significant increase in risk for PTLD (p = 0.52). These two studies[18,19] highlighted the different interpretations possible from similar datasets depending upon the variables analysed and the differences in study design. In an attempt to resolve some of these conflicts, Hanto[36] pointed out the following differences between the studies: (i) the follow-up was censored at 727 days post-transplant in the Cherikh et al. study, but no censoring was done in the Bustami et al. study; (ii) there were different time periods: 1997–2000 for the Cherikh et al. study and 1996–2002 for the Bustami et al. study; (iii) the study population incorporated both primary living and deceased donor kidney transplants in the Cherikh et al. study, whereas it was restricted to primary cadavaric kidney transplants in the Bustami et al. study; and (iv) CMV serostatus and acute rejection profile were used in the Cherikh et al. study only.

Confusing the issue further was another nearly simultaneous publication from the European Transplant Collaborative Study group by Opelz and Dohler.[15] Analysis of 12-month follow-up data (i.e. a short follow-up period) of cadaveric kidney allograft patients transplanted in centers from Europe and the US from 1988 to 2001 demonstrated no increased risk for non-Hodgkin's lymphoma (a very

different and more restrictive outcome variable than PTLD) with anti-IL-2 receptor monoclonal antibody use.

Most recently, Caillard et al. performed an analysis of USRDS data of kidney transplants between 1996 and 2001.[16] This study did not demonstrate a higher risk for PTLD when anti-IL-2 receptor antibody use as a group was analysed (adjusted RR = 1.16; 95% CI 0.82,1.65; p = 0.39).

3.3 Alemtuzumab and PTLD

Alemtuzumab (also known as campath-1H) is a humanised monoclonal antibody targeted against the CDw52 membrane antigen of lymphocytes (figure 1). This antibody has a long half-life and causes profound lymphocyte depletion for up to 3 months after administration.[37] Alemtuzumab is approved for use in haematopoietic malignancies and has recently been tried in solid-organ transplantation. The data regarding association with PTLD are limited at this time. Knechtle et al.[38] administered alemtuzumab with a reduced corticosteroid dosage to 126 consecutive renal transplant recipients at their centre and found no cases of PTLD. Watson et al.[39] reported single-centre 5-year data on kidney transplant recipients from England. There was only one case of plasmacytoid lymphoma in the alemtuzumab group and none in the control group in their small series of 33 patients. McCurry et al.[40] reported on alemtuzumab use in lung transplants but did not mention any cases of PTLD in their report. All series used historical controls. The only randomised trial to date compared alemtuzumab with antithymocyte globulin or daclizumab in 90 renal transplant recipients.[41] The preliminary short-term results did not report any cases of PTLD in any of the treatment groups.

3.4 Belatacept and PTLD

Though belatacept (also known as LEA 29Y) is not yet commercially available, there is a recent report of its investigational use in kidney transplant recipients.[42] Belatacept blocks the costimulatory signal two between CD28 on the antigen-presenting cells and the B-7 family (CD80, CD86) on T cells (figure 1). The greater specificity of action of belatacept should theoretically allow for preservation of those components of the immune system that protect against viral infections. Intensive or less-intensive belatacept was used (in combination with basiliximab, mycophenolate mofetil and corticosteroids as induction) in a three-arm trial comparing belatacept with ciclosporin. Of note, PTLD was seen in 3 of 218 patients, 2 of whom developed primary EBV infection and then developed PTLD after belatacept was replaced with conventional immunosuppression. In this study, patients received both the selective agent belatacept along with the less selective agent basiliximab on days 0–1. Trying to determine the true risk for PTLD with belatacept use will probably require its use without any concomitant nonselective immunosuppression agent.

3.5 Monoclonal Antibodies as a Group and PTLD

Some groups have attempted to also determine the RR for PTLD development if any monoclonal antibody induction therapy was used. Thus, use of any monoclonal agent for induction (i.e. muromonab CD3, basiliximab or daclizumab) increased the adjusted RR for PTLD to 1.72 (95% CI 1.04, 2.83) according to Cherikh et al.[19] If monoclonal antibodies were used for rejection rescue, then the adjusted RR was only 1.17 (95% CI 0.37, 3.69; p = 0.78).

3.6 Polyclonal Antibodies and PTLD

Several different polyclonal agents have been used post-transplant. These antibodies bind to several epitopes on the T cell and their exact mechanisms of action are not fully elucidated. Najarian et al.[43] developed the earliest forms of antilymphocytic globulin, followed by antithymocytic globulins from horse and rabbit sera. All of these agents were reported in initial studies to improve acute rejection rates. Bustami et al.,[18] using SRTR data, analysed the risk for PTLD development if transplant recipients were administered either equine-derived or rabbit-derived antithymocyte globulin. Antithymocyte globulin from horse serum was not significantly

associated with a higher risk (adjusted RR = 1.50; 95% CI 0.93, 2.43; p = 0.10), whereas rabbit-derived antithymocyte globulin was associated with higher risk (adjusted RR = 3.00; 95% CI 1.53, 5.89; p = 0.001). The Cherikh et al.[19] study of UNOS data also looked at polyclonal agents as a group but did not separate them out. In their study, polyclonal antibody use for induction was not associated with higher risk for PTLD (adjusted RR 1.29; 95% CI 0.82, 2.03; p = 0.27). Similarly, polyclonal antibody use as rejection rescue therapy was also not associated with PTLD (adjusted RR = 1.35; 95% CI 0.33, 5.47; p = 0.67).

UNOS data was recently re-analysed to look at all the polyclonal agents separately with regard to their risk for PTLD.[20] In this analysis, the different polyclonal agents, such as equine-derived antithymocyte globulin, rabbit-derived antithymocyte globulin and antilymphocytic globulin, were compared with no induction, excluding all patients who received any monoclonal antibody induction. Since equine-derived antithymocyte globulin and antilymphocytic globulin are older products, data from the whole UNOS database from 1987 to 2003 were analysed and time of follow-up was not censored. Living donor transplants or re-transplants were not excluded, since the rationale for exclusion is tenuous at best. Finally, variables in the model that have virtually no impact on PTLD, but often get included by virtue of their impact upon adult transplant graft survival, were excluded. In this analysis, antilymphocytic globulin (adjusted RR = 1.35, 95% CI 1.09, 1.68) and equine-derived antithymocyte globulin (adjusted RR = 1.61, 95% CI 1.24, 2.10), but not rabbit-derived antithymocyte globulin (adjusted RR = 1.17, 95% CI = 0.87, 1.58), were associated with significantly higher risk for PTLD. Although the follow-up periods were shorter in the rabbit-derived-antithymocyte globulin group, an analysis of paediatric patients, who typically develop PTLD early, did not reveal a higher risk for PTLD with rabbit-derived antithymocyte globulin.

Hardinger et al.[44] reported a retrospective 5-year review of data from an initial 1-year prospective study of rabbit-derived antithymocyte globulin (Thymoglobulin®)[1] versus equine-derived antithymocyte globulin in renal transplantation. In their analysis, there was a statistically higher incidence of malignancy (including PTLD cases) with equine-derived versus rabbit-derived antithymocyte globulin (21% vs 6%; p = 0.01). However, there were only two PTLD cases in the equine-derived antithymocyte globulin arm and none in the rabbit-derived antithymocyte globulin arm. An earlier paper from the same group compared muromonab CD3 with equine-derived antithymocyte globulin and reported a 2% rate of PTLD with equine-derived antithymocyte globulin and 3% with muromonab CD3.[45] Both rates would have been high in that time period for kidney transplant recipients but were not statistically different from each other. Similar studies in the paediatric heart transplant population have very small numbers of PTLD cases and thus are hard to interpret.[46,47]

In Europe, a different form of rabbit-derived antithymocyte globulin (ATG-Fresenius®) is also available. A head-to-head study of the Thymoglobulin® and the Fresenius formulations was conducted by Norrby and Olausson,[48] but only a précis of the results was published. The authors reported no significant differences in infectious complications between the two agents but did not specifically mention PTLD. A recent paper by Ducloux et al.[49] reviewed retrospective data from a single French centre regarding CMV infection and malignancy after administration of either agent. The Fresenius product was used from 1993 onwards but was temporarily unavailable from February 1995 to August 1996, during which time Thymoglobulin® was used. After August 1996, the centre used either agent in alternating fashion. There was a trend (though not statistically significant) towards higher lymphoma rates in the Thymoglobulin® group than in the ATG-Fresenius® group (4.6% vs 1.5%; p = 0.10).

1 The use of trade names is for product identification purposes only and does not imply endorsement.

4. Conclusions

Many studies document a higher RR for PTLD development with the use of different induction antibody agents. Most of these are retrospective studies of large databases that can evaluate long-term follow-up and represent a 'real world' situation but cannot evaluate the totality of immunosuppression or eliminate confounders. A few studies do not show any elevated risk of PTLD with induction antibody use. Some of these studies are retrospective and similar in design to the studies that document a higher risk. All prospective induction antibody drug trials, which are typically sponsored by drug companies, have not shown an elevated PTLD risk with any of the commercially available induction antibody agents to date. This result should not be surprising, since a finding of higher PTLD risk would very likely preclude further development of that drug. While prospective randomised clinical trials eliminate many confounders, they typically have: (i) shorter follow-up times; (ii) endpoints that focus more on acute rejection rather than long-term graft survival and complications; and (iii) a study subject selection bias. All of these characteristics preclude definitive conclusions regarding PTLD risk using only prospective randomised trials. Therefore, at this point in time, no conclusions can be drawn with certainty about elevated risk for PTLD after induction antibody use. A prospective trial of antibody induction that uses PTLD as a primary endpoint and has a long-term follow-up would be desirable, but probably impractical and prohibitively expensive. However, a more realistic and achievable goal would be to incorporate viral serological testing pre-transplant and serial viral polymerase chain reaction monitoring post-transplant in future prospective transplant trials.

This author would also recommend that the transplant community evaluate the broader issue of infections and all malignancies when deciding whether antibody induction agent use is justified or not. A recent randomised controlled trial of immunosuppression in paediatric heart transplant recipients showed greater infectious deaths in children who received rescue treatment with rabbit-derived antithymocyte globulin after daclizumab induction.[50] Besides PTLD, other malignancies to keep in mind include skin cancers and renal carcinoma. Other infections such as BK virus nephropathy in kidney transplant recipients[51] or hepatitis C infection in liver/renal allografts[52,53] also have a significant impact upon graft survival and function. In the USRDS 2003 report,[54] there were significantly increased hazard ratios for worse death-censored graft survival after viral or bacterial infections in kidney transplant recipients. Thus, infections can impact graft survival independently of their effects on patient mortality. The totality of infections/malignancies risk could be weighed against the benefits of more prolonged patient and graft survival in individualised situations to determine the optimal use of induction antibody therapy.

Acknowledgements

Dr Dharnidharka has received honoraria from Astellas and is supported in part by NIH grant # 1R21DK069535. The author has no conflicts of interest relevant to the contents of this article.

References

1. Green M, Webber S. Posttransplantation lymphoproliferative disorders. Pediatr Clin North Am 2003; 50 (6): 1471-91
2. Nalesnik MA. Posttransplantation lymphoproliferative disorders (PTLD): current perspectives. Semin Thorac Cardiovasc Surg 1996; 8 (2): 139-48
3. Faye A, Vilmer E. Post-transplant lymphoproliferative disorder in children: incidence, prognosis, and treatment options. Paediatr Drugs 2005; 7 (1): 55-65
4. Harris NL, Jaffe ES, Diebold J, et al. The World Health Organization classification of hematological malignancies report of the Clinical Advisory Committee Meeting, Airlie House, Virginia, November 1997. Mod Pathol 2000; 13 (2): 193-207
5. Jaffe ES, Banks PM, Nathwani B, et al. Recommendations for the reporting of lymphoid neoplasms: a report from the Association of Directors of Anatomic and Surgical Pathology. Mod Pathol 2004; 17 (1): 131-5
6. Walker RC, Paya CV, Marshall WF, et al. Pretransplantation seronegative Epstein-Barr virus status is the primary risk factor for posttransplantation lymphoproliferative disorder in adult heart, lung, and other solid organ transplantations. J Heart Lung Transplant 1995; 14 (2): 214-21
7. Penn I, Porat G. Central nervous system lymphomas in organ allograft recipients. Transplantation 1995; 59: 240-4
8. Dharnidharka VR, Harmon WE. Management of pediatric postrenal transplantation infections. Semin Nephrol 2001; 21 (5): 521-31
9. Rubin RH, Tolkoff-Rubin NE. Antimicrobial strategies in the care of organ transplant recipients. Antimicrob Agents Chemother 1993; 37 (4): 619-24

10. Walker RC, Marshall WF, Strickler JG, et al. Pretransplantation assessment of the risk of lymphoproliferative disorder. Clin Infect Dis 1995; 20 (5): 1346-53
11. Dharnidharka VR, Tejani AH, Ho PL, et al. Post-transplant lymphoproliferative disorder in the United States: young Caucasian males are at highest risk. Am J Transplant 2002; 2 (10): 993-8
12. Birkeland SA, Hamilton-Dutoit S. Is posttransplant lymphoproliferative disorder (PTLD) caused by any specific immunosuppressive drug or by the transplantation per se? Transplantation 2003; 76 (6): 984-8
13. Dharnidharka VR. Sirolimus in pediatric solid organ transplantation. Pediatr Transplant 2005; 9 (4): 427-9
14. Halloran PF. Immunosuppressive drugs for kidney transplantation. N Engl J Med 2004; 351 (26): 2715-29
15. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant 2004; 4 (2): 222-30
16. Caillard S, Dharnidharka V, Agodoa L, et al. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation 2005; 80 (9): 1233-43
17. Swinnen LJ, Costanzo-Nordin MR, Fisher SG, et al. Increased incidence of lymphoproliferative disorder after immunosuppression with the monoclonal antibody OKT3 in cardiac-transplant recipients. N Engl J Med 1990; 323 (25): 1723-8
18. Bustami RT, Ojo AO, Wolfe RA, et al. Immunosuppression and the risk of post-transplant malignancy among cadaveric first kidney transplant recipients. Am J Transplant 2004; 4 (1): 87-93
19. Cherikh WS, Kauffman HM, McBride MA, et al. Association of the type of induction immunosuppression with posttransplant lymphoproliferative disorder, graft survival, and patient survival after primary kidney transplantation. Transplantation 2003; 76 (9): 1289-93
20. Dharnidharka VR, Stevens G. Risk for post-transplant lymphoproliferative disorder after polyclonal antibody induction in kidney transplantation. Pediatr Transplant 2005; 9: 622-6
21. Wilde MI, Goa KL. Muromonab CD3: a reappraisal of its pharmacology and use as prophylaxis of solid organ transplant rejection. Drugs 1996; 51 (5): 865-94
22. Benfield MR, Tejani A, Harmon WE, et al. A randomized multicenter trial of OKT3 mAbs induction compared with intravenous cyclosporine in pediatric renal transplantation. Pediatr Transplant 2005; 9 (3): 282-92
23. Peraira JR, Segovia J, Fuertes B, et al. Current induction immunosuppression and post-heart transplant lymphoproliferative disorders. Transplant Proc 2003; 35 (5): 2009-10
24. Van Gelder T, Warle M, Ter Meulen RG. Anti-interleukin-2 receptor antibodies in transplantation: what is the basis for choice? Drugs 2004; 64 (16): 1737-41
25. Boggi U, Danesi R, Vistoli F, et al. A benefit-risk assessment of basiliximab in renal transplantation. Drug Saf 2004; 27 (2): 91-106
26. Carswell CI, Plosker GL, Wagstaff AJ. Daclizumab: a review of its use in the management of organ transplantation. Biodrugs 2001; 15 (11): 745-73
27. Chapman TM, Keating GM. Basiliximab: a review of its use as induction therapy in renal transplantation. Drugs 2003; 63 (24): 2803-35
28. Onrust SV, Wiseman LR. Basiliximab. Drugs 1999; 57 (2): 207-13, discussion 214
29. Kahan BD, Rajagopalan PR, Hall M. Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody: United States Simulect Renal Study Group. Transplantation 1999; 67 (2): 276-84
30. Nashan B, Moore R, Amlot P, et al. Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients: CHIB 201 International Study Group. Lancet 1997; 350 (9086): 1193-8
31. Nashan B, Light S, Hardie IR, et al. Reduction of acute renal allograft rejection by daclizumab: Daclizumab Double Therapy Study Group. Transplantation 1999; 67 (1): 110-5
32. Vincenti F, Kirkman R, Light S, et al. Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation: Daclizumab Triple Therapy Study Group. N Engl J Med 1998; 338 (3): 161-5
33. Cibrik DM, Kaplan B, Meier-Kriesche HU. Role of anti-interleukin-2 receptor antibodies in kidney transplantation. BioDrugs 2001; 15 (10): 655-66
34. Adu D, Cockwell P, Ives NJ, et al. Interleukin-2 receptor monoclonal antibodies in renal transplantation: meta-analysis of randomised trials. BMJ 2003; 326 (7393): 789
35. Keown P, Balshaw R, Khorasheh S, et al. Meta-analysis of basiliximab for immunoprophylaxis in renal transplantation. BioDrugs 2003; 17 (4): 271-9
36. Hanto DW. Association of type of induction with posttransplant lymphoproliferative disorders [letter]. Am J Transplant 2004; 4 (9): 1552
37. Waldmann H, Hale G. CAMPATH: from concept to clinic. Philos Trans R Soc Lond B Biol Sci 2005; 360: 1707-11
38. Knechtle SJ, Fernandez LA, Pirsch JD, et al. Campath-1H in renal transplantation: the University of Wisconsin experience. Surgery 2004; 136 (4): 754-60
39. Watson CJ, Bradley JA, Friend PJ, et al. Alemtuzumab (CAMPATH 1H) induction therapy in cadaveric kidney transplantation: efficacy and safety at five years. Am J Transplant 2005; 5 (6): 1347-53
40. McCurry KR, Iacono A, Zeevi A, et al. Early outcomes in human lung transplantation with thymoglobulin or Campath-1H for recipient pretreatment followed by posttransplant tacrolimus near-monotherapy. J Thorac Cardiovasc Surg 2005; 130 (2): 528-37
41. Ciancio G, Burke GW, Gaynor JJ, et al. A randomized trial of three renal transplant induction antibodies: early comparison of tacrolimus, mycophenolate mofetil, and steroid dosing, and newer immune-monitoring. Transplantation 2005; 80 (4): 457-65
42. Vincenti F, Larsen C, Durrbach A, et al. Costimulation blockade with belatacept in renal transplantation. N Engl J Med 2005; 353 (8): 770-81
43. Najarian JS, Simmons RL, Condie RM, et al. Seven years' experience with antilymphoblast globulin for renal transplantation from cadaver donors. Ann Surg 1976; 184 (3): 352-68
44. Hardinger KL, Schnitzler MA, Miller B, et al. Five-year follow up of thymoglobulin versus ATGAM induction in adult renal transplantation. Transplantation 2004; 78 (1): 136-41
45. Brennan DC, Schnitzler MA, Baty JD, et al. A pharmacoeconomic comparison of antithymocyte globulin and muromonab CD3 induction therapy in renal transplant recipients. Pharmacoeconomics 1997; 11 (3): 237-45
46. Di Filippo S, Boissonnat P, Sassolas F, et al. Rabbit antithymocyte globulin as induction immunotherapy in pediatric heart transplantation. Transplantation 2003; 75 (3): 354-8

47. Chin C, Pittson S, Luikart H, et al. Induction therapy for pediatric and adult heart transplantation: comparison between OKT3 and daclizumab. Transplantation 2005; 80 (4): 477-81
48. Norrby J, Olausson M. A randomized clinical trial using ATG Fresenius or ATG Merieux as induction therapy in kidney transplantation. Transplant Proc 1997; 29 (7): 3135-6
49. Ducloux D, Kazory A, Challier B, et al. Long-term toxicity of antithymocyte globulin induction may vary with choice of agent: a single-center retrospective study. Transplantation 2004; 77 (7): 1029-33
50. Hershberger RE, Starling RC, Eisen HJ, et al. Daclizumab to prevent rejection after cardiac transplantation. N Engl J Med 2005; 352 (26): 2705-13
51. Ramos E, Drachenberg CB, Papadimitriou JC, et al. Clinical course of polyoma virus nephropathy in 67 renal transplant patients. J Am Soc Nephrol 2002; 13 (8): 2145-51
52. Neumann UP, Neuhaus P. Course and treatment of recurrent hepatitis C after liver transplantation. Minerva Gastroenterol Dietol 2004; 50 (1): 61-6
53. Abbott KC, Bucci JR, Matsumoto CS, et al. Hepatitis C and renal transplantation in the era of modern immunosuppression. J Am Soc Nephrol 2003; 14 (11): 2908-18
54. United States Renal Data System 2003 report [online]. Available from URL: http://www.usrds.org [Accessed 2006 Feb 24]

Correspondence and offprints: Dr *Vikas R. Dharnidharka*, Division of Pediatric Nephrology, University of Florida, 1600 SW Archer Road, PO Box 100296, Gainesville, FL 32610-0296, USA.
E-mail: vikasmd@peds.ufl.edu