Infectious Complications of Antilymphocyte Therapies in Solid Organ Transplantation

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Antilymphocyte therapies are widely used for immunosuppression in solid organ transplantation. These agents have varied mechanisms of action, with resulting differences in the intensity and duration of immunosuppression and in associated infectious complications. Induction therapy with antithymocyte globulins is associated with a greater incidence of cytomegalovirus, Epstein-Barr virus, and BK polyomavirus infections, compared with therapy with interleukin (IL)–2a receptor antagonists. However, long-term experience with the IL-2a receptor antagonists is lacking. By contrast, the treatment of graft rejection with T cell–depleting antibodies is associated with an increased risk of opportunistic infections. This is likely a reflection of the intensification of immunosuppression in the treatment of graft rejection and, often, a failure to link the use of antilymphocyte agents to prophylaxis for infection. The use of T cell–depleting agents, especially in the treatment of acute graft rejection, must be linked to monitoring and risk-adjusted prophylaxis for *Pneumocystis*, other fungi, Epstein-Barr virus, BK polyomavirus, and cytomegalovirus infection.

Increasing rates of infection after solid organ transplantation have been attributed to use of antilymphocyte induction therapies and intensification of regimens for maintenance immunosuppression [1]. Antilymphocyte therapies are widely used in organ transplantation for induction therapy and treatment of graft rejection. Each agent has distinct mechanisms of action, with differences in the intensity and duration of immunosuppression. Infections commonly associated with these agents necessitate the development of appropriate preventative strategies.

Induction therapy blocks T cell activation and antigen recognition at the time of transplantation, particularly in recipients at high immunologic risk of graft rejection. This strategy minimizes exposure to nephrotoxic calcineurin inhibitors and reduces the use of corticosteroids and other maintenance therapies [2]. The most frequently used induction agents include polyclonal antithymocyte globulin (ATG); T cell–depleting agents from rabbit (rATG) or horse (hATG; lymphocyte immunoglobulin [equine antithymocyte globulin]); basiliximab and daclizumab, non-T cell–depleting monoclonal antibodies against IL-2α receptor (IL-2R; anti-CD25); and alemtuzumab, a pan-T cell–depleting anti-CD52 monoclonal antibody. Use of OKT3 (muromonab-CD3), a murine monoclonal, T cell–depleting antibody is less common. The T cell–depleting agents are also used in the treatment of acute graft rejection. Other agents are being investigated for use in transplantation, including antibodies to recombinant human leukocyte-associated functional antigen 1, antibody-associated immunotoxins, and fusion proteins of human leukocyte-associated functional antigen 3 with immunoglobulin fragments.

Most trials of antilymphocyte therapies have focused on graft rejection rates, graft function, and other noninfectious outcomes. Reporting of specific infections is generally limited to cytomegalovirus (CMV), Epstein-Barr virus (EBV), and BK polyomavirus (BKV) infections, with few data regarding specific syndromes or pathogens.

**ATG**

The most commonly used ATGs are polyclonal antibodies prepared from sera from rabbits or horses that have been immunized with thymocytes or T cell lines. rATG and hATG are commonly used in the United States, whereas ATG-Fresenius—prepared from rabbits injected with Jurkat cells—is used extensively in Europe. ATGs are not interchangeable [3–7]. All ATGs provide dose-dependent depletion of T cells. Effects on T cell depletion and risk of infection depend on the dosing...
strategy (i.e., total dose and duration). Typical ATG induction therapy takes 3–5 days (range, 1–10 days) [8–11]. Longer courses are used to avoid calcineurin inhibitor–induced nephrotoxicity.

rATG has a half-life of 30 days [12]. In addition to T cell depletion, rATG induces apoptosis of B cell lineages and interferes with dendritic cell, regulatory T cell, and natural killer cell functions [13]. Although levels of rATG decrease by 1 month after initiation of treatment, significant long-term deficits in T cell reconstitution that have been linked to impaired thymopoiesis often persist beyond 1 year [9, 14, 15]. CD3⁺ cell suppression is less intense and of shorter duration after hATG administration than after rATG administration, with absolute lymphopenia resolving within 14 days after treatment initiation [9]. ATG-Fresenius (9 mg/kg/day for 5 doses) induces rapid T cell depletion that persists for up to 1 year after treatment, with gradual recovery to pretransplantation levels by day 730 [14]. The development of neutralizing antibodies against xenogeneic immunoglobulin may limit the efficacy of subsequent courses of ATG. Administration of ATG is often associated with syndromes including fever and chills and, occasionally, hypotension, chest pains, serum sickness, congestive heart failure, pulmonary edema, leukopenia, thrombocytopenia, eosinophilia, or rash.

**ATG and the Risk of Infection**

**Bacterial infection.** The impact of ATG on bacterial infections is unclear. Multiple cofactors are generally present, including technical complications from surgery, urinary and vascular catheters, and complex immunosuppressive regimens. However, bacterial infections are the most common form of infection reported after rATG induction therapy (table 1) [16–23]. In kidney and kidney-pancreas transplantation, urinary tract infections are most common, followed by wound infections [9, 16–19, 21, 24]. Bacteremia, sepsis, and pneumonia have also been reported [17–19, 32, 33]. Enterobacteriaceae, most often *Escherichia coli* and *Enterococcus* species, are the most-frequently isolated uropathogens [16]. *Nocardia* infections have been reported in 3 lung transplant recipients (infections were due to *Nocardia nova*, *Nocardia farcinica*, and *Nocardia asteroides* complex) after induction therapy with rATG, despite prophylaxis with trimethoprim-sulfamethoxazole; these infections reflect profound immunosuppression, antimicrobial resistance, or inadequate dosing [34]. In most prospective trials, ATG was not associated with an increased risk of bacterial infection, compared with that risk with no induction therapy [24] or other induction therapies (e.g., IL–2R antagonists and alemtuzumab) (table 1) [17, 18, 26, 28, 29, 31]. Sepsis and multiple renal allograft abscesses (due to *Pseudomonas aeruginosa*) have been reported after rATG treatment for acute graft rejection [35, 36]. In a small series, treatment of acute graft rejection with ATG in liver transplant recipients was not associated with increased risk of bacterial infections, compared with that risk for patients with graft rejection treated with steroids or patients who did not experience graft rejection [37].

**CMV.** The association between antithymocyte therapies and CMV infection is well established [17, 24, 38–42]. Fever and the release of TNFα after ATG administration stimulate cellular nuclear factor κB and viral replication via nuclear factor κB binding to the promoter region of the CMV immediate-early antigen gene [43, 44]. Additional factors in CMV activation may include the depletion of T helper cells, inversion of the CD4/CD8 ratio, and shifts toward Th2 cytokines [3, 45]. The timing and incidence of CMV infection after ATG induction therapy depends on the type and dosage of ATG, donor and recipient CMV serologic status before transplantation, and whether CMV prophylaxis was given (tables 1 and 2). Most trials have included asymptomatic infection (i.e., infection detectable by microbiologic assay) with CMV syndrome (fever and neutropenia) and tissue-invasive disease in their criteria for CMV infection. In most prospective, randomized trials comparing ATG with other induction agents, the incidence of CMV infection was not increased when induction therapy was coupled with adequate CMV prophylaxis [18, 25–28, 31]. In a study without CMV prophylaxis, the rate of CMV infection was higher in the rATG group than it was in the basiliximab group (38% vs. 11.7%; *P* = .005) [17]. In one study in which CMV infection was more common with daclizumab therapy than with hATG therapy, more recipients at high risk of infection (i.e., CMV-seronegative recipients of organs from seropositive donors) received daclizumab therapy [29].

In general, anti–graft-rejection therapy with ATG without CMV prophylaxis is associated with an increased rate and severity of CMV infection in renal transplant recipients [47]. Inflammation associated with acute graft rejection may contribute to CMV reactivation during immunosuppression [47]. In simultaneous pancreas-kidney transplant recipients, treatment of graft rejection with rATG was associated with earlier and more-severe CMV infection, compared with treatment with ATG-Fresenius or daclizumab induction [40]. In a study of renal transplant recipients, a higher rate of CMV infection associated with basiliximab therapy was attributed to greater use of concomitant cytolytic therapy (ATG or OKT3) among patients receiving basiliximab than among patients receiving rATG (17.5% vs. 7.8%; *P* = .02) [21].

**EBV and EBV-induced posttransplantation lymphoproliferative disorder (PTLD).** The incidence of malignancy in general, and PTLDs in particular, is increased among organ transplant recipients, compared with that in the general population [48–57]. In most cases, PTLD is caused by the transformation of B lymphocytes by EBV [58–64]. In EBV-seronegative trans-
Table 1. Risk of cytomegalovirus (CMV) and other infections in randomized, prospective trials, by induction therapy.

<table>
<thead>
<tr>
<th>Study, treatment group</th>
<th>Transplant type</th>
<th>Duration of follow-up</th>
<th>Maintenance immunosuppression therapy</th>
<th>CMV prophylaxis</th>
<th>CMV serostatus D+/R−, no. (%) of patients</th>
<th>CMV infection, no. (%) of patients</th>
<th>Other infections, no. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mourad et al. [24]</td>
<td>Kidney</td>
<td>12 months</td>
<td>Tacrolimus, azathioprine, steroids</td>
<td>ACV or GCV induction, 51%; no induction, 31.6%</td>
<td>rATG, 1.25 mg/kg × 10 days</td>
<td>21 (13.9)</td>
<td>NS</td>
</tr>
<tr>
<td>No rATG (n = 158)</td>
<td>Kidney</td>
<td>12 months</td>
<td>Tacrolimus, azathioprine, steroids</td>
<td>ACV or GCV induction, 51%; no induction, 31.6%</td>
<td>None</td>
<td>25 (15.8)</td>
<td>30 (19.0)</td>
</tr>
<tr>
<td>Hartwig et al. [25]</td>
<td>Lung</td>
<td>8 years</td>
<td>CsA, azathioprine, steroids</td>
<td>IV GCV, twice daily × 2 weeks, followed by 4 times daily × 2</td>
<td>rATG, 1.5 mg/kg × 3 days</td>
<td>Excluded</td>
<td>13 (5.9)</td>
</tr>
<tr>
<td>No rATG (n = 22)</td>
<td>Lung</td>
<td>8 years</td>
<td>CsA, azathioprine, steroids</td>
<td>IV GCV, twice daily × 2 weeks, followed by 4 times daily × 2</td>
<td>None</td>
<td>Excluded</td>
<td>10 (45)</td>
</tr>
<tr>
<td>Hardinger et al. [7]</td>
<td>Kidney</td>
<td>5 years</td>
<td>CsA, azathioprine, steroids</td>
<td>Oral GCV, 1 g 3 times daily × 3–6 months</td>
<td>Thymoglobulin, 1.5 mg/kg × 7 days</td>
<td>8 (17)</td>
<td>NS</td>
</tr>
<tr>
<td>L-IG (n = 24)</td>
<td>Kidney</td>
<td>5 years</td>
<td>CsA, azathioprine, steroids</td>
<td>Oral GCV, 1 g 3 times daily × 3–6 months</td>
<td>L-IG, 15 mg/kg × 7 days</td>
<td>5 (21)</td>
<td>8 (33)</td>
</tr>
<tr>
<td>Lebranchu et al. [17]</td>
<td>Kidney</td>
<td>6 months</td>
<td>CsA, MMF, steroids</td>
<td>None</td>
<td>rATG, 1.0–1.5 mg/kg/day × 6–10 days</td>
<td>11 (22)</td>
<td>NS</td>
</tr>
<tr>
<td>Basiliximab (n = 51)</td>
<td>Kidney</td>
<td>6 months</td>
<td>CsA, MMF, steroids</td>
<td>None</td>
<td>Basiliximab, 20 mg on day 0 and day 4</td>
<td>9 (18)</td>
<td>6 (11.7)</td>
</tr>
<tr>
<td>Brennan et al. [21]</td>
<td>Kidney</td>
<td>12 months</td>
<td>CsA, MMF, steroids</td>
<td>Oral or IV GCV × 14 days, followed by oral GCV × 3 months</td>
<td>rATG, 1.5 mg/kg/day × 5 days</td>
<td>21 (14.9)</td>
<td>NS</td>
</tr>
<tr>
<td>rATG (n = 141)</td>
<td>Kidney</td>
<td>12 months</td>
<td>CsA, MMF, steroids</td>
<td>Oral or IV GCV × 14 days, followed by oral GCV × 3 months</td>
<td>rATG, 1.5 mg/kg/day × 5 days</td>
<td>21 (14.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment</td>
<td>Organ</td>
<td>Duration</td>
<td>Immunosuppression</td>
<td>Prophylaxis</td>
<td>CMV</td>
<td>Overall</td>
<td>Angiogram</td>
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<tr>
<td>Basiliximab (n = 137)</td>
<td>Kidney</td>
<td>12 months</td>
<td>CsA, MMF, steroids</td>
<td>Oral or IV GCV × 14 days, followed by oral GCV × 3 months</td>
<td>Basiliximab, 20 mg on day 0 and day 4</td>
<td>31 (22.6)</td>
<td>24 (17.9)</td>
</tr>
<tr>
<td>Matte et al. [26] (n = 80)</td>
<td>Cardiac</td>
<td>6 months</td>
<td>CsA, MMF, steroids</td>
<td>For CMV D+/R−, oral GCV or VGCV × 3 months; other, per local practice</td>
<td>Basiliximab, 20 mg on day 0 and day 4</td>
<td>11 (28.9)</td>
<td>6 (15.8)</td>
</tr>
<tr>
<td>Basiliximab (n = 38)</td>
<td>Cardiac</td>
<td>6 months</td>
<td>CsA, MMF, steroids</td>
<td>For CMV D+/R−, oral GCV or VGCV × 3 months; other, per local practice</td>
<td>Basiliximab, 20 mg on day 0 and day 4</td>
<td>14 days, followed by oral GCV/H11003, 3 months</td>
<td></td>
</tr>
<tr>
<td>Mattei et al. [26] (n = 80)</td>
<td>Cardiac</td>
<td>6 months</td>
<td>CsA, MMF, steroids</td>
<td>For CMV D+/R−, oral GCV or VGCV × 3 months; other, per local practice</td>
<td>Basiliximab, 20 mg on day 0 and day 4</td>
<td>11 (28.9)</td>
<td>6 (15.8)</td>
</tr>
<tr>
<td>Abou-Ayache et al. [27] (n = 115)</td>
<td>Kidney</td>
<td>12 months</td>
<td>CsA, MMF, steroids</td>
<td>Oral GCV 1 g 2 times daily × 3.5 months</td>
<td>Basiliximab, 20 mg on day 0 and day 4</td>
<td>18 (23)</td>
<td>NS</td>
</tr>
<tr>
<td>Daclizumab (n = 58)</td>
<td>Kidney</td>
<td>12 months</td>
<td>CsA, MMF, steroids</td>
<td>Oral GCV 1 g 3 times daily × 3.5 months</td>
<td>Daclizumab, 1 mg/kg/day every 2 weeks × 5 doses</td>
<td>19 (35)</td>
<td>21 (39)</td>
</tr>
<tr>
<td>Sollinger et al. [28] (n = 138)</td>
<td>Kidney</td>
<td>12 months</td>
<td>CsA or tacrolimus, MMF, steroids</td>
<td>GCV or VGCV</td>
<td>Basiliximab, 20 mg on day 0 and day 4</td>
<td>11 (17)</td>
<td>NS</td>
</tr>
<tr>
<td>Basiliximab (n = 70)</td>
<td>Kidney</td>
<td>12 months</td>
<td>CsA, MMF, steroids</td>
<td>Inconsistent (1 center, no prophylaxis for 21 patients in basiliximab group)</td>
<td>Basiliximab, 20 mg on day 0 and day 4</td>
<td>...</td>
<td>...</td>
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<tr>
<td>Muliken et al. [29] (n = 50)</td>
<td>Lung</td>
<td>12 months</td>
<td>CsA or tacrolimus, MMF, steroids</td>
<td>GCV or VGCV</td>
<td>Basiliximab, 20 mg on day 0 and day 4</td>
<td>1 (4)</td>
<td>.05</td>
</tr>
<tr>
<td>VIG (n = 25)</td>
<td>Lung</td>
<td>12 months</td>
<td>CsA or tacrolimus, MMF, steroids</td>
<td>GCV or VGCV</td>
<td>Basiliximab, 20 mg on day 0 and day 4</td>
<td>7 (28)</td>
<td>12 (72)</td>
</tr>
<tr>
<td>VIG (n = 216)</td>
<td>Cardiac</td>
<td>12 months</td>
<td>CsA, MMF, steroids</td>
<td>GCV 5–10 mg/kg/ day × 2 weeks, then follow local protocol</td>
<td>Daclizumab, 1 mg/kg × 5 doses</td>
<td>47 (21.8)</td>
<td>.77</td>
</tr>
<tr>
<td>VIG (n = 216)</td>
<td>Cardiac</td>
<td>12 months</td>
<td>CsA, MMF, steroids</td>
<td>GCV 5–10 mg/kg/ day × 2 weeks, then follow local protocol</td>
<td>Daclizumab, 1 mg/kg × 5 doses</td>
<td>47 (21.8)</td>
<td>.77</td>
</tr>
<tr>
<td>No daclizumab (n = 218)</td>
<td>Cardiac</td>
<td>12 months</td>
<td>CsA, MMF, steroids</td>
<td>GCV 5–10 mg/kg/day × 2 weeks, then follow local protocol</td>
<td>None</td>
<td>50 (22.9)</td>
<td>12 (5.8)</td>
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<tr>
<td>Ashcroft et al. [18] (n = 130)</td>
<td>Kidney and pancreas</td>
<td>9 months</td>
<td>Tacrolimus, MMF, steroids</td>
<td>Oral VGCV × 3–6 months</td>
<td>rATG, alternate days</td>
<td>10 (15)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Alemtuzumab (n = 64)</td>
<td>Kidney and pancreas</td>
<td>9 months</td>
<td>Tacrolimus, MMF, steroids</td>
<td>Oral VGCV × 3–6 months</td>
<td>Alemtuzumab, 30 mg once</td>
<td>15 (23)</td>
<td>4 (6.25)</td>
</tr>
<tr>
<td>Ciancio et al. [31] (n = 90)</td>
<td>Kidney</td>
<td>15 months</td>
<td>Tacrolimus, MMF, steroids</td>
<td>IV GCV × 3 days, followed by oral VGCV × 3 months</td>
<td>rATG, 1 mg/kg/day × 7 days</td>
<td>...</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Alemtuzumab (n = 30)</td>
<td>Kidney</td>
<td>15 months</td>
<td>Tacrolimus, MMF, steroids</td>
<td>IV GCV × 3 days, followed by oral VGCV × 3 months</td>
<td>Alemtuzumab, 0.3 mg/kg on day 0 and day 4</td>
<td>...</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Daclizumab (n = 30)</td>
<td>Kidney</td>
<td>15 months</td>
<td>Tacrolimus, MMF, steroids</td>
<td>IV GCV × 3 days, followed by oral VGCV × 3 months</td>
<td>Daclizumab, 1 mg/kg/day on day 0 and every 2 weeks × 4 doses</td>
<td>...</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

**NOTE.** CMV infection includes asymptomatic CMV infection (antigenemia, PCR detection), CMV syndrome, and CMV disease. ACV, acyclovir; ATG, antithymocyte globulin; CsA, cyclosporine A; D+R−, donor seropositive and recipient seronegative; GCV, ganciclovir; IV, intravenous; L-IG, lymphocyte immunoglobulin; MMF, mycophenolate mofetil; NS, not significant (exact P value not reported); rATG, rabbit ATG; VGCV, valganciclovir.
plant recipients, the risk of PTLD is increased by coinfection with CMV and increased intensity of immunosuppression [60, 65]. Induction and graft-rejection therapies using various antilymphocyte globulins have been associated with an increased risk of PTLD (table 3) [66–71]. Not all studies support this association (table 3) [70–72]; many of these studies are affected by variability in risk factors between patients, including variability in the type and dosage of induction therapy, type of organs transplanted, maintenance of immunosuppression, EBV serostatus of donor and recipient, and duration of follow-up. The highest risk of PTLD is in EBV-seronegative recipients of organs from seropositive donors, particularly children, who require long-term monitoring, especially after intensification of immunosuppression.

BKV. Evidence is emerging that links ATG induction therapy to increased rates of BKV viremia and BKV-associated nephropathy. BKV-associated nephropathy is an infectious injury to renal allografts that affects 1%–10% of kidney transplant recipients and is associated with the intensity of immunosuppression [76]. Some studies link ATG induction therapy to the risk of BKV viremia and BKV-associated nephropathy [77–80]. rATG induction therapy has been found to be an independent risk factor for BKV-associated nephropathy, as were tacrolimus-mycophenolate mofetil and corticosteroid maintenance therapy [77, 78]. In a prospective trial, BKV viremia occurred in 19.4% of renal transplant recipients at 6 months and was associated with higher induction doses of rATG [80]. In a retrospective cohort, induction with polyclonal antibodies was associated with an increased rate of BKV-associated nephropathy [79]. The use of antilymphocyte globulins for the treatment of steroid-resistant graft rejection has been associated with increased BKV replication in patients also receiving tacrolimus- or mycophenylate mofetil-based regimens. Use of pulsed-dose corticosteroids is a major risk factor for BKV-associated nephropathy [81].

Hepatitis C Virus (HCV). The use of induction therapy in HCV-infected organ transplant recipients, especially in liver recipients, may increase HCV replication and accelerate progression to cirrhosis. This progression is accelerated by CMV coinfection. Our experience demonstrates accelerated HCV replication with rATG induction therapy for liver transplantation but no increased rate of hepatic graft injury, especially in patients who tolerate antiviral therapy. HCV infection is associated with increased mortality in kidney transplant recipients [82, 83]; however, anti–T cell therapy (rATG or basiliximab) was not associated with accelerated viral infection, cirrhosis, or increased mortality in HCV-seropositive renal transplant recipients [84, 85].

Fungal infection. Pneumonia due to Pneumocystis species and other invasive fungal infections have been reported in solid-organ transplant patients who have received rATG induction therapy in the absence of prophylaxis [17–19, 21, 26, 28, 29, 31, 32]. In most randomized studies, the risk of fungal infection after ATG therapy was similar among different ATG agents (table 1). False-positive assay results for Histoplasma antigens may occur in patients receiving rATG therapy [86, 87]. In a retrospective, multivariate analysis of renal transplant recipients, the rate of invasive fungal infection was not increased by ATG induction, whereas graft rejection and graft-rejection therapy increased the risk of invasive fungal infection [88].

OKT3 (MUROMONAB-CD3)

OKT3 is a T cell–depleting mouse monoclonal antibody that has been associated with an increased rate of severe infection (notably CMV reactivation [89–91] and fungal infection [88]) and an increased risk of PTLD [67, 70, 92, 93]. The frequency of OKT3 use has decreased because of the availability of agents with fewer first-dose–related adverse effects (i.e., fever, rigors, chest pain, dyspnea, hypotension, nausea, vomiting, and diarrhea). Patients who receive OKT3 commonly develop antidiotypic antibodies that block efficacy with subsequent administration [94].

IL-2R ANTAGONISTS (ANTI-CD25)

IL-2R antagonists (e.g., basiliximab and daclizumab) are monoclonal antibodies that target CD25, the α-chain of the receptor that is expressed on the surface of early progenitors of T and B cells and by activated mature T and B lymphocytes; resting lymphocytes are not targeted. CD25 participates in lymphocyte differentiation, activation, and proliferation. These agents are used for induction therapy and in maintenance immunosuppression. Because of the relatively recent introduction of these agents, clinical experience remains limited but suggests that the number of infectious complications may be reduced, compared with that for other induction therapies. These agents are not generally used for the treatment of acute graft rejection.

Basiliximab. Basiliximab is a chimeric murine-human monoclonal antibody that binds selectively to the high-affinity IL-2R [95–97]. Basiliximab is generally administered within 2 h before transplantation and 4 days after transplantation. Basiliximab has a long half-life (13.4 days in adults and 9.4 days in children) [98, 99]. Induction therapy achieves complete IL-2R saturation and suppression for 4–6 weeks in adult kidney transplant recipients [96, 97, 99]. In pediatric kidney transplantation, the mean duration of saturation is 42 days [100].

Daclizumab. Daclizumab is a humanized IL-2R antagonist that contains the hypervariable region of the murine antibody against the IL-2R α-subunit [95]. Daclizumab is administered every 2 weeks for 5 doses. The half-life of Daclizumab is 20 days [101]. The dose used for induction therapy saturates the IL-2R on circulating lymphocytes for at least 3 months after transplantation [101].
### Table 2. Induction therapies and mean time to onset of cytomegalovirus (CMV) infection.

<table>
<thead>
<tr>
<th>Study, induction therapy</th>
<th>Type of transplant</th>
<th>Maintenance immunosuppression</th>
<th>CMV serology D+/R−, no. (%) of patients</th>
<th>CMV prophylaxis</th>
<th>Incidence of CMV infection, % of patients</th>
<th>Time to onset of CMV infection, median days (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abou-Ayache [27]</td>
<td>Kidney</td>
<td>CsA, MMF, steroids</td>
<td>18 (33)</td>
<td>D+/R−, universal prophylaxis with GCV × 3.5 months; D+/R+ or D−/R+, preemptive therapy</td>
<td>51 (infection, syndrome, and disease)</td>
<td>29 (16–89)</td>
</tr>
<tr>
<td>Daclizumab (n = 54)</td>
<td>Kidney</td>
<td>CsA, MMF, steroids</td>
<td>19 (35)</td>
<td>D+/R−, universal prophylaxis with GCV × 3.5 months; D+/R+ or D−/R+, preemptive therapy</td>
<td>39 (CMV infection, syndrome, and disease)</td>
<td>57 (29–168)</td>
</tr>
<tr>
<td>Huurman [40]</td>
<td>Pancreas-kidney</td>
<td>CsA, MMF, steroids</td>
<td>5 (26.3)</td>
<td>Universal prophylaxis with GCV × 3–4 months</td>
<td>52.6 (viremia)</td>
<td>114.5 (34–180)</td>
</tr>
<tr>
<td>Daclizumab (n = 20)</td>
<td>Pancreas-kidney</td>
<td>CsA, MMF, steroids</td>
<td>4 (20)</td>
<td>Universal prophylaxis with GCV × 3–4 months</td>
<td>60 (viremia)</td>
<td>159.5 (139–180)</td>
</tr>
<tr>
<td>Peleg et al. [46]; alemtuzumab (n = 547)</td>
<td>Any</td>
<td>Tacrolimus monotherapy</td>
<td>Unknown</td>
<td>Universal prophylaxis × 6 months for kidney, pancreas, lung, intestinal, multivisceral; preemptive therapy for liver recipients</td>
<td>26 (CMV disease)</td>
<td>85 (7–254)</td>
</tr>
</tbody>
</table>

**NOTE.** ATG, antithymocyte globulin; CsA, cyclosporin A; D, donor CMV serostatus; GCV, ganciclovir; R, recipient CMV serostatus; rATG, rabbit ATG.
**Bacterial infection.** No increase in the overall rate of bacterial infection was noted with IL-2R antagonists, compared with other induction therapies or placebo (table 1) [17, 28, 102–104]. Higher mortality associated with infection was observed among patients receiving daclizumab in a placebo-controlled study of cardiac transplant recipients who also received cytolytic therapy (i.e., OKT3 and ATG) [30]. Infections included sepsis (6 cases), CMV infection (1 case), and cryptococcal meningitis (1 case); the role of daclizumab in these complications remains unclear [30].

**CMV.** Patients receiving IL-2R antagonists experience rates of CMV infection that are similar to those among patients receiving placebo or other induction therapies (table 1) [30, 96, 101–103, 105–108]. Receipt of cytolytic anti–graft-rejection treatment with basiliximab was associated with higher rates of CMV infection, compared with receipt of ATG in renal transplant recipients (17.5% vs. 7.8%; P = .02) [21].

**EBV and EBV-induced PTLD.** Most studies have not demonstrated an increased risk of PTLD after induction therapy with IL-2R antagonists (table 3) [17, 28, 57, 68–70, 72, 108].

**HCV.** The effect of IL-2R antagonists on HCV infection is unknown. One study demonstrated higher rates of HCV infection recurrence among liver recipients after receipt of daclizumab [109], whereas other studies have demonstrated no impact [110–112].

**Fungal infection.** The incidence of fungal infection among recipients of IL-2R antagonists was similar to the incidence among recipients of placebo, no induction therapy, or other induction therapies (table 1) [21, 22, 26, 30, 31, 96, 102, 103, 105, 107, 113, 114].

**ALEMTUZUMAB**

Alemutzumab is a humanized monoclonal antibody directed against the membrane glycoprotein CD52 on lymphocytes (T and B cells), monocytes and macrophages, and natural killer cells. Alemutzumab achieves pan–T cell depletion; CD4 and CD8 cell counts reach a nadir 4 weeks after initiation of therapy and remain at <25% of baseline values for 9 months [115]. Data regarding infectious complications remain limited, because alemutzumab is used in induction therapy in a small number of clinical centers. Some late invasive viral and fungal infections have been observed in patients after induction and graft-rejection therapy with alemutzumab. Additional prospective data are needed.

**Bacterial infection.** Alemutzumab is used at a lower dosage in induction therapy for solid organ transplantation (20–30 mg for 1 or 2 doses), compared with the dosage used for cancer therapy. Induction therapy with alemutzumab is associated with a low incidence of bacterial infection, compared with historical regimens or with other therapies (table 1) [18, 31, 34, 73, 74, 114, 116–121]. Infection occurred earlier among patients who received alemutzumab for graft-rejection therapy (72.5 days; range, 2–325 days) than among patients who received alemutzumab for induction therapy (120 days; range, 31–328 days; P = .09) [46]. Disseminated and pulmonary nocardiosis and tuberculous and nontuberculous pneumonia (due to Mycobacterium kansasii) have been described after treatment with alemutzumab, mainly in patients who received alemutzumab for treatment of acute graft rejection.

**Viral infection.** Of 547 organ transplant recipients treated with alemutzumab without antiviral prophylaxis, 56 (10%) developed 62 opportunistic infections [46], including 16 (26%) CMV infections, 12 (19%) BKV infections, and 3 (5%) EBV infections with PTLD [46]. CMV disease occurred within 3 months after graft-rejection therapy with alemutzumab [46]. Many patients (65%) who received alemutzumab for treatment of acute graft rejection also received another type of lymphocyte-depleting antibody, most commonly rATG [46]. In a single-center, 5-year trial of induction therapy with alemutzumab in renal transplantation, compared with other induction agents, a lower incidence of CMV infection was demonstrated with alemutzumab using acyclovir for CMV prophylaxis in high-risk recipients [74]. No tissue-invasive CMV infection, PTLD, or BKV-associated nephropathy was demonstrated in pediatric kidney recipients treated with alemutzumab induction [122]. In a retrospective study of induction therapy in renal transplantation comparing alemutzumab with ATGs (rabbit and equine) and IL-2R antagonists, alemutzumab therapy was associated with a greater incidence of CMV infection, compared with that in the IL-2R antagonist group (24.6% vs. 9.3%; P = .01), with a rate similar to that in the rATG group [114]. There was also a trend toward more BKV infections among patients receiving alemutzumab [114].

**Fungal infection.** Invasive fungal infections have been described after alemutzumab therapy, including invasive aspergillosis, mucormycosis, Scedosporium infection, Histoplasma capsulatum infection, Blastomyces dermatitidis infection, and cryptococcal infection [46, 117, 123]. The risk of fungal infection among transplant recipients treated with alemutzumab induction therapy appears to be similar to that for patients treated with other induction therapy agents [18, 114]. However, a greater risk of invasive fungal infection (mostly esophageal candidiasis) exists after treatment for acute graft rejection; most infections occurred within 3 months after the start of therapy [46].

**Parasitic infection.** Amebic meningitis due to Balamuthia mandrillaris and Toxoplasma pneumonia has been described in patients receiving alemutzumab for acute graft rejection [46].
### Table 3. Induction therapy and risk of posttransplantation lymphoproliferative disorder (PTLD).

<table>
<thead>
<tr>
<th>Drug, study number</th>
<th>Study type</th>
<th>Database</th>
<th>Period</th>
<th>Type of transplant</th>
<th>Duration of follow-up</th>
<th>RR (95% CI) of PTLD</th>
<th>P</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>hATG: 1 rATG 1</td>
<td>Retrospective data analysis</td>
<td>SRTR (3752/41,686 recipients)</td>
<td>1996–2002</td>
<td>Kidney</td>
<td>Censored</td>
<td>1.50 (0.93–2.43)</td>
<td>.10</td>
<td>[67]</td>
</tr>
<tr>
<td>2</td>
<td>Retrospective data analysis</td>
<td>SRTR (2376/41,686 recipients)</td>
<td>1996–2002</td>
<td>Kidney</td>
<td>Censored</td>
<td>3.0 (1.53–5.89)</td>
<td>.001</td>
<td>[67]</td>
</tr>
<tr>
<td>3</td>
<td>Randomized prospective study</td>
<td>90 patients</td>
<td>2002–2004</td>
<td>Kidney</td>
<td>15 months</td>
<td>No PTLD</td>
<td></td>
<td>[72]</td>
</tr>
<tr>
<td>4</td>
<td>Retrospective data analysis</td>
<td>UNOS-OPTN (12,051/84,368 recipients)</td>
<td>1987–2003</td>
<td>Kidney</td>
<td>Median, 368 days</td>
<td>1.17 (0.87–1.58)</td>
<td>.29</td>
<td>[71]</td>
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<tr>
<td>5</td>
<td>Retrospective data analysis</td>
<td>UNOS-OPTN (685/5072 recipients)</td>
<td>1987–2003</td>
<td>Pediatric kidney</td>
<td>Median, 368 days</td>
<td>1.51 (0.78–2.93)</td>
<td>[71]</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Retrospective data analysis</td>
<td>UNOS-OPTN (13,110/59,560 recipients)</td>
<td>2000–2004</td>
<td>Kidney</td>
<td>730 days</td>
<td>1.63</td>
<td>.01</td>
<td>[69]</td>
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<tr>
<td>L-IG 1</td>
<td>Retrospective data analysis</td>
<td>UNOS-OPTN (8076/84,368 recipients)</td>
<td>1987–2003</td>
<td>Kidney</td>
<td>Median, 1433 days</td>
<td>1.61 (1.24–2.10)</td>
<td>&lt;.001</td>
<td>[71]</td>
</tr>
<tr>
<td>2</td>
<td>Retrospective data analysis</td>
<td>UNOS-OPTN (620/5072 recipients)</td>
<td>1987–2003</td>
<td>Pediatric kidney</td>
<td>Median, 1433 days</td>
<td>2.162 (1.22–3.82)</td>
<td>.008</td>
<td>[71]</td>
</tr>
<tr>
<td>ALG 1</td>
<td>Retrospective data analysis</td>
<td>UNOS-OPTN (16,108/84,368 recipients)</td>
<td>1987–2003</td>
<td>Kidney</td>
<td>Median, 2055 days</td>
<td>1.35 (1.09–1.68)</td>
<td>.006</td>
<td>[71]</td>
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<tr>
<td>2</td>
<td>Retrospective data analysis</td>
<td>UNOS-OPTN (1334/5072 recipients)</td>
<td>1987–2003</td>
<td>Pediatric kidney</td>
<td>Median, 2055 days</td>
<td>1.008 (0.58–1.76)</td>
<td>[71]</td>
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<tr>
<td>ATG (all) 1</td>
<td>Retrospective data analysis</td>
<td>UNOS-OPTN (38,519 recipients)</td>
<td>1997–2000</td>
<td>Kidney</td>
<td>727 days</td>
<td>1.29 (0.82–2.03)</td>
<td>.27</td>
<td>[70]</td>
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<tr>
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<td>Retrospective data analysis</td>
<td>USRDS (4353/25127 recipients)</td>
<td>1996–2000</td>
<td>Kidney</td>
<td>Censored</td>
<td>1.55 (1.2–1.99)</td>
<td>.001</td>
<td>[68]</td>
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<td>Basiliximab 1</td>
<td>Retrospective data analysis</td>
<td>SRTR (5169/41,686 recipients)</td>
<td>1996–2002</td>
<td>Kidney</td>
<td>Censored</td>
<td>1.83 (1.05–3.18)</td>
<td>.032</td>
<td>[67]</td>
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<td>Retrospective data analysis</td>
<td>UNOS-OPTN (14,182/59,560 recipients)</td>
<td>2000–2004</td>
<td>Kidney</td>
<td>730 days</td>
<td>0.84</td>
<td>.33</td>
<td>[69]</td>
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</table>

Daclizumab
<table>
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<tr>
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<th>Study Details</th>
<th>Outcomes</th>
<th></th>
<th>RR (95% CI)</th>
<th>P Value</th>
<th>Reference</th>
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<tbody>
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<td>SRTR (3377/41,686 recipients)</td>
<td>Kidney</td>
<td>Censored</td>
<td>1.92 (1.08–3.41)</td>
<td>.027</td>
<td>[67]</td>
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<td>2</td>
<td>Randomized prospective study</td>
<td>90 patients</td>
<td>Kidney</td>
<td>15 months</td>
<td>No PTLD</td>
<td></td>
<td>[72]</td>
</tr>
<tr>
<td>3</td>
<td>Retrospective data analysis</td>
<td>UNOS-OPTN (7511/59,560 recipients)</td>
<td>Kidney</td>
<td>730 days</td>
<td>0.64</td>
<td>.06</td>
<td>[69]</td>
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<tr>
<td></td>
<td>Anti-IL-2R as a group</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>Retrospective data analysis</td>
<td>UNOS-OPTN (7800/38,519 recipients)</td>
<td>Kidney</td>
<td>727 days</td>
<td>1.14 (0.77–1.70)</td>
<td>.52</td>
<td>[70]</td>
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<tr>
<td>2</td>
<td>Retrospective data analysis</td>
<td>USRDS (3936/25,127 recipients)</td>
<td>Kidney</td>
<td>Censored</td>
<td>1.16 (0.82–1.65)</td>
<td>.39</td>
<td>[68]</td>
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<td></td>
<td>Alemtuzumab</td>
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<tr>
<td>1</td>
<td>Retrospective single-center study</td>
<td>126 patients</td>
<td>Kidney</td>
<td>Censored</td>
<td>No PTLD</td>
<td></td>
<td>[73]</td>
</tr>
<tr>
<td>2</td>
<td>Prospective single-center study</td>
<td>33 patients</td>
<td>Kidney</td>
<td>5 years</td>
<td>1 case</td>
<td></td>
<td>[74]</td>
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<td>3</td>
<td>Prospective single-center study</td>
<td>10 patients</td>
<td>Lung</td>
<td>6 months</td>
<td>No PTLD</td>
<td></td>
<td>[34]</td>
</tr>
<tr>
<td>4</td>
<td>Randomized prospective study</td>
<td>90 patients</td>
<td>Kidney</td>
<td>15 months</td>
<td>No PTLD</td>
<td></td>
<td>[72]</td>
</tr>
<tr>
<td>5</td>
<td>Retrospective data analysis</td>
<td>UNOS-OPTN (1691/59,560 recipients)</td>
<td>Kidney</td>
<td>730 days</td>
<td>1.15</td>
<td>.74</td>
<td>[69]</td>
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<tr>
<td></td>
<td>Belatacept and basiliximab</td>
<td>Randomized prospective study</td>
<td>218 patients</td>
<td>13 months</td>
<td>3 cases^a</td>
<td></td>
<td>[75]</td>
</tr>
</tbody>
</table>

**NOTE.** ALG, antilymphocyte globulin; ATG, antithymocyte globulin; hATG, horse ATG; L-IG, lymphocyte immunoglobulin; rATG, rabbit ATG; RR, relative risk; SRTR, Scientific Registry of Transplant Recipients; UNOS-OPTN, United Network for Organ Sharing and Organ Procurement and Transplant Network; USRDS, United States Renal Data System.

^a One patient who developed PTLD after receipt of belatacept also received OKT3 for treatment of acute graft rejection.
CHRONIC INDUCTION THERAPY AGENTS (ABATACEPT AND BELATACEPT)

Abatacept and belatacept are fusion proteins composed of Fc fragments of a human IgG1 immunoglobulin linked to the extracellular domain of cytotoxic T lymphocyte antigen 4 (CTLA-4) that block T cell activation by preventing T cell costimulation. Experience with these agents remains limited. Three cases of PTLD have been reported in kidney transplant recipients who received intensive treatment with belatacept (table 3) [75].

RECOMMENDATIONS: MONITORING FOR INFECTION AND PREVENTATIVE THERAPIES

Experience with antilymphocyte therapies has provided a predictability of infectious complications based on the intensity and duration of T cell depletion. Strategies should be developed to monitor and prevent common infections associated with antilymphocyte therapies [124].

Bacterial and fungal infections. Patients receiving induction therapies do not require routine laboratory monitoring for bacterial or fungal infections. Because of the duration of effect of prophylaxis for pneumonia due to Pneumocystis carinii, it should be prolonged (duration, 6–12 months) when T cell–depleting agents are used in induction or graft rejection therapy. Trimethoprim-sulfamethoxazole (single strength, 80/400 mg daily) prevents pneumonia due to Pneumocystis species and other opportunistic infections (i.e., infection due to Nocardia, Toxoplasma, or Listeria species). Other prophylactic regimens against pneumonia due to P. carinii do not offer the same protection. Patients with active CMV or HCV infection who have poor allograft function or who are treated for graft rejection should receive prophylaxis for longer periods (i.e., 6 months to life).

Individuals receiving induction therapy with T cell–depleting agents who have a history of exposure (i.e., seropositivity) to endemic fungi (i.e., the fungi that cause histoplasmosis, coccidioidosis, blastomycosis) or to Cryptococcus species should receive prophylaxis (duration, 6–12 months) with fluconazole (200–400 mg daily; for infection due to Coccidioides, Histoplasma, or Cryptococcus species) or itraconazole (200 mg orally daily; for infection due to Histoplasma or Blastomyces species), with adjustment in doses of any calcineurin inhibitors or rapamycin. Monitoring with use of antigen assays or immunohasays for Histoplasma and Cryptococcus species (and more recently for species that cause coccidioides and blastomycosis) may be useful; cross-reactivity is common. Comprehensive long-term data on infections associated with IL-2R antagonists are lacking.

CMV prevention. Patients who are at risk of CMV infection (i.e., either the organ donor or recipient is CMV seropositive) should be monitored by quantitative CMV load or antigenemia assay every 2 weeks for 6 months after induction therapy in the absence of anti-CMV prophylaxis. CMV monitoring and prophylaxis (~3 months) should be extended or reinstituted for at-risk individuals after the use of T cell–depleting agents for treatment of graft rejection (tables 1 and 2). For transplantations in which the donor and recipient are both CMV seronegative, antiviral prophylaxis (e.g., famiclovir, valacyclovir, or acyclovir) for 4–6 months is recommended for prevention of infection with herpes simplex virus or varicella-zoster virus.

EBV and EBV-induced PTLD. The association between T cell depletion or chronic induction therapy (abatacept and belatacept) and a possible risk of PTLD supports the monitoring of EBV-seronegative recipients of organs from seropositive donors with use of quantitative molecular assays (plasma or whole blood) monthly for at least 1 year after induction therapy [124]. For patients with detectable EBV loads, consideration should be given to decreasing the intensity of immunosuppression and to increasing the monitoring of EBV loads. Quantitative EBV assays of whole blood have higher sensitivity than do serum assays; PTLD can develop in patients with low EBV loads [125].

BKV. Kidney recipients who are receiving induction therapy with T cell–depleting agents should be monitored for BKV infection with use of a sensitive urine (either cytopathology for decoy cells or a quantitative, nucleic acid–based viral load assay) or blood (DNA) screening test at least monthly for ~6 months. Any unexplained increase in serum creatinine level should prompt examination of a renal biopsy specimen with use of immunostaining or in situ hybridization for the detection of BKV [76, 81, 124, 126].

HCV. In patients who are HCV seropositive, a quantitative HCV RNA load measurement is recommended at baseline and at 3, 6, 9, and 12 months after transplantation [124]. Quantitative HCV load does not correlate with the degree of hepatic injury [127], and examination of biopsy specimens will be needed to guide decisions regarding antiviral therapy [124].

SUMMARY

Infectious risks are greater when antilymphocyte therapies are used in the treatment of graft rejection, compared with the use of these therapies in induction immunosuppression. Antiviral prophylaxis will reduce the risk for CMV infection associated with induction therapy with ATG. BKV replication and BKV-associated nephrophyt occur earlier and are more common with induction therapy. In contrast, patients who receive IL-2R antagonists for induction therapy experience a lower incidence of infection overall and of PTLD. The use of T cell–depleting agents (e.g., ATG, OKT3, and alemtuzumab) for graft-rejection or induction therapy should be linked to appropriate monitoring and/or prophylaxis for pneumonia due
to *P. carinii* and for CMV and fungal infection. Monitoring of EBV in seronegative recipients of organs from EBV-seropositive donors and monitoring of BKV in renal transplant recipients should be performed using quantitative assays for patients who are receiving T cell-depleting agents.

**Acknowledgments**

_Potential conflicts of interest._ J.A.F. has served as a consultant for Bristol-Myers Squibb, Merck, Hoffman-La Roche, T2 Biosystems, Astellas, and FDA/NCI—Xenotransplantation; has served on the scientific advisory board for Primera; has served on the speakers’ bureau for Hoffman-La Roche; and has received corporate grant support from PATH Alliance (Axim/Astellas). J.A.F. has patents for molecular cloning of antigens shared by rat- and human-derived _Pneumocystis carinii_ (patent S442050; GenBank accession numbers L43850, L43851, and L43852) and molecular sequence by rat- and human-derived _Pneumocystis carinii_ (patent 5442050; GenBank accession numbers AF038600, AF038601, and AF038599). N.C.I.: no conflicts.

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