Alemtuzumab (Campath)

Number: 0764

Aetna considers alemtuzumab (Campath) medically necessary for the treatment of any of the following conditions:

- Angioimmunoblastic T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified, anaplastic large cell lymphoma, or enteropathy-associated T-cell lymphoma – Second-line therapy or subsequent therapy for relapsed or refractory disease in persons with no intention to transplant; or
- Adult T-cell leukemia/lymphoma – Second-line therapy (with intention to proceed to high-dose therapy/allogeneic stem cell rescue [HDT/ASCR]) or subsequent therapy to HDT/ASCR as a single agent for nonresponders to first-line therapy for acute or lymphoma subtypes; or
- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
  - First-line therapy with or without rituximab for CLL/SLL with del(17p)/TP53 mutation; or
  - Therapy for relapsed or refractory disease; or

Policy History

Last Review
12/10/2020
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Next Review: 09/09/2021

Definitions

Additional Information

Clinical Policy Bulletin
Notes

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*
• Graft versus host disease, acute, prophylaxis and treatment; or

• Hepato-splenic gamma-delta T-cell lymphoma – Second-line and subsequent therapy as a single-agent for refractory disease after 2 primary treatment regimens in persons with no intention to transplant; or

• Mycosis fungoides or Sezary syndrome:
  - Systemic therapy for tumors with aggressive growth rate in persons with no intention to transplant, with or without skin directed therapies (Stage IB, IIA-IIB) or radiation therapy (Stage IV); or
  - Therapy in individuals with stage III or IV mycosis fungoides or Sezary syndrome that is refractory to multiple previous therapies or progression; or

• Peripheral T-cell lymphomas – Relapsed/refractory peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, nodal peripheral T-cell lymphoma with TFH phenotype, or follicular T-cell lymphoma, - second line or subsequent therapy as a single agent in persons with no intention to transplant; or

• Primary cutaneous anaplastic large cell lymphoma (ALCL) with multifocal lesions or cutaneous ALCL with regional nodes (excludes systemic ALCL) – Single-agent therapy for relapsed or refractory disease; or

• T-cell prolymphocytic leukemia – As a single agent, in combination with pentostatin, or following FMC (fludarabine, mitoxantrone, and cyclophosphamide) regimen as primary treatment for symptomatic disease or second-line therapy; or

• T-cell large granular lymphocytic leukemia – Second-line therapy as a single agent for persons with progressive or refractory disease to all first-line therapies.
Aetna considers alemtuzumab experimental and investigational for the following indications (not an all-inclusive list) because its effectiveness for these indications has not been established:

- Acute lymphoblastic leukemia
- Aplastic anemia
- Arthritis
- Autoimmune cytopenias
- Autoimmune hemolytic anemia
- Eosinophilic myeloid disorders/eosinophilic diseases
- Guillain-Barre syndrome
- Histiocytic sarcoma
- Malignant histiocytosis
- Myelin oligodendrocyte glycoprotein (MOG)-associated encephalomyelitis
- Myelodysplastic syndrome
- Natural killer (NK) cell lymphoma
- Polyradiculoneuropathies (e.g., Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy)
- Pure red cell aplasia
- Rasmussen encephalitis
- Scleroderma/systemic sclerosis
- Severe combined immunodeficiency
- Solid organ transplantation (including antibody induction therapy and antibody-mediated rejection)
- Sporadic inclusion body myositis
- Systemic lupus erythematosus
- T-cell non-Hodgkin lymphomas other than those listed above
- Uveitis
- Vasculitis
- Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma.

For alemtuzumab (Lemtrada) for multiple sclerosis, see
Dosing Recommendations

Recommended dosage and administration for CLL/SLL

- Administer as an IV infusion over 2 hours (Not as IV push or bolus)
- Gradually escalate to the maximum recommended single dose of 30 mg
- Maintenance dose: 30 mg per day, 3 times per week on alternate days
- Total duration of therapy, including dose escalation is 12 weeks.

Refer to protocol by which member is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Please consult Full Prescribing Information for recommendations for dose reductions, delays, or when to discontinue.

Background

Alemtuzumab (Campath) is a recombinant DNA-derived, humanized monoclonal antibody. It is directed against a small (21 to 28 kD) glycosylphosphatidylinositol-anchored glycoprotein, CD52, which is expressed on the surface of normal as well as malignant B- and T-lymphocytes, natural killer cells, monocytes, macrophages, but not on hematopoietic progenitor cells. Thus, alemtuzumab has a potential broad application across a spectrum of B- and T-cell malignancies. The proposed mechanism of action for alemtuzumab is antibody-dependent lysis of leukemic cells following cell surface binding.
In a retrospective study, Fiegl et al (2006) evaluated the benefit of alemtuzumab monotherapy in unselected patients with advanced, previously treated chronic lymphocytic leukemia (CLL) who received treatment in the routine clinical setting. Data were collected from 115 consecutive subjects who received alemtuzumab therapy at 25 participating centers in Austria. Patients received a median of 3 prior lines of therapy (range of 1 to 11), and 59% had fludarabine-refractory disease. Alemtuzumab was administered intravenously or subcutaneously with a planned schedule of 30 mg 3 times per week for up to 12 weeks. Patients received valacyclovir and trimethoprim/sulfamethoxazole for anti-infective prophylaxis. The overall response rate was 23%, with complete responses achieved in 5% of patients. Stable disease (SD) was achieved in 36% of patients. After a median follow-up of 17.5 months, the median overall survival (OS) was 20.2 months for all patients. A multi-variate Cox regression analysis that included pre-treatment baseline characteristics, response to therapy, and cumulative dose of alemtuzumab indicated that bulky lymphadenopathy, the administration of greater than or equal to 3 previous therapies, and lack of response to alemtuzumab remained significant independent risk factors for inferior OS. The median OS had not been reached for responding patients. The median OS was 29.5 months for patients with SD and 10.8 months for patients with progressive disease (PD). The authors concluded that the broad use of alemtuzumab in the routine clinical practice setting is feasible and active in unselected patients with pre-treated CLL, and the current results confirmed the activity and safety of this agent, as reported in previously published clinical studies.

Alemtuzumab initially received accelerated approval in 2001 from the U.S. Food and Drug Administration (FDA) for the treatment of fludarabine-refractory CLL. Additional clinical data were required to confirm its benefit in this setting and in patients previously untreated. On September 19, 2007, the FDA expanded the labeling and granted regular approval for single-agent alemtuzumab for the treatment of B-cell CLL.
Alemtuzumab (Campath) is available as Campath in 30 mg/mL (30 mg) single use vials. The FDA-approved labeling of Campath recommends to administer alemtuzumab as an IV infusion over 2 hours. The labeling recommends to escalate to the recommended dose of 30 mg/day of alemtuzumab three times per week for 12 weeks.

Black Box Warnings:

- **Cytopenias:** Serious, including fatal, pancytopenia/marrow hypoplasia, autoimmune idiopathic thrombocytopenia, and autoimmune hemolytic anemia can occur in patients receiving Campath (alemtuzumab). Single doses of Campath (alemtuzumab) greater than 30 mg or cumulative doses greater than 90 mg per week increase the incidence of pancytopenia.

- **Infusion Reactions:** Campath (alemtuzumab) administration can result in serious, including fatal, infusion reactions. Carefully monitor patients during infusions and withhold Campath (alemtuzumab) for Grade 3 or 4 infusion reactions. Gradually escalate Campath (alemtuzumab) to the recommended dose at the initiation of therapy and after interruption of therapy for 7 or more days.

- **Infections:** Serious, including fatal, bacterial, viral, fungal, and protozoan infections can occur in patients receiving Campath (alemtuzumab). Administration prophylaxis against Pneumocystis jiroveci pneumonia (PJP, also known as PCP) and herpes virus infections.

Campath (alemtuzumab) should not be used in the following:
- Members with active systemic infection or underlying immunodeficiency (i.e. HIV) other than CLL induced immunodeficiency.
- Members with autoimmune cytopenias or recurrent/persistent severe cytopenias.

Hillmen and co-workers (2007) performed a randomized trial to assess the safety and effectiveness of intravenous alemtuzumab compared with chlorambucil in first-line treatment of CLL. Patients received alemtuzumab (30 mg 3 times per week, for up to 12 weeks) or chlorambucil (40 mg/m^2 every 28 days, for up to 12 months). The primary end point was progression-free survival (PFS). Secondary end points included overall response rate (ORR), complete response (CR), time to alternative therapy, safety, and OS. A total of 297 patients were randomly assigned to receive alemtuzumab (n = 149) or chlorambucil (n = 148). Alemtuzumab-treated subjects had superior PFS, with a 42% reduction in risk of progression or death (hazard ratio [HR] = 0.58; p = 0.0001), and a median time to alternative treatment of 23.3 months versus 14.7 months for chlorambucil-treated subjects (HR = 0.54; p = 0.0001). The ORR was 83% with the alemtuzumab group (24% CR) versus 55% with the chlorambucil group (2% CR); differences in ORR and CR were highly significant (p < 0.0001). Elimination of minimal residual disease occurred in 11 of 36 complete responders to alemtuzumab versus none to chlorambucil. Adverse events profiles were similar, except for more infusion-related and cytomegalovirus (CMV) events with alemtuzumab and more nausea and vomiting with chlorambucil. Cytomegalovirus events had no apparent impact on effectiveness. The authors concluded that as first-line treatment for patients with CLL, alemtuzumab demonstrated significantly improved PFS, time to alternative treatment, ORR and CR, and minimal residual disease-negative remissions compared with chlorambucil, with predictable and manageable toxicity.
Besides its use in the treatment of CLL and other lymphoid neoplasms, alemtuzumab has also been studied as an immunosuppressive agent in bone marrow/solid organ transplantation and in the treatment of autoimmune disorders including arthritis, autoimmune cytopenias and vasculitis (Reiff, 2005; Lee and D'Cruz, 2008). However, its clinical value for these indications has not been established.

In a phase II study, Kennedy and associates (2003) assessed the safety, tolerability and effectiveness of alemtuzumab in patients with relapsed or refractory advanced stage cutaneous T-cell lymphoma (CTCL). A total of 8 patients were enrolled, 7 with mycosis fungoides/Sezary syndrome (MF/SS) and 1 with large-cell transformation of MF. Seven patients had disease refractory to multiple previous therapies. Alemtuzumab (30 mg) was administered intravenously 3 times per week for 12 weeks or until maximum response. The ORR was 38 %, with 3 patients achieving partial remission (PR), 2 patients with SD and 3 patients with PD during treatment. The time to progression was short, with all patients developing PD within 4 months of starting alemtuzumab. Response duration in the 3 PR patients was also brief, with responses lasting less than 3 months in all 3 cases. Significant hematological and immunosuppressive toxicity was observed, with both grade 3 to 4 cytopenias and significant infectious complications occurring in a majority of cases. The authors concluded that these findings suggested that in heavily pre-treated, refractory, advanced stage MF/SS, although alemtuzumab has biological activity, it is associated with significant toxicity and only modest clinical utility. As such, combination regimens incorporating alemtuzumab merit further investigation in this difficult to treat patient group.

In another phase II study, Lundin and co-workers (2003) evaluated the safety and effectiveness of alemtuzumab in 22 patients with advanced MF/SS. Most patients had stage III or IV disease, reduced performance status, and severe itching. The ORR rate was 55 %, with 32 % of patients in CR and 23
% in PR. Sezary cells were cleared from the blood in 6 of 7 (86 %) patients, and CR in lymph nodes was observed in 6 of 11 (55 %) patients. The effect was better on erythroderma (ORR, 69 %) than on plaque or skin tumors (ORR, 40 %) and in patients who had received 1 to 2 previous regimens (ORR, 80 %) than in those who had received 3 or more prior regimens (ORR, 33 %). Itching, self-assessed on a 0 to 10 visual analog scale, was reduced from a median of 8 before treatment to 2 at the end of therapy. Median time to treatment failure was 12 months (range of 5 to 32+ months).

Cytomegalovirus re-activation (causing fever without pneumonitis and responding to ganciclovir) occurred in 4 (18 %) patients. Six additional patients had suspect or manifest infection (fever of unknown origin, n = 3; generalized herpes simplex, n = 1; fatal aspergillosis, n = 1). One patient had fatal mycobacterium pneumonia at 10+ months. All serious infectious adverse events (except CMV) occurred in patients who had received 3 or more prior regimens. Progression of squamous cell skin carcinoma was noted in 1 patient. The authors noted that alemtuzumab shows promising clinical activity and an acceptable safety profile in patients with advanced MF/SS, particularly in patients with erythroderma and severe itching and those who were not heavily pre-treated.

Capalbo et al (2003) reported the use of alemtuzumab as salvage treatment in 3 patients with advanced MF/SS who had previously been treated with conventional chemotherapy. Two patients (case 1 and case 2), aged 42 and 68 years, respectively, were heavily pre-treated (more than 3 prior therapy regimens, including autologous transplantation in case 2) and refractory to conventional chemotherapy, and the 3rd patient (case 3), aged 80 years, who had refused any chemotherapy, had been resistant to treatment with cyclosporine and steroids. Alemtuzumab was administered intravenously, after an escalating dose from 3 to 10 mg, at the dose of 30 mg, 3 times weekly, to a total dose of 1080, 223, and 480 mg, respectively. The patients with SS (case 2 and
case 3) showed clearance of circulating Sézary cells and clinical improvement of the skin lesions after 2 weeks of treatment. Two patients (case 1 and case 3) completed the treatment (12 and 6 weeks) without significant toxicity, the former achieving a PR and the latter a clinical CR. The patient (case 2) who suffered from ischemic cardiopathy and diabetes quickly achieved clinical improvement of the SS, but he died because of a myocardial infarction after 3 weeks of treatment. This report showed that the treatment with alemtuzumab is active even in patients with advanced refractory MF/SS. The authors concluded that further clinical observations on a larger cohort of patients are needed to establish if alemtuzumab may have a role as first-line therapy in addition to conventional therapy including chemotherapy.

Muraro and Bielekova (2007) reviewed the mechanism(s) of action as well as safety and effectiveness of some of the most promising new therapeutic strategies for MS. Fingolimod (FTY720) is a novel oral immunomodulating agent that acts through preventing lymphocyte re-circulation from lymphoid organs. Monoclonal antibody therapy has provided investigators the opportunity to rationally direct the therapeutic intervention against specific molecules. Targeting molecules of the immune system such as CD52 (alemtuzumab), CD25 (daclizumab), VLA-4 (natalizumab) and CD20 (rituximab) have resulted in potent immunomodulatory effects through sometimes unpredicted mechanisms. The potential of immunoglobulins to induce re-myelination in the central nervous system is being investigated in an attempt to develop therapies promoting tissue repair and functional recovery. The evidence supporting the potential of these emerging immunotherapies suggested that strong progress is being made in the development of effective cures for MS. Waubant (2007) noted that there are several phase III clinical trials in relapsing-remitting MS with promising agents, including intravenous agents administered once- or twice-yearly (alemtuzumab, rituximab) and oral agents (FTY720, fumaric acid, laquinomod).
Lee and D'Cruz (2008) reviewed novel therapies for the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitides (AAV). Tumour necrosis factor (TNF)-alpha antagonism with infliximab has been described favourably in retrospective series and open-label trials. However, evidence from the WGET (Wegener's Granulomatosis Etanercept Trial) does not support the clinical use of etanercept, and a significantly higher malignancy rate following TNF-alpha inhibition questions the role of this approach. Uncontrolled evidence alone supports remission induction with rituximab-mediated B-cell depletion and may be less effective in predominantly granulomatous AAV. Remission following T-cell depletion can be achieved with alemtuzumab and anti-thymocyte globulin (ATG), but it is unclear what the clinical role will be for these agents in AAV. In addition, these agents are associated with prolonged lymphopenia and pulmonary complications, respectively. Stem cell transplantation to support immune reconstitution following the use of such agents has been studied in AAV, but trials included very few patients.

Alemtuzumab has been examined for use in allogeneic organ transplantation. While recent studies demonstrated a conspicuous effect of alemtuzumab on peripheral dendritic cells (DC) in clinical graft-versus-host disease (GVHD), its effectiveness in patients receiving allogeneic organ transplants is still undefined. Kirsch and colleagues (2006) evaluated the peripheral DC repertoire in kidney transplant recipients after either alemtuzumab induction therapy followed by FK506 monotherapy or after conventional immunosuppression (FK506, mycophenolate mofetil and steroids) without any induction agent. Induction with alemtuzumab caused a strong and sustained reduction of the total number of peripheral DC and a significant shift from myeloid to plasmacytoid DC subsets (mDC/pDC ratio) as early as 1 month post-transplantation. These data showed that alemtuzumab induction targets the peripheral DC repertoire, which might add another mechanism allowing
immunosuppressive drug minimization. The authors stated that more studies are needed to further elucidate the functional significance of these finding in the setting of allogeneic organ transplantation.

In a phase II clinical trial, Martinez et al (2009) examined the safety and effectiveness of alemtuzumab in treating steroid-refractory acute GVHD (aGVHD) grade II or higher after stem cell transplantation. A total of 10 adult patients (6 with aGVHD grade III and 4 with aGVHD grade IV) were included in the study. Nine patients had gastrointestinal tract involvement, 7 had skin involvement, and 5 had liver involvement. Five patients responded to treatment, 2 with CR and 3 with partial response. Eight infectious events (4 of grade 3 to 4) and 7 CMV re-activations were observed. Six patients had grade 3 to 4 cytopenia. All 10 patients died (7 resulting from aGVHD progression, 2 from severe infection, and 1 from to leukemia relapse), at a median of 40 days (range of 4 to 88 days) after alemtuzumab treatment. Overall, these findings suggested that steroid-refractory aGVHD may be improved by treatment with alemtuzumab, but that this treatment does not overcome the dismal prognosis of patients with severe aGVHD, demonstrating the need for alternative therapies to treat this complication.

Huang et al (2007) noted that the use of alemtuzumab for induction therapy in kidney transplantation has been increasing. These researchers presented a report of graft outcomes associated with alemtuzumab induction from the Organ Procurement and Transplantation Network/United Network for Organ Sharing database. A total of 14,362 deceased donor kidney transplants from 2003 to 2004 received no induction (n = 4,364), anti-thymocyte globulin (ATG; n = 4,930), interleukin-2 receptor antagonists (IL-2RA; n = 4,378), or alemtuzumab (n = 690). Acute rejection (AR) within the initial hospitalization, 6 months, and 1 year; graft survival; and rejection-free survival were examined. Graft and rejection-free survival of alemtuzumab recipients maintained...
with tacrolimus (FK) or cyclosporine (CSA), mycophenolate mofetil (MMF), and steroids versus no calcineurin inhibitors (CNI), MMF, and steroids were compared. Alemtuzumab recipients had less AR during the initial hospitalization (2.3 %) than no induction, ATG, and IL-2RA (7.6 %, 3.4 %, and 4.8 %, respectively; p < 0.001). There was increased AR at 6 months and 1 year with alemtuzumab (14.5 % and 19.2 %, respectively) compared to no induction (12.7 % and 14.8 %, p < 0.001), ATG (8.2 % and 10.2 %, p < 0.001), and IL-2RA (11.1 % and 13.0 %, p < 0.001) with no difference in adjusted relative risk for graft loss. Alemtuzumab recipients receiving FK or CSA, MMF, and steroids had increased graft (FK/MMF/steroids, p < 0.001, CSA/MMF/steroids, p = 0.007) and rejection-free survival (FK/MMF/steroids, p < 0.001, CSA/MMF/steroids, p = 0.006) over 24 months compared to no CNI, MMF, and steroids. The authors concluded that despite reduced early rejection, AR rates at 6 months and 1 year with alemtuzumab induction exceeded other forms of induction therapy. Maintenance with CNI-based immunosuppression may improve graft and rejection-free survival compared to CNI-free regimens among alemtuzumab recipients.

Reams et al (2007) noted that despite substantial improvements in early survival after lung transplantation, refractory acute rejection (RAR) and bronchiolitis obliterans syndrome (BOS) remain major contributors to transplant-related morbidity and mortality. These investigators examined the effectiveness of alemtuzumab in the treatment of RAR (n = 12) and BOS (n = 10) after human lung transplantation. All patients failed conventional treatment with methylprednisolone and ATG and received strict infection prophylaxis. Alemtuzumab significantly improved histological rejection scores in RAR. Total rejection grade/biopsy was 1.98 +/- 0.25 preceding alemtuzumab versus 0.33 +/- 0.14 post-treatment, p < 0.0001 (with a similar number of biopsies/patient per respective time interval). Freedom from BOS was observed in 65 % of RAR patients 2 years after alemtuzumab treatment.
Although there was no statistically significant change in forced expiratory volume in 1 second (FEV1) before and after alemtuzumab treatment in patients with BOS, a stabilization or improvement in BOS grade occurred in 70% of patients. Patient survival 2 years after alemtuzumab for BOS was 69%. Despite a dramatic decline in CD4 counts in alemtuzumab-treated patients, only 1 patient developed a lethal infection. Thus, these findings provided the first evidence that alemtuzumab is a potentially useful therapy in lung transplant recipients with RAR or BOS.

Ciancio and Burke (2008) noted that kidney transplantation has become the treatment of choice for both the quality of life and survival in patients with end-stage renal disease (ESRD). However, the immunosuppressive regimen that allows optimal kidney transplant outcome remains elusive. One of the more promising induction agents, alemtuzumab, was introduced to kidney transplantation by Calne in the late 1990s with low dose cyclosporine A monotherapy, with the hope of establishing “prope” or near tolerance. Subsequent pilot studies with alemtuzumab alone or monotherapy (DSG, Rapa) demonstrated high rates of AR along with occasional humoral components that lead to abandoning the concept of alemtuzumab as a "magic bullet" to achieve tolerance, "prope" or otherwise. Many programs have since modified maintenance immunosuppression using low dose tacrolimus, and shown acceptable rates of AR, with relatively low incidence of viral infection and lympho-proliferative disorders along with cost benefit. However, there are only 3 prospective, randomized studies, which are small with 1 year or less follow-up, and most published series utilized historical control groups with relatively short follow-up. The authors stated that since extrapolation from short-term data is far from secure, long-term, prospective, randomized studies with alemtuzumab are needed to ascertain the optimal immunosuppressive regimen.
Shapiro et al (2007) employed antibody pre-conditioning with alemtuzumab and post-transplant immunosuppression with low-dose tacrolimus monotherapy in 26 consecutive pediatric kidney transplant recipients. Mean recipient age was 10.7 +/- 5.8 years, 7.7% were undergoing re-transplantation, and 3.8% were sensitized, with a panel reactive antibody greater than 20%. Mean donor age was 32.8 +/- 9.2 years. Living donors were utilized in 65% of the transplants. Mean cold ischemia time was 27.6 +/- 6.4 hours. The mean number of HLA mismatches was 3.3 +/- 1.3. Mean follow-up was 25 +/- 8 months. One- and 2-year patient survival was 100% and 96%, respectively. One- and 2-year graft survival was 96% and 88%, respectively. Mean serum creatinine was 1.1 +/- 0.6 mg/dL, and calculated creatinine clearance was 82.3 +/- 29.4 mL/min/1.73 m(2). The incidence of pre-weaning AR was 11.5%; the incidence of delayed graft function was 7.7%. Eighteen (69%) of the children were tapered to spaced tacrolimus monotherapy, 10.5 +/- 2.2 months after transplantation. The incidence of CMV, post-transplant lymphoproliferative disorder, and BK virus was 0%; the incidence of post-transplant diabetes was 7.7%. The authors stated that although more follow-up is clearly needed, antibody pre-conditioning with alemtuzumab and tacrolimus monotherapy may be a safe and effective regimen in pediatric renal transplantation.

In a long-term, prospective randomized study, Ciancio and colleagues (2008) examined thymoglobulin versus alemtuzumab (with lower dose maintenance immunosuppression) versus daclizumab in renal transplantation at 24 months of follow-up. A total of 90 deceased donor (DD) first renal transplant recipients were randomized into 3 different antibody induction groups: group A, thymoglobulin (Thymo); group B, alemtuzumab; and group C, daclizumab (Dac). In groups A and C, the target trough levels of tacrolimus were 8 to 10 ng/mL, 1 g of MMF was administered twice-daily with maintenance methylprednisolone. In group B, target tacrolimus trough
levels were 4 to 7 ng/mL, 500 mg MMF administered twice-daily, without methylprednisolone. African-Americans and Hispanics comprised more than 50% in each group. A minimum follow-up of 27 months showed no overall group differences in patient or graft survival (p = 0.89 and 0.66), but a trend toward worse death-censored graft survival in group B (p = 0.05). Acute rejection rates were not significantly different: 6 (20%), 7 (23%), and 7 (23%) in groups A, B, and C, respectively. The incidence of chronic allograft nephropathy was higher in group B than in groups A and C (p = 0.008). The mean calculated creatinine clearance at 24 months was 81.1 +/- 5.5, 64.4 +/- 4.5, and 80.7 +/- 5.7 in groups A, B, and C, respectively (p = 0.01 for B versus average of A and C). The authors concluded that in this randomized 27-month minimum follow-up trial of predominantly non-Caucasian DD renal transplant recipients with alemtuzumab induction, lower maintenance tacrolimus, MMF, and steroid avoidance appeared less effective than either Thymo or Dac with higher maintenance immunosuppression.

Gomez-Almaguer and co-workers (2008) evaluated the safety and effectiveness of alemtuzumab in treating steroid-refractory acute GVHD (aGVHD), greater than or equal to grade II following hematopoietic stem cell transplantation (HSCT). A total of 18 patients received subcutaneous alemtuzumab 10 mg daily on 5 consecutive days. Response was assessed at day 28 following initiation of alemtuzumab. Eight patients had grade II aGVHD, 8 had grade III, and 2 had grade IV. The main organ involved was the liver in 4 patients, gastrointestinal (GI) tract in 5, skin in 3, skin and liver in 3, and skin and GI tract in 3. Fifteen patients (83%) responded to alemtuzumab, including 6 (33%) with CR. All 3 unresponsive patients died of GVHD. Ten of 15 responders are alive at median follow-up of 11 months (range of 3 to 24 months). Infections occurred in 14 patients, including CMV re-activation in 11. Grade 3 neutropenia and thrombocytopenia occurred in 6 and 4
patients, respectively. The authors concluded that alemtuzumab was well-tolerated, and induced promising response rates in steroid-refractory aGVHD.

In a prospective randomized study, Margreiter and associates (2008) examined the use of alemtuzumab and tacrolimus monotherapy following deceased donor renal transplantation. A total of 65 patients in the study group received induction with alemtuzumab followed by delayed tacrolimus monotherapy, while the 66 patients in the control group were started on tacrolimus in combination with MMF and steroids. Tacrolimus levels of 8 to 12 ng/ml for the first 6 months and 5 to 8 ng/ml thereafter were aimed for in both groups. At 12 months the biopsy-proven rejection rate was 20 % in the study group and 32 % in the control group (p = 0.09). Patient survival at 1 year was 98 % for both groups. Graft survival was 96 % for the study group versus 90 % for the control group (p = 0.18). Graft function was identical in both groups. Adverse events were similar in both groups apart for more CMV infections in the study group. At the end of the first year 82 % of the patients in the study group were steroid-free and 71 % continued on tacrolimus monotherapy. These results suggested that alemtuzumab induction together with tacrolimus monotherapy is at least as efficient in renal transplantation as is a tacrolimus-based triple-drug regimen with a similar safety profile but more CMV infections.

Schadde et al (2008) compared outcomes of induction therapy with alemtuzumab with interleukin-2 (IL-2) receptor antagonists (RA) and anti-lymphocyte antibodies. These researchers employed a retrospective sequential study design to examine 170 recipients of kidneys from donor after cardiac death (DCD) for survival, graft survival, time to first rejection, glomerular filtration and complications. Patients were stratified into high-risk and low-risk groups based on the following criteria: panel of reactive antibodies greater than 20 %, re-transplantation, Afro-American race. Induction with alemtuzumab was compared with ATG in the high-risk and with IL-2RA in the low-
risk group. Patients received triple immunosuppression with steroids, MMF and calcineurin inhibitors. Patient survival, graft survival, rejection rate and glomerular filtration rate did not significantly differ between patients treated with alemtuzumab versus IL-2RAs or ATG. There was a trend towards reduced graft survival and patient survival in the alemtuzumab group. There was an increased incidence of CMV infections in the alemtuzumab-induced group and a trend towards increased BK virus and bacterial infections. Induction of DCD kidney transplants with alemtuzumab compared to IL-2RA and ATG has no significant impact on AR. It appears however that CMV infections are increased in patients induced with alemtuzumab. The authors concluded that induction with alemtuzumab does not confer any advantage over traditional induction agents.

In a meta-analysis, Shou et al (2009) examined the safety and effectiveness of induction therapy with alemtuzumab in kidney transplantation (KTx). Relevant papers were searched, essentially in the PubMed database and the Cochrane library. After a thorough review, randomized controlled trials (RCTs) comparing the outcome of KTx using alemtuzumab induction therapy (test group) with a control group were collected according to the inclusion criteria. Data of general characteristic of studies and major outcomes of KTx were extracted and meta-analyses were performed with RevMan 4.2 software. The odds ratio (OR) with a 95 % confidence intervals (CI) was the principle measurement of effect. A total of 5 RCTs were included. The Chi-square test showed no significant between-study heterogeneity, thus fixed effect model was employed. Sub-group analysis with studies including alemtuzumab induction followed by a tacrolimus-based immunosuppressive regimen showed that the acute rejection rate (ARR) was lower relative to the control (OR = 0.59, 95 % CI: 0.34 to 1.01, p = 0.05). However, meta-analysis with all included studies revealed that neither ARR nor patient/graft survival rates differ significantly between the test and the control group, but the CMV infection rate was
higher in the test group (OR 2.50, 95 % CI: 1.22 to 5.12, p = 0.01). A great number of the test group recipients safely remained on a regimen that was steroid-free and with a reduced dose of conventional immunosuppressive drugs. The authors concluded that alemtuzumab induction therapy for KTx was an effective and safe protocol in the tested follow-up period. Steroid avoidance and a dose reduction of conventional immunosuppressive drugs after alemtuzumab induction therapy may have clinical importance. However, they stated that high quality RCTs with larger population and longer follow-up are needed for a more accurate and objective appraisal of this novel protocol.

Rabie and Nevo (2009) noted that immune-mediated polyradiculoneuropathies are usually categorized into (i) Guillain-Barré syndrome (GBS), and (ii) chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). In children, sub-acute inflammatory demyelinating polyradiculoneuropathy is included in CIDP. Immune polyradiculoneuropathies are not exclusively demyelinating, and axonal forms also responding favorably to immunotherapy occur. Evidence-based data on efficacy of therapy in children is lacking, relying on retrospective data, open label studies on small numbers of children, and mainly adult derived data. Immunotherapy (intravenous immunoglobulin [IVIG] and plasmapheresis) shortens GBS recovery time with most children recovering completely. Childhood CIDP usually responds to steroids and slow tapering is required to prevent relapses. Plasmapheresis and IVIG are also effective. Children with CIDP who are resistant to steroids, IVIG, and steroid-dependent patients present a therapeutic challenge. Immunosuppressive agents including methotrexate, azathioprine and cyclosporine are helpful in some cases. Anecdotal reports of treatment with interferons alpha or beta and monoclonal antibodies against specific B-cell antigens (e.g., rituximab, alemtuzumab) have been described in limited case reports. Furthermore, in a review on current treatments
of CIDP (Brannagan, 2009), alemtuzumab is not listed as one of the therapeutic options.

Dalakas et al (2009) examine if one series of alemtuzumab infusions in patients with sporadic inclusion-body myositis (sIBM) depletes not only peripheral blood lymphocytes but also endomysial T cells and alters the natural course of the disease. A total of 13 sIBM patients with established 12-month natural history data received 0.3 mg/kg/day alemtuzumab for 4 days. The study was powered to capture greater than or equal to 10% increase strength 6 months after treatment. The primary end-point was disease stabilization compared to natural history, assessed by bi-monthly Quantitative Muscle Strength Testing and Medical Research Council strength measurements. Lymphocytes and T cell subsets were monitored concurrently in the blood and the repeated muscle biopsies. Alterations in the mRNA expression of inflammatory, stressor and degeneration-associated molecules were examined in the repeated biopsies. During a 12-month observation period, the patients' total strength had declined by a mean of 14.9% based on Quantitative Muscle Strength Testing. Six months after therapy, the overall decline was only 1.9% (p < 0.002), corresponding to a 13% differential gain. Among those patients, 4 improved by a mean of 10% and 6 reported improved performance of daily activities. The benefit was more evident by the Medical Research Council scales, which demonstrated a decline in the total scores by 13.8% during the observation period but an improvement by 11.4% (p < 0.001) after 6 months, reaching the level of strength recorded 12 months earlier. Depletion of peripheral blood lymphocytes, including the naive and memory CD8+ cells, was noted 2 weeks after treatment and persisted up to 6 months. The effector CD45RA(+)CD62L(-) cells, however, started to increase 2 months after therapy and peaked by the 4th month. Repeated muscle biopsies showed reduction of CD3 lymphocytes by a mean of 50% (p < 0.008), most prominent in the improved patients, and reduced mRNA expression of stressor molecules Fas, Mip-1a and alphaB-crystallin; the
mRNA of desmin, a regeneration-associated molecule, increased. This proof-of-principle study provided insights into the pathogenesis of inclusion-body myositis and concluded that in siIBM one series of alemtuzumab infusions can slow down disease progression up to 6 months, improve the strength of some patients, and reduce endomysial inflammation and stressor molecules. The authors stated that these encouraging results, the first in siIBM, warrant a future study with repeated infusions.

In a phase II clinical study, Angiolillo et al (2009) examined the effects of Campath-1H in children with relapsed or refractory acute lymphoblastic leukemia (ALL). A total of 13 eligible patients were enrolled in this trial. Campath-1H was initially administered as an intravenous infusion over 2 hrs, 5 times per week for 1 week, then 3 times per week for 3 additional weeks. Patients with SD or better on day 29 could continue on to combination therapy with Campath-1H, methotrexate, and 6-mercaptopurine for 2 additional cycles. One of 13 patients enrolled had a CR to Campath-1H and 4 had SD. Dose limiting toxicity occurred in 2 out of 9 fully evaluable patients (grade IV pain and grade III allergic reaction/hypersensitivity). No patients received combination therapy. Serum Campath-1H concentrations appeared to be somewhat lower in children with ALL compared with adult patients with CLL. The authors concluded that although a single CR was observed, activity of single agent Campath-1H appears limited. They stated that these findings do not support future single agent evaluation of Campath-1H in children with relapsed ALL.

Gotlib (2010) assessed recent developments in the classification and treatment of eosinophilic myeloid disorders in the context of reactive, lymphocyte-variant, and idiopathic eosinophilias. The revised 2008 World Health Organization (WHO) classification recognizes both molecularly defined (myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1) and undefined (chronic eosinophilic leukemia, not otherwise
specified) eosinophilic myeloid disorders. An increasingly sophisticated understanding of the molecular underpinnings of eosinophilia has translated into rational use of biologically targeted therapies such as imatinib mesylate. Conventional cytotoxics and interferon-alpha still have an established role in treating these diseases. Although studied in idiopathic hyper-eosinophilic syndrome, the therapeutic niche of mepolizumab and alemtuzumab antibody therapy in eosinophilic myeloid diseases has yet to be established.

Gotlib (2011) stated that the eosinophilias entail a broad range of non-hematological (secondary or reactive) and hematological (primary, clonal) disorders with potential for end-organ damage. Hyper-eosinophilia has generally been defined as a peripheral blood eosinophil count greater than 1,500/mm(3) and may be associated with tissue damage. After exclusion of secondary causes of eosinophilia, diagnostic evaluation of primary eosinophilias relies on a combination of morphologic review of the blood and marrow, standard cytogenetics, fluorescent in situ-hybridization, flow immunocytometry, and T-cell clonality assessment to detect histopathologic or clonal evidence for an acute or chronic myeloid or lymphoproliferative disorder. Disease prognosis relies on identifying the subtype of eosinophilia. After evaluation of secondary causes of eosinophilia, the 2008 WHO establishes a semi-molecular classification scheme of disease subtypes including myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1, chronic eosinophilic leukemia, not otherwise specified (CEL, NOS), lymphocyte-variant hypereosinophilia, and idiopathic hyper-eosinophilic syndrome (HES), which is a diagnosis of exclusion. The goal of therapy is to mitigate eosinophil-mediated organ damage. For patients with milder forms of eosinophilia (e.g. less than 1,500/mm(3)) without symptoms or signs of organ involvement, a watch and wait approach with close-follow-up may be undertaken. Identification of re-arranged PDGFRA or PDGFRB is critical because of the exquisite responsiveness of these diseases to
imatinib. Corticosteroids are first-line therapy for patients with lymphocyte-variant hypereosinophilia and HES. Hydroxyurea and interferon-alpha have demonstrated efficacy as initial treatment and steroid-refractory cases of HES. In addition to hydroxyurea, second line cytotoxic chemotherapy agents and hematopoietic stem cell transplantation have been used for aggressive forms of HES and CEL with outcomes reported for limited numbers of patients. Furthermore, the author noted that although clinical trials have been performed with anti IL-5 (mepolizumab) and anti-CD52 (alemtuzumab) antibodies, their therapeutic niche in primary eosinophilic diseases and HES have yet to be established.

Ong and Denton (2010) reviewed the evidence and recent developments leading to novel therapeutics in scleroderma. Recent advances have been made in understanding the key pathogenetic aspects of scleroderma, and these have led to potential targeted therapeutic agents for the management of these patients. Preliminary data from early clinical trials suggest that tyrosine kinase molecules may be potential candidates for therapy, especially in the fibrotic phase of the disease. On the basis of the new insights into the key role of effector T cells, in particular Th-17 and T regulatory subsets, T-cell-directed therapies including halofuginone, basiliximab, alemtuzumab, abatacept and rapamycin have been proposed to be clinically beneficial. By analogy, recent clinical studies with rituximab in diffuse cutaneous systemic sclerosis lend support that B cells may be important in the pathogenesis of the disease. Endothelin receptor antagonists, 3-Hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, and phosphodiesterase type V inhibitor have been shown to be useful to treat the vascular manifestations associated with systemic sclerosis. Hematopoietic stem cell transplantation following immune ablation holds considerable promise in resetting of the immune system, and trial results are awaited. The authors concluded that although there is still no treatment that is unequivocally effective for scleroderma, there have been some promising developments over the past number of
years with identification of novel candidate targets and innovative strategies, including targeted immunomodulatory therapies, tyrosine kinase inhibitors and agents that may promote vascular repair. They stated that these recent findings will need to be confirmed by larger, multi-center, RCTs.

In a pilot study, Risitano et al (2010) examined the effectiveness of alemtuzumab-based experimental immunosuppressive treatment (IST) regimen in 35 patients with severe aplastic anemia (AA), pure red cell (PRCA) or pure white cell aplasia (PWCA). Alemtuzumab total dose was 73 to 103 mg (subcutaneous), followed by cyclosporine. No serious toxicity due to the regimen was observed. Adverse events were clinically irrelevant; infectious events were rare. The total response rate was 58 %, 84 % and 100 % in severe AA, PRCA and PWCA, respectively, with corresponding 6-month cumulative response probabilities of 84 %, 84 % and 100 %.

The authors concluded that subcutaneous alemtuzumab is a feasible and sufficiently safe IST regimen for patients suffering from immune-mediated marrow failures. The findings of this pilot study were confounded by the concomitant use of alemtuzumab and cyclosporine. The authors also noted that these findings paved the way of systematic investigation in comparisons to standard immunosuppressive regimens.

Gomez-Almaguer et al (2010) treated 14 AA patients with alemtuzumab (median age of 23 years). Ten milligrams of alemtuzumab were injected subcutaneously each day for 5 consecutive days. Cyclosporine A was also administered orally at a dose of 2 mg/kg every 12 hrs for 3 months, and then gradually tapered. Response to alemtuzumab was followed for a median of 20 months. There were 8 responses (57.1 %), 2 complete and 6 partial. Whereas 6 (42.8 %) patients were non-responders. Median complete blood count values on alemtuzumab responders were Hb 13.1 mg/dL, absolute neutrophil count 2.4 x 10(9)/L, and platelets 97.5 x 10(9)/L.

The authors concluded that a good response was produced in
57% of AA patients with the administration of alemtuzumab, who lacked a stem cell donor. Again, the findings of this study were confounded by the concomitant use of alemtuzumab and cyclosporine. The authors also noted that more studies are needed regarding the use of alemtuzumab in AA.

Shukla et al (2012) noted that histiocytic sarcoma (HS) is an exceedingly rare tumor and carries a dismal prognosis when patients present with advanced-stage disease. Because of the poor response rates to conventional chemotherapy and the rarity of the disease, no standard of care exists for patients with HS. The authors reported the single-agent use of alemtuzumab in 2 patients who had advanced-stage HS. Two patients with chemotherapy-refractory, metastatic HS with tumors that expressed the CD52 antigen received a prolonged course of treatment with the anti-CD52 monoclonal antibody alemtuzumab. Resected tumor samples from both patients demonstrated CD52 expression. Both patients had marked responses to alemtuzumab. One patient had a CR with no evidence of disease for greater than 5 years. The second patient had a major response to alemtuzumab and also remained alive with no evidence of disease for greater than 4 years. The authors concluded that further studies need to be performed to examine CD52 expression and function in HS, as well as the role of alemtuzumab in a larger cohort of patients since the clinical impact of alemtuzumab in the 2 patients described in this report was very encouraging.

Tzachanis et al (2014) reported on the case of a 79-year old man with chronic lymphocytic leukemia who presented with GBS with features overlapping with the Miller Fisher syndrome and Bickerstaff brainstem encephalitis and positive anti-ganglioside GQ1b antibody about 6 months after treatment with bendamustine and rituximab. His clinical and neurologic condition continued to deteriorate despite sequential treatment with corticosteroids, IVIG and plasmapheresis, but in the end,
he had a complete and durable response to treatment with alemtuzumab. The findings of this single-case study needs to be validated by well-designed studies.

Menge and colleagues (2014) stated that alemtuzumab is a humanized monoclonal antibody that rapidly depletes CD52+ cells of the lymphoid lineage from peripheral blood, but spares lymphoid precursor cells. Clinical efficacy and safety data from clinical phase II and III trials -- all using interferon-β-1a as active comparator -- were summarized and placed in perspective. These researchers further analyzed the differential reconstitution of T and B cells as a potential mode of action and the pathogenic link to treatment-emergent secondary autoimmune conditions. Given recent positive opinions by regulatory agencies, this new drug will be positioned for the treatment of active relapsing-remitting MS and enlarge our therapeutic armamentarium. Moreover, they noted that Genzyme has announced that it is preparing to re-submit an application to the FDA for approval in the U.S. addressing the agency’s concerns.

Chow and Chan (2013) reported on the cases of 3 patients with pure red cell aplasia (with or without co-existing large granular lymphocytic leukemia, who remained transfusion-dependent despite treatment with established first-line therapy) who were treated with low-dose subcutaneous alemtuzumab 15 mg twice to thrice per week, for 3 to 4 weeks. The mean response time was 17 days compared with a response time of at least 61 days on standard first-line therapy. There were no serious side-effects and the mean duration of remission was 13 months. The authors concluded that low-dose subcutaneous alemtuzumab is a safe and effective treatment for pure red cell aplasia and further trials should be conducted to compare the long-term effectiveness of this treatment with conventional therapy.
Dvorak and colleagues (2014) stated that for infants with severe combined immunodeficiency (SCID) the ideal conditioning regimen before allogeneic hematopoietic cell transplantation would omit cytotoxic chemotherapy to minimize short- and long-term complications. These researchers performed a prospective pilot trial with alemtuzumab monotherapy to overcome natural killer-cell mediated immunologic barriers to engraftment. They enrolled 4 patients who received CD34-selected haploidentical cells, 2 of whom failed to engraft donor T cells. The 2 patients who engrafted had delayed T-cell reconstitution, despite rapid clearance of circulating alemtuzumab. The authors concluded that although well-tolerated, alemtuzumab failed to overcome immunologic barriers to donor engraftment. Furthermore, alemtuzumab may slow T-cell development in patients with SCID in the setting of a T-cell depleted graft.

Kim and colleagues (2014) stated that antibody-mediated rejection (AMR), also known as B-cell-mediated or humoral rejection, is a significant complication after kidney transplantation that carries a poor prognosis. Although fewer than 10% of kidney transplant patients experience AMR, as many as 30% of these patients experience graft loss as a consequence. Although AMR is mediated by antibodies against an allograft and results in histologic changes in allograft vasculature that differ from cellular rejection, it has not been recognized as a separate disease process until recently. With an improved understanding about the importance of the development of antibodies against allografts as well as complement activation, significant advances have occurred in the treatment of AMR. The standard of care for AMR includes plasmapheresis and IVIG that remove and neutralize antibodies, respectively. Agents targeting B cells (rituximab and alemtuzumab), plasma cells (bortezomib), and the complement system (eculizumab) have also been used successfully to treat AMR in kidney transplant recipients. The authors concluded that the high cost of these medications, their use for unlabeled indications, and a lack of prospective
studies evaluating their safety and effectiveness limit the routine use of these agents in the treatment of AMR in kidney transplant recipients.

The 3C Study Collaborative Group (Haynes et al, 2014) evaluated the safety and effectiveness of alemtuzumab-based induction treatment compared with basiliximab-based induction treatment in patients receiving kidney transplants. For this randomized trial, these researchers enrolled patients aged 18 years and older who were scheduled to receive a kidney transplant in the next 24 hours from 18 transplant centers in the UK. Using minimized randomization, these investigators randomly assigned patients (1:1; minimized for age, sex, and immunological risk) to either alemtuzumab-based induction treatment (i.e., alemtuzumab followed by low-dose tacrolimus and mycophenolate without steroids) or basiliximab-based induction treatment (basiliximab followed by standard-dose tacrolimus, mycophenolate, and prednisolone). Subjects were reviewed at discharge from hospital and at 1, 3, 6, 9, and 12 months after transplantation. The primary outcome was biopsy-proven acute rejection at 6 months, analyzed by intention to treat. Between Oct 4, 2010, and Jan 21, 2013, the authors randomly assigned 852 participants to treatment: 426 to alemtuzumab-based treatment and 426 to basiliximab-based treatment. Overall, individuals allocated to alemtuzumab-based treatment had a 58 % proportional reduction in biopsy-proven acute rejection compared with those allocated to basiliximab-based treatment (31 [7 %] patients in the alemtuzumab group versus 68 [16 %] patients in the basiliximab group; hazard ratio (HR) 0.42, 95 % CI: 0.28 to 0.64; log-rank p < 0.0001). They detected no between-group difference in treatment effect on transplant failure during the first 6 months (16 [4 %] patients versus 13 [3 %] patients; HR 1.23, 0.59 to 2.55; p = 0.58) or serious infection (135 [32 %] patients versus 136 [32 %] patients; HR 1.02, 0.80 to 1.29; p = 0.88). During the first 6 months after transplantation, 11 (3 %) patients given alemtuzumab-based treatment and 6 (1 %) patients given basiliximab-based treatment died (HR 1.79, 95
% CI: 0.66 to 4.83; p = 0.25). The authors concluded that compared with standard basiliximab-based treatment, alemtuzumab-based induction therapy followed by reduced CNI and mycophenolate exposure and steroid avoidance reduced the risk of biopsy-proven acute rejection in a broad range of patients receiving a kidney transplant. Moreover, they stated that long-term follow-up of this trial are needed to determine if these effects translate into differences in long-term transplant function and survival.

Hayes and colleagues (2014) noted that there is an increasing trend in the use of induction immunosuppression in children undergoing lung transplantation (LTx). To evaluate the effect of this practice on survival, the United Network for Organ Sharing (UNOS) was queried from 1987 to 2012, restricting analysis to transplant patients 6 to 17 years old from 2001 to 2012, who received no induction (NONE) or induction (INDUCED) with the contemporary agents of basiliximab, alemtuzumab, thymoglobulin, anti-lymphocyte globulin (ALG), or ATG. Of 23,951 lung transplants, 330 met inclusion criteria with 177 (54 %) being INDUCED. Of the INDUCED agents, 121 (68 %) were basiliximab, 3 (2 %) alemtuzumab, and 53 (30 %) ALG/ATG/thymoglobulin. The mean patient age was 13.6 (SD = 3.2) and 14 (SD = 3.0) years for the INDUCED and NONE groups, respectively. The median survival in the INDUCED group was 77.4 months (95 % CI: 46.1 to 125.6) compared with 50.8 months (95 % CI: 42.9 to 61.3) for the NONE (log-rank p-value = 0.3601). The most common cause of death was due to allograft failure or pulmonary complications with only 1 patient dying from post-transplant lymphoproliferative disorder. The estimated hazard ratio for INDUCED versus NONE was 0.859 (95 % CI: 0.620 to 1.191; p = 0.3618); there were no significant confounders or effect modifiers among the demographic and clinical variables. The authors concluded that antibody-based induction immunosuppression with contemporary agents had a trend toward a protective, but not statistically significant, effect in 6-to 17-year old patients.
Penninga and associates (2014) noted that liver transplantation is an established treatment option for end-stage liver failure. To-date, no consensus has been reached on the use of immunosuppressive T-cell antibody induction for preventing rejection after liver transplantation. In a Cochrane review, these investigators evaluated the benefits and harms of immunosuppressive T-cell specific antibody induction compared with placebo, no induction, or another type of T-cell specific antibody induction for prevention of acute rejection in liver transplant recipients. They searched The Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Science Citation Index Expanded, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) until September 2013. Randomized clinical trials assessing immunosuppression with T-cell specific antibody induction compared with placebo, no induction, or another type of antibody induction in liver transplant recipients were selected for analysis. The inclusion criteria stated that participants within each included trial should have received the same maintenance immunosuppressive therapy. These researchers planned to include trials with all of the different types of T-cell specific antibodies that are or have been used for induction (i.e., polyclonal antibodies (rabbit of horse ATG), or ALG), monoclonal antibodies (muromonab-CD3, anti-CD2, or alemtuzumab), and interleukin-2 receptor antagonists (daclizumab, basiliximab, BT563, or Lo-Tact-1)). The authors used RevMan analysis for statistical analysis of dichotomous data with risk ratio (RR) and of continuous data with mean difference (MD), both with 95 % CIs. They assessed the risk of systematic errors (bias) using bias risk domains with definitions. They used trial sequential analysis to control for random errors (play of chance) and presented outcome results in a summary of findings table.

These investigators included 19 RCTs with a total of 2,067 liver transplant recipients. All 19 trials were with high risk of bias. Of the 19 trials, 16 trials were 2-arm trials, and 3 trials
were 3-arm trials. The authors found 25 trial comparisons with antibody induction agents: interleukin-2 receptor antagonist (IL-2 RA) versus no induction (10 trials with 1,454 participants); monoclonal antibody versus no induction (5 trials with 398 subjects); polyclonal antibody versus no induction (3 trials with 145 participants); IL-2 RA versus monoclonal antibody (1 trial with 87 participants); and IL-2 RA versus polyclonal antibody (2 trials with 112 participants). Thus, these researchers were able to compare T-cell specific antibody induction versus no induction (17 trials with a total of 1,955 participants). Overall, no difference in mortality (RR 0.91; 95 % CI: 0.64 to 1.28; low-quality of evidence), graft loss including death (RR 0.92; 95 % CI: 0.71 to 1.19; low-quality of evidence), and adverse events ((RR 0.97; 95 % CI: 0.93 to 1.02; low-quality evidence) outcomes was observed between any kind of T-cell specific antibody induction compared with no induction when the T-cell specific antibody induction agents were analyzed together or separately. Acute rejection seemed to be reduced when any kind of T-cell specific antibody induction was compared with no induction (RR 0.85, 95 % CI: 0.75 to 0.96; moderate-quality evidence), and when trial sequential analysis was applied, the trial sequential monitoring boundary for benefit was crossed before the required information size was obtained. Furthermore, serum creatinine was statistically significantly higher when T-cell specific antibody induction was compared with no induction (MD 3.77 μmol/L, 95 % CI: 0.33 to 7.21; low-quality evidence), as well as when polyclonal T-cell specific antibody induction was compared with no induction, but this small difference was not clinically significant. These investigators found no statistically significant differences for any of the remaining predefined outcomes -- infection, cytomegalovirus infection, hepatitis C recurrence, malignancy, post-transplant lymphoproliferative disease, renal failure requiring dialysis, hyperlipidemia, diabetes mellitus, and hypertension -- when the T-cell specific antibody induction agents were analyzed together or separately. Limited data were available for meta-analysis on drug-specific adverse events such as hematological adverse
events for ATG. No data were found on quality of life. When T-cell specific antibody induction agents were compared with another type of antibody induction, no statistically significant differences were found for mortality, graft loss, and acute rejection for the separate analyses. When interleukin-2 receptor antagonists were compared with polyclonal T-cell specific antibody induction, drug-related adverse events were less common among participants treated with interleukin-2 receptor antagonists (RR 0.23, 95% CI: 0.09 to 0.63; low-quality evidence), but this was caused by the results from 1 trial, and trial sequential analysis could not exclude random errors. These researchers found no statistically significant differences for any of the remaining pre-defined outcomes: infection, cytomegalovirus infection, hepatitis C recurrence, malignancy, post-transplant lymphoproliferative disease, renal failure requiring dialysis, hyperlipidemia, diabetes mellitus, and hypertension. No data were found on quality of life. The authors concluded that the effects of T-cell antibody induction remain uncertain because of the high risk of bias of the RCTs, the small number of RCTs reported, and the limited numbers of participants and outcomes in the trials. They noted that T-cell specific antibody induction seems to reduce acute rejection when compared with no induction. No other clear benefits or harms were associated with the use of any kind of T-cell specific antibody induction compared with no induction, or when compared with another type of T-cell specific antibody. They stated that more RCTs are needed to assess the benefits and harms of T-cell specific antibody induction compared with placebo, and compared with another type of antibody, for prevention of rejection in liver transplant recipients. They stated that such trials ought to be conducted with low risks of systematic error (bias) and low risk of random error (play of chance).

Simonini and colleagues (2015) examined in children and adults with autoimmune chronic uveitis (ACU), the evidence regarding the effectiveness and the safety of switching to a non-anti-TNF biologic modifier immunosuppressant treatment
(NTT) currently available in clinical practice. These investigators performed a systematic search between January 2000 and April 2014 using EMBASE, Ovid MEDLINE, Evidence Based Medicine Reviews-ACP Journal Club, Cochrane libraries, and EBM Reviews. Studies investigating the effectiveness of NTT as a biologic modifier immunosuppressant medication for ACU, refractory to topical and/or systemic steroid therapy, were eligible for inclusion. The primary outcome measure was the improvement of intraocular inflammation, as defined by the Standardization of the Uveitis Nomenclature (SUN) working group criteria. These researchers determined a combined estimate of the proportion of subjects responding to NTT. They initially identified 526 articles, of which 89 were potentially eligible. From the selection process, a total of 10 retrospective chart reviews and a randomized single-blind controlled study, providing a total of 12 children and 34 adults, were deemed eligible: 3 articles looked at rituximab, 3 at abatacept, 3 at tocilizumab, and the remaining 1 at alemtuzumab and the other at anakinra. Before the NTT treatment, all the eligible subjects received several combinations of 1 or more disease modifying anti-rheumatic drugs (DMARDs) and at least 1 anti-TNF strategy. With the exclusion of 7 adults enrolled in the RCT, 8 of 12 children and 18 of 27 adults responded to NTT treatment: 0.66 was the combined estimate of the proportion of subjects improving on NTT treatment in children (95% CI: 0.46 to 0.99) and in adults (95% CI: 0.49 to 0.84). Further statistical comparison between different NTT strategies was not possible due to the small sample size. The authors concluded that although RCTs are needed, the available evidence suggests the clinical use of a NTT strategy in selected categories of ACU, refractory to previous course of immunosuppressive treatment, DMARDs, as well as anti-TNFα, in adults as well as children. 

Alemtuzumab is usually administered as an intravenous infusion over a 2-hr period. The most common side effects associated with its use are infusion reactions (e.g., chills, dyspnea, hypotension, nausea, pyrexia, rash, tachycardia, and
urticaria), cytopenias (e.g., anemia, lymphopenia, neutropenia, and thrombocytopenia), immunosuppression/infections (e.g., CMV infection, CMV viremia, and other infections), GI symptoms (e.g., emesis, nausea, and abdominal pain), and neurological symptoms (e.g., anxiety and insomnia).

Kidney Transplantation

In a meta-analysis, Zheng and Song (2017) compared the benefits and safety of alemtuzumab (ALEM) with those of antithymocyte globulin (ATG) for induction therapy. A systematic literature search in 3 electronic databases, including PubMed, EmBase, and Cochrane Library, since inception through October 2016, was conducted to identify potential RCTs for inclusion. Trials that investigated the risk of biopsy-proven acute rejection (BPAR), mortality, graft failure, delayed graft function (DGF), chronic allograft nephropathy (CAN), infections, cytomegalovirus (CMV) infections, new-onset diabetes mellitus after transplant (NODAT), and granulocyte colony stimulation factor (GCSF) use in kidney transplant recipients who received ALEM or ATG as an induction therapy were included. Relative risk (RR) and 95% CIs were calculated using a random-effects model. A total of 6 RCTs involving 446 kidney transplantation patients were included in this analysis. The effects of ALEM therapy were not significantly different from those of ATG therapy, including the incidence of BPAR (RR: 0.77; 95% CI: 0.51 to 1.18; p=0.229), mortality (RR: 0.64; 95% CI: 0.30 to 1.39; p=0.263), graft failure (RR: 0.81; 95% CI: 0.49 to 1.33; p=0.411), DGF (RR: 1.00; 95% CI: 0.60 to 1.67; p=0.999), CAN (RR: 1.42; 95% CI: 0.44 to 4.57; p=0.556), infections (RR: 1.00; 95% CI: 0.74 to 1.35; p=0.999), CMV infections (RR: 0.70; 95% CI: 0.38 to 1.30; p=0.263), NODAT (RR: 0.50; 95% CI: 0.18 to 1.36; p=0.174), and GCSF use (RR: 1.16; 95% CI: 0.81 to 1.66; p=0.413). Sensitivity analyses were consistent with the overall analysis for all effects except CAN, suggesting that the risk of CAN might be higher with ALEM therapy than ATG therapy (RR: 2.45; 95% CI: 1.02 to 5.94; p=0.046). The authors
concluded that the findings of this study suggested that the beneficial effects of ALEM therapy were greater than those of ATG therapy in kidney transplantation patients; however, the effects were not statistically significant because of the limited number of trials. They stated that further large-scale RCTs are needed to verify the treatment effects of ALEM.

van der Zwan and colleagues (2018) reviewed the pharmacokinetics, pharmacodynamics, and use of ALEM in kidney transplantation. A systematic literature search was conducted using Ovid Medline, Embase, and Cochrane Central Register of controlled trials. No pharmacokinetic or dose-finding studies of ALEM have been performed in kidney transplantation. Although such studies were conducted in patients with CLL and MS, these findings could not be directly extrapolated to transplant recipients, because CLL patients have a much higher load of CD52-positive cells and, therefore, target-mediated clearance will differ between these 2 indications. Alemtuzumab used as induction therapy in kidney transplantation resulted in a lower incidence of acute rejection compared to basiliximab therapy and comparable results as compared with rabbit ATG (rATG). Alemtuzumab used as anti-rejection therapy resulted in a comparable graft survival rate compared with rATG, although infusion-related side effects appeared to be less. The authors concluded that there is a need for pharmacokinetic and dose-finding studies of ALEM in kidney transplant recipients to establish the optimal balance between efficacy and toxicity. Furthermore, RCTs with sufficient follow-up are needed to provide further evidence for the treatment of severe kidney transplant rejection.

Sparkes and colleagues (2019) performed a 12-month, prospective, non-randomized, open-label, single-center, pilot study to examine the use of belatacept therapy combined with alemtuzumab induction in renal allografts with pre-existing pathology, as these kidneys may be more susceptible to additional toxicity when exposed to calcineurin inhibitors post-transplant. A total of 19 belatacept recipients were matched
retrospectively to a cohort of tacrolimus recipients on the basis of pre-implantation pathology. The estimated glomerular filtration rate (GFR) was not significantly different between belatacept and tacrolimus recipients at either 3 or 12 months post-transplant (59 versus 45, p = 0.1 and 56 versus 48 ml/min/1.72/m², p = 0.3). Biopsy-proven acute rejection rates at 12 months were 26% in belatacept recipients and 16% in tacrolimus recipients (p = 0.7). Graft survival at 1 year was 89% in both groups. Alemtuzumab induction combined with either calcineurin inhibitor or co-stimulatory blockade therapies resulted in similar acceptable 1-year outcomes in kidneys with pre-existing pathologic changes. The authors stated that longer-term follow-up are needed to identify preferential strategies to improve outcomes of kidneys at a higher risk for poor function.

van der Zwan and colleagues (2020) noted that rATG is currently the treatment of choice for glucocorticoid-resistant, recurrent, or severe AR. However, rATG is associated with severe infusion-related side effects. Alemtuzumab is incidentally given to kidney transplant recipients as treatment for AR. In the current study, the outcomes of patients treated with alemtuzumab for AR were compared with those of patients treated with rATG for AR. The patient-, allograft-, and infection-free survival and adverse events (AEs) of 116 alemtuzumab-treated patients were compared with those of 108 patients treated with rATG for AR. Propensity scores were used to control for differences between the 2 groups. Patient- and allograft-survival of patients treated with either alemtuzumab or rATG were not different [HR 1.14, 95% CI: 0.48 to 2.69, p = 0.77, and HR 0.82, 95% CI: 0.45 to 1.5, p = 0.52, respectively]. Infection-free survival after alemtuzumab treatment was superior compared with that of rATG-treated patients (HR 0.41, 95% CI: 0.25 to 0.68, p < 0.002). Infusion-related AEs occurred less frequently after alemtuzumab treatment. The authors concluded that alemtuzumab therapy may therefore be an alternative therapy for glucocorticoid-resistant, recurrent, or severe acute kidney transplant
rejection. Moreover, these researchers stated that further studies, preferably multi-center RCTs, are needed to examine the potential advantages of alemtuzumab for severe rejection.

The authors stated that this study had several drawbacks. First, this was a retrospective single-center study. Second, several variables (including time period, the use of induction therapy and others) were different between the patients treated with alemtuzumab and the patients treated with rATG. A propensity score analysis was performed to correct for potential differences between the alemtuzumab and rATG group, however, these investigators could not exclude the possibility that other (unmeasured) confounding factors influenced the outcomes of this analysis. Currently, these data offer the best available evidence for the treatment of AR with alemtuzumab as it is unlikely that a RCT comparing alemtuzumab with other anti-rejection therapies will be performed anytime soon. Third, the allograft survival of patients who were treated with alemtuzumab appeared (although not significant) to be worse compared with rATG-treated patients. Again, these researchers could not exclude the possibility that inclusion of more patients may have resulted in a significant difference between the 2 groups. Fourth, in this trial, 93.8 % of alemtuzumab-treated patients were treated with basiliximab induction therapy. In the U.S., only 33.8 % of kidney transplant recipients are treated with basiliximab, whereas 65.9 % of patients receive induction therapy with T cell-depleting antibodies. These researchers did not know the influence of this difference on the outcomes after alemtuzumab therapy for AR. Fifth, due to the unavailability of data on donor-specific anti-HLA antibodies in the rATG-treated patients, it was not possible to apply the Banff 2017 classification on biopsies of these patients, which may have biased the diagnosis of acute antibody-mediated rejection.

**Autoimmune Hemolytic Anemia**
McAlister and colleagues (2019) noted that autoimmune hemolytic anemia occurs as a consequence of an interaction of IgG antibodies with protein antigens expressed on red blood corpuscles. Glucocorticoids are the mainstay of treatment for autoimmune hemolytic anemia. For patients not responding to initial therapy, other agents such as rituximab, immunosuppressive therapy, or splenectomy are considered. When refractory to these treatment options, alemtuzumab is an alternative agent. However, long-term outcomes of patients supporting its use are lacking. These researchers presented 3 patients with refractory autoimmune hemolytic anemia treated with alemtuzumab.

An UpToDate review on "Autoimmune hemolytic anemia in children: Treatment and outcome" (Ware, 2018) does not mention alemtuzumab as a therapeutic option.

Furthermore, an UpToDate review on "Warm autoimmune hemolytic anemia: Treatment" (Schrier, 2018) states that "Less experience is available with use of the monoclonal anti-CD52 antibody alemtuzumab (Campath-1H), alone or in combination with low-dose rituximab, which may be associated with disease response but also with profound immunosuppression and development of opportunistic infections".

Malignant Histiocytosis

Abid and colleagues (2017) noted that secondary malignant histiocytosis (SMH) is an exceedingly rare, life-threatening condition that invariably occurs in the presence of an underlying monoclonal hematologic disorder. Prognosis of SMH remains dismal and there is no established treatment. These investigators reported a case of a patient who developed SMH during induction chemotherapy for his underlying pre-B-ALL, that caused persistently high fevers and was only diagnosed by a marrow while cytopenic in phase II induction. He was treated with alemtuzumab-based therapy that reduced the histiocytic infiltration of the bone marrow from
80% to 15% and made him eligible to undergo T-cell replete allogeneic stem transplantation from his sibling. The authors concluded that this report was the first to highlight the role of alemtuzumab in clonal disorders originating from transdifferentiation. They stated that the alemtuzumab-based regimen should be reserved only for carefully selected allogeneic transplant patients Moreover, they stated that further studies are needed to better understand the transdifferentiation phenomenon involved in SMH so that specific molecular targets can be identified in order to improve the dismal outlook associated with SMH.

Myelin Oligodendrocyte Glycoprotein (MOG)-Associated Encephalomyelitis

Wildemann and colleagues (2017) stated that myelin oligodendrocyte glycoprotein (MOG) immunoglobulin G (IgG)-associated encephalomyelitis (EM) is a rare autoimmune disorder that displays substantial clinic-radiologic overlap with aquaporin-4 (AQP4)-IgG-seropositive neuromyelitis optica spectrum disorders (NMOSD) and classic multiple sclerosis (MS). The long-term outcome is often poor. Recent evidence suggested that many disease-modifying agents approved for the treatment of MS may be ineffective or even harmful in AQP4-IgG-positive and MOG-IgG-positive patients. These investigators reported on the use of alemtuzumab in a patient with MOG-EM. Treatment with alemtuzumab was paralleled by the occurrence of several new relapses and of multiple new brain and spinal cord lesions, corroborating the hypothesis that MS and MOG-EM are 2 immuno-pathophysiologically distinct diseases requiring differential treatment. The authors concluded that although the optimal long-term treatment of patients with MOG-EM remains speculative, therapeutic depletion of B cells may be particularly useful in this rare disorder and thus may turn out to be the most promising strategy to counteract both antibody-associated autoimmune disorders of the CNS and classic MS.
Rasmussen Encephalitis

Liba and colleagues (2017) noted that Rasmussen encephalitis (RE) is a rare but devastating uni-hemispheric brain disorder that often affects children. The clinical picture is characterized by intractable focal epilepsy and progressive decline of functions associated with the affected hemisphere. Despite its known inflammatory background and T-cell involvement, immunotherapy appears to slow rather than halt disease progression, and hemispherotomy appears to be the only solution for intractable epilepsy. A potential early therapeutic window has been suggested, and new therapeutic agents have become available. Alemtuzumab has previously been considered as a possible treatment option for RE, but clinical data are limited. In a single-case study, these researchers examined the effects of alemtuzumab and intrathecal methotrexate in the treatment of Rasmussen encephalitis. The objective of this combined therapy was to deplete T cells from the peripheral blood and influence the inflammatory process behind the blood-brain barrier. However, the patient (7-year old boy) experienced a life-threatening systemic reaction immediately after alemtuzumab administration and later on, the clinical stabilization seemed to be dependent on intrathecal MTX. It was not possible to continue with this therapy because of its known cumulative side effects and neurotoxicity. The authors believed the brain biopsy demonstrated that it was possible to temporarily control brain inflammation, but at the cost of inappropriate risks. They hypothesized that their aggressive immunotherapy failed for the following reasons: First, they missed the early therapeutic window, and secondly, the pathology of RE is more complex, and the immunosuppression was not enough to cure the disease.

Systemic Lupus Erythematosus
Burt and colleagues (2018) noted that some patients with systemic lupus erythematosus (SLE) are refractory to traditional therapies, dependent on chronic corticosteroids, have organ damage, and are at high risk of mortality. In this group of patients, these investigators reported outcome at a median of 5 years after autologous hematopoietic stem cell transplant (HSCT) using 2 different non-myeloablative regimens; 4 patients received a conditioning regimen of cyclophosphamide (200 mg/kg) and alemtuzumab (60 mg), while 26 patients underwent conditioning with cyclophosphamide (200 mg/kg), rATG (Thymoglobulin) (55 mg/kg), and rituximab 1000 mg. Unselected peripheral blood stem cells were infused on day 0. There were no treatment related deaths. Of the 4 patients treated with cyclophosphamide and alemtuzumab, none entered remission. For the 26 patients treated with cyclophosphamide, rATG, and rituximab, disease remission defined as no immune suppressive drugs except hydroxychloroquine and/or 10 mg or less of prednisone a day was 92 % at 6 months, 92 % at 1 year, 81 % at 2 years, 71 % at 3 years, and 62 % at 4 and 5 years post-HSCT. The authors concluded that autologous HSCT outcome is dependent on the conditioning regimen but prior organ damage may cause lingering symptoms.

Furthermore, an UpToDate review on "Overview of the management and prognosis of systemic lupus erythematosus in adults" (Wallace, 2018) does not mention alemtuzumab as a therapeutic option.

Heart Transplantation

Li and associates (2018) stated that heart transplantation (HT) and lung transplantation (LT) are high-risk procedures, requiring intensive immunosuppressive therapy for preventing organ rejection. Alemtuzumab is increasingly used for induction therapy compared with conventional agents. In a systematic review and meta-analysis, these researchers compared the efficacy of alemtuzumab with traditional
therapeutic drugs. PubMed and Embase were searched to October 1, 2017, for articles on alemtuzumab in cardio-thoracic transplant surgery. Of the 433 studies retrieved, 8 were included in the final meta-analysis. In LT, alemtuzumab use was associated with lower odds of acute cellular rejection (ACR) compared with ATG (OR, 0.21; 95% CI: 0.11 to 0.40; p < 0.001), lower ACRs (OR, 0.12; 95% CI: 0.03 to 0.55; p < 0.01), and lower infection rates (OR, 0.69; 95% CI: 0.35 to 1.36; p = 0.33) when compared with basiliximab. Multi-variate meta-regression analysis found that mean age, male sex, single lung transplant, double lung transplant, CMV or Epstein-Barr virus (EBV) status, idiopathic pulmonary fibrosis, cystic fibrosis, and mean ischemic time did not significantly influence acute rejection outcomes. For HT, alemtuzumab use was associated with lower ACRs when compared with tacrolimus (OR, 0.44; 95% CI: 0.30 to 0.66; p < 0.001). The authors concluded that alemtuzumab use was associated with lower rejection rates when compared with conventional induction therapy agents (ATG, basiliximab, and tacrolimus) in HT and LT; however, this was based on observational studies. These researchers stated that RCTs are needed to verify its clinical use.

Gale and colleagues (2019) noted that the use of alemtuzumab for induction therapy in orthotopic heart transplantation (HT) remains controversial, despite its observed benefits in other transplant populations. These researchers examined if alemtuzumab conferred a lower risk of rejection while reducing toxicities commonly attributed to standard immunosuppression in orthotopic HT. They included adult patients who underwent orthotopic HT and received induction therapy with alemtuzumab (n = 26) or standard immunosuppression (n = 26). The primary end-point was freedom from grade greater than or equal to 2 rejection at 12 months. Baseline characteristics were similar between the groups with the exception of poorer renal function in the alemtuzumab group (p < 0.05). The primary end-point of freedom from grade greater than or equal to 2 rejection at 12
months was not different between alemtuzumab and standard therapy (76.9 % versus 96.2 %, p = 0.077), likely due to similarities in the rates of AMR in the 2 groups. However, grade greater than or equal to 2 ACR was considerably lower with alemtuzumab (0 % versus 19.2 %, p = 0.02), as was ACR of any severity (50 % versus 7.7 %, p = 0.004). Deterioration in renal function was significantly greater among patients receiving standard therapy as evidenced by decreases in GFR (-25.6 versus -9.2 ml/min, p = 0.032). No differences in hematologic or infectious complications were observed. The authors concluded that alemtuzumab reduced several important rejection-related outcomes while ameliorating the toxicities associated with standard immunosuppression therapy, making it a promising agent for induction in orthotopic HT.

Lung Transplantation

Benazzo and colleagues (2019) noted that the value of induction therapy in lung transplantation is controversial. According to the International Society of Heart and Lung Transplantation (ISHLT), only about 50 % of patients transplanted within the last 10 years received induction therapy. In a retrospective analysis, these investigators reviewed their institutional experience to examine the impact of induction therapy on short- and long-term outcomes. Between 2007 and 2015, a total of 446 patients with a complete follow-up were included in this study. Analysis comprised long-term kidney function, infectious complications, incidence of rejection and OS. A total of 231 patients received alemtuzumab, 50 patients ATG and 165 patients did not receive induction therapy (NI). The alemtuzumab-treated group revealed the lowest rate of chronic kidney insufficiency (NI: 52.2 %; ATG: 60 %; alemtuzumab: 36.6 %; p = 0.001). Both the NI group (p < 0.001) and the ATG group (p = 0.010) showed a significant increase of serum creatinine during follow-up compared to alemtuzumab-treated patients. Furthermore, the alemtuzumab-treated group experienced the
lowest rate of infection in the 1st year following transplantation. Finally, improved survival, low rates of ACR, lymphocytic bronchiolitis (LB) and chronic lung allograft dysfunction (CLAD) were found in patients treated either with alemtuzumab or ATG. The authors concluded that alemtuzumab induction therapy followed by reduced maintenance immunosuppression was associated with a better kidney function compared to no induction and ATG. Survival rate as well as freedom from ACR and CLAD were comparable between alemtuzumab and ATG. These researchers stated that based on these findings, they are currently plan a prospective, randomized trial to further reduce the cumulative dose of tacrolimus and to examine the immunomodulatory potential of alemtuzumab.

The authors stated that this study had several drawbacks. First, it was based on a retrospective analysis, including patients from a single center. Compositions of the groups were naturally influenced by changes in the institutional routine and by availability of specific treatment possibilities. In order to mitigate these limitations, these investigators performed a multi-variable analysis adjusting for time-effect. Second, an era effect could not be excluded since alemtuzumab was the most recently introduced induction therapy. Thus, the results might partially reflected recent improvements of post-operative care and long-term follow-up and not the specific immunosuppression regimen. Third, patients were not routinely screened for donor specific antibody formation and similarly, diagnostic work-up for AMR became a clinical routine only in the last years. Thus, this could not be examined in this retrospective study.

**Natural Killer (NK) Cell Lymphoma**

In a phase-I/II clinical trial, Roswarski and colleagues (2019) examined the feasibility and clinical efficacy of the combination of alemtuzumab with dose-adjusted etoposide / cyclophosphamide / doxorubicin / vincristine / prednisone (DA-EPOCH) as up-front therapy for untreated aggressive T-cell
and NK-cell lymphomas. A total of 30 patients were treated with the study regimen, consisting of alemtuzumab on day 1 of a 21-day cycle with standard dosing of DA-EPOCH for 6 to 8 cycles. Alemtuzumab 30-mg IV was used for the phase-II component. Of 30 treated patients, 17 had a CR and 8 had a PR (83.3 % ORR). The median OS and PFS were 20.2 and 6.6 months, respectively. There were 5 treatment-related deaths on study mainly due to infectious complications, including 1 case each of disseminated toxoplasmosis and pneumonia and 2 cases of sepsis. The authors concluded that alemtuzumab with DA-EPOCH was of limited clinical utility due to unacceptable toxicity, despite the high rate of CR.

**Sporadic Inclusion Body Myositis**

Ioannis and colleagues (2019) noted that sporadic inclusion body myositis is the most common inflammatory myopathy over the age of 50. The etiopathogenesis of the disease remains unclear and there is no effective treatment. These investigators reviewed the latest evidence in the treatment of sporadic inclusion body myositis, focusing on alemtuzumab and bimagrumab. They searched multiple Internet databases to find the most recent studies and clinical trials on the safety, tolerability and efficacy of alemtuzumab and bimagrumab in sporadic inclusion body myositis. These researchers found 1 small series trial on alemtuzumab, and 4 trials on bimagrumab, with 1 of them being an extension phase-III clinical trial. The first clinco-pathological trial on bimagrumab showed promising evidence; the findings were partially confirmed by the double-blinded controlled multi-center trial, however the primary end-point of improving 6-meter walking distance (6MWD) or improving the muscle strength has not been reached. The evidence from the alemtuzumab trial was also promising, however the risk of bias of the study was relatively high, because it was an open-label study, the number of patient was low, and the yearly disease progression was much higher than in other recent studies. The authors concluded that although both alemtuzumab and bimagrumab
were well-tolerated and showed promising results, the alemtuzumab trial had a relatively high-risk of bias, the bimagrumab trial did not reach the primary end-point; these findings need to be interpreted with caution.

**T-Cell Non-Hodgkin Lymphoma**

Poggio and colleagues (2018) stated that T-cell non-Hodgkin lymphoma (T-NHL) is a rare and heterogeneous group of neoplasms of the lymphoid system. With the exception of a few relatively indolent entities, T-NHL is typically aggressive, treatment resistant, and associated with poor prognosis. Relatively few options with proven clinical benefit are available for patients with relapsed or refractory disease. Immunotherapy has emerged as a promising treatment for the management of patients with hematological malignancies. The identification of tumor antigens has provided a large number of potential targets. Thus, several monoclonal antibodies (alemtuzumab, SGN-30, brentuximab vedotin, and mogamulizumab), directed against tumor antigens, have been examined in different subtypes of T-NHL. In addition to targeting antigens involved in cancer cell physiology, antibodies can stimulate immune effector functions or counteract immunosuppressive mechanisms. Chimeric antigen receptor (CAR)-T cells directed against CD30 and immune checkpoint inhibitors are currently being investigated in clinical trials. The authors concluded that current patient outcomes high-lighted the need for additional therapies and novel regimens in relapsed and refractory T-NHL.

**National Comprehensive Cancer Network (NCCN) Recommendations**

The NCCN Drugs & Biologics Compendium (NCCN, 2019) recommends the use of alemtuzumab for the following indications:
**Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma**

- Therapy for relapsed or refractory disease with or without del(17p)/TP53 mutation as a single agent or in combination with rituximab in patients with indications for treatment. [2A]

- First-line therapy with or without rituximab for CLL/SLL with del(17p)/TP53 mutation in patients with indications for treatment [2A]

**Primary Cutaneous Lymphomas**

**Mycosis Fungoides/Sezary Syndrome**

- Systemic therapy as primary treatment for [2A]
  - stage III MF
  - stage IV Sezary syndrome

- Systemic therapy as treatment for [2A]
  - relapsed or persistent stage IA mycosis fungoides (MF) with B1 blood involvement, with or without skin-directed therapy
  - relapsed or persistent stage IB-IIA MF with B1 blood involvement, with or without skin-directed therapy
  - stage IIB MF with limited tumor lesions refractory to multiple previous therapies, with or without skin-directed therapy
  - relapsed or refractory stage IIB MF with generalized tumor lesions, with or without skin-directed therapies
  - stage IIB MF with generalized tumor lesions that is refractory to multiple previous therapies or progression
  - relapsed or persistent stage III MF, with or without skin-directed therapies
• stage III MF that is refractory to multiple previous therapies
• relapsed or persistent stage IV Sezary syndrome
• relapsed or persistent stage IV non Sezary or visceral disease (solid organ), with or without radiation therapy for local control
• large cell transformation (LCT) with limited cutaneous lesions that is refractory to multiple previous therapies
• relapsed or persistent LCT with generalized cutaneous or extracutaneous lesions, with or without skin-directed therapy

Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders

• Therapy for primary cutaneous anaplastic large cell lymphoma (ALCL) with multifocal lesions, or cutaneous ALCL with regional nodes (excludes systemic ALCL), as a single agent for relapsed/refractory disease [2A]

T-Cell Lymphomas

Adult T-Cell Leukemia/Lymphoma

• Second-line or subsequent therapy as a single agent for nonresponders to first-line therapy for acute or lymphoma subtypes [2A]

Hepatosplenic Gamma-Delta T-Cell

• Second-line and subsequent therapy as a single agent for refractory disease after 2 primary treatment regimens in patients with no intention to transplant [2A]

Granular Lymphocytic Leukemia
• Second-line therapy for patients with progressive or refractory disease to all first-line therapies as a single agent [2A]

Peripheral T-Cell Lymphomas

• Second-line and subsequent therapy for relapsed/refractory peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, nodal peripheral T-cell lymphoma with TFH phenotype, or follicular T-cell lymphoma, in patients with no intention to transplant as a single agent [2A]

T-Cell Prolymphocytic Leukemia

• Used for symptomatic disease as a single agent (preferred), following FMC (fludarabine, mitoxantrone, cyclophosphamide), or in combination with pentostatin as [2A]

  • primary treatment
  • second-line therapy if no response or progressive disease following primary treatment

Appendix

Note on US Campath Distribution Program:

Genzyme has developed the Campath Distribution Program to ensure continued access to Campath (alemtuzumab) for appropriate patients. Effective September 4, 2012 Campath will no longer be available commercially, but will be provided through the Campath Distribution Program free of charge. In
order to receive Campath, the healthcare provider is required to document and comply with certain requirements. Please contact the numbers below to learn more.

Campath Distribution Program: 1-877-422-6728

Genzyme Medical Information: 1-800-745-4447 Option #2

Website: Campath (http://www.campath.com).

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+#":

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<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other CPT codes related to the CPB:</td>
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<tr>
<td>38204</td>
<td>Bone marrow or stem cell services/procedures</td>
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<tr>
<td>38242</td>
<td></td>
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<tr>
<td>81404</td>
<td>Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)</td>
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<td>96365</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour</td>
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<tr>
<td>96366</td>
<td>each additional hour (List separately in addition to code for primary procedure)</td>
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12/23/2020
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<td>each additional hour (List separately in addition to code for primary procedure)</td>
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<tr>
<td>96413</td>
<td>Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug</td>
</tr>
<tr>
<td>96415</td>
<td>each additional hour (List separately in addition to code for primary procedure)</td>
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</table>

**HCPCS codes covered if selection criteria are met:**

- J0202 Injection, alemtuzumab, 1 mg

**Other HCPCS codes related to the CPB:**

- J7512 Prednisone, immediate release or delayed release, oral, 1 mg
- J8530 Cyclophosphamide, oral, 25 mg
- J9000 Doxorubicin HCl, 10 mg
- J9070 Cyclophosphamide, 100 mg
- J9185 Fludarabine phosphate, 50 mg
- J9268 Injection, pentostatin, 10 mg
- J9293 Injection, mitoxantrone hydrochloride, per 5 mg
- J9370 Vincristine sulfate, 1 mg
- Q0083 - Q0085 Chemotherapy administration
- Q2050 Injection, doxorubicin hydrochloride, liposomal, not otherwise specified, 10 mg
- S0172 Chlorambucil, oral, 2 mg
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<th>Code Description</th>
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<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived stem-cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition</td>
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ICD-10 codes covered if selection criteria are met:

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<td>C82.99</td>
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<td>C83.00</td>
<td>Other named variants of lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue</td>
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<td>C83.80</td>
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<td>Angioimmunoblastic T-cell lymphoma</td>
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<td>Primary cutaneous CD30-positive T-cell proliferations [relapsed or refractory cutaneous ALCL with regional nodes]</td>
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<td>Adult T-cell lymphoma/leukemia (HTLV-1-associated)</td>
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<td>Disease of blood and blood-forming organs, unspecified [cytopenia]</td>
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<td>Other encephalitis and encephalomyelitis [myelin oligodendrocyte glycoprotein (MOG) -associated encephalomyelitis] [Rasmussen encephalitis]</td>
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<td>Arthropathy associated with infections</td>
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<td>M05.00 - M19.93</td>
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The above policy is based on the following references:


Evidence-based Series No. 6-16. Toronto, ON: Cancer Care Ontario (CCO); June 14, 2006.


62. Schadde E, D'Alessandro AM, Knechtle SJ, et al. Alemtuzumab induction and triple maintenance...


64. Schrier SL. Warm autoimmune hemolytic anemia: Treatment. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed June 2018.


70. Simonini G, Cimaz R, Jones GT, Macfarlane GJ. Non-anti-TNF biologic modifier drugs in non-infectious refractory chronic uveitis: The current evidence from a


80. Ware RE. Autoimmune hemolytic anemia in children: Treatment and outcome. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed June 2018.


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Amendment to
Aetna Clinical Policy Bulletin Number: Alemtuzumab
(Campath)

There are no amendments for Medicaid.

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