Abstract

Successful attenuation of allograft rejection rate is a major clinical aspect in transplant. The CD52 binding monoclonal antibody CAMPATH1 or alemtuzumab, in this aspect, shows a promise as an effective immunomodifier. This humanized monoclonal antibody efficiently depletes CD52-bearing mature B- and T lymphocytes from circulation and thereby causes transient lymphopenia, a condition for generalized immunosuppression. Alemtuzumab is an approved drug for the treatment of B cell chronic lymphocytic leukemia. However, its implication in transplant as nonsteroidal drug is a growing area of investigation. Here, we provided a brief account on alemtuzumab as an immunomodifier in allotransplant.

Key words: Alemtuzumab, CD52, Transplant, Antibody, Monoclonal, Lymphocyte

Introduction

Alemtuzumab (commercially known as CAMPATH or Lemtrada) is a humanized monoclonal antibody raised against CD52, a membrane bound cell surface marker (21-28 kDa) found primarily on B and T lymphocytes. The abundance of CD52 is small to moderate in macrophages, monocytes, and natural killer cells. The stem cells, erythrocytes or platelets express little CD52, thus do not efficiently respond to the drug.\(^\text{5}\)

The introduction of alemtuzumab in transplant along with broad-spectrum antibiotics is a new way of treatment strategy adding to existing steroid therapy. The vision for developing treatment approach using monoclonal antibodies in general, has several targeted aims: (a) induction of antibody dependent cellular cytotoxicity (ADCC): immunotherapeutic strategy for cancer; (b) induction of antitoxin: vaccination strategy to neutralize effect of toxin and microbial infection; (c) attenuation of adverse effect of self-antigen during autoimmune diseases by successful depletion of autoantigen; and (d) maintenance of peripheral tolerance by attenuating graft-versus-host disease (GVHD) in allogenic transplant.

In Figure 1, we described the targeted use of alemtuzumab as immunomodifier in transplant therapy.

Alemtuzumab interacts with CD52 cell surface marker

CD52 is a glycophaspatidylinositol phosphate (GPI) anchored transmembrane protein.\(^\text{6}\) The demonstrated evidence suggests that, CD52 along with other GPI anchored proteins CD55 and CD59, regulate cell proliferation in in B cell chronic lymphocytic leukemia.\(^\text{5,7}\) The drug induces the caspase independent apoptotic signal pathway.\(^\text{8-11}\) The cross-linking of membrane bound CD52 induces intracellular signaling to apoptosis. On the other hand, the emergence of soluble CD52 in circulation initiates different signaling events to activate classic complement cascade through C1q activation and facilitates formation of immune complex.\(^\text{12-14}\) The GPI anchored cell surface proteins CD59, CD55, CD46, and CD35 regulate the complement cascade.

Reference: Humanized Monoclonal Antibody Alemtuzumab Treatment in Transplant

Meghnad Bhowmick, Farah Auckbarallee, Page Edgar, Amitabha Ray, Subhajit Dasgupta

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Recent investigations indicate that the monoclonal antibody also recognizes CD52-like human epididymis glycoprotein and alter the lipid raft microdomain of the cell membrane; thus initiating immobilization of the sperm head causing sperm capacitation the terminal step during maturation of mammalian spermatozoa. In transplant, continuous high doses of alemtuzumab treatment is because drastic lymphocytopenia that causes generalized immunosuppression and invites opportunistic infection. Thus, alemtuzumab dosage, duration of treatment, and combination strategy with other immunomodifiers are critical for successful transplant therapy.

Pharmacological aspects of alemtuzumab: dosages, routes, and duration of treatment
Recent advancements in allograft and/or transplant procedures have demonstrated the efficacy of low doses of alemtuzumab in delaying graft rejection. The Table 1 provides a summary of recent experimental and clinical trials on transplant involving the use of alemtuzumab. The treatment using combination of alemtuzumab with immunosuppressant along with stem cells is a promising therapeutic strategy. However, prevention of opportunistic infections with proper choice of antibiotics is an issue to be resolved in treatment procedure. A 2014 update indicated therapeutic use of alemtuzumab in transplant and a way to find remedies for opportunistic infections.

To prevent allergic manifestation and infusion reactions such as pyrexia, chills, hypotension, urticaria, and dyspnea during beginning stage of treatment, it is recommended to use slow intravenous infusion of alemtuzumab over a period of 2 hours or subcutaneous routes with dosages in escalating 3 mg, 10 mg and 30 mg, or 30 mg per kg body weight for 3 days a week. The mean volume of distribution after intravenous infusion is 0.18 L/kg. The mean half-life is 11 hours after the first 30 mg infusion of the drug.

Alemtuzumab as immunomodifier in transplant therapy
The selective use of immunosuppressing compounds has gained a degree of importance in transplant therapy. The meta-analysis data suggest use of alemtuzumab as immunomodifier in transplant. Recently, Zhang and associates showed that peripheral blood of relapsing remitting multiple sclerosis (RRMS) patients demonstrated significant decrease of circulatory CD4 and CD8 cells at day 7 after alemtuzumab treatment. The status of such condition persists until 12 months after treatment initiation. However, a remarkable alteration in T cell repertoire after alemtuzumab treatment

![Figure 1. Efficacy of Alemtuzumab in Transplant Therapy](image-url)
of RRMS patients showed an increase in CD4CD25CD127low Treg cell population in peripheral blood after a month of treatment, but not after 7 days, when nearly all CD4 and CD8 cells were found depleted from blood. The observations indicate an enlightened future of alemtuzumab in treatment of RRMS. Not only that, immunomodifier effect of the monoclonal antibody can effectively be implemented in transplant maintaining peripheral tolerance. A few relevant investigations suggest that depletion of alloimmune responsive CD4, CD8 cells along with up-regulation of peripheral tolerance through generation of Treg cells is a therapeutic approach for treatment of RRMS and organ transplant.24-26 The mean time of reconstitution of CD19, CD8, and CD4 was found 6, 10, and 36 months after alemtuzumab treatment.24 Different investigators also suggest a combination of alemtuzumab and T cell depleting antibody (antithymocyte globulin) as a low-risk steroid-free treatment strategy for kidney transplant.27,29

Modern research on transplant therapy approach using alemtuzumab demonstrate lower acute rejection rates in combination with the immunosuppressive drug, calcineurin inhibitor, tacrolimus (Fujimycin, FK-506).34 The macrolide lactone tacrolimus reduces activation of NF AT in T cells thus attenuates IL2 gene expression. The benefit of combination therapy using tacrolimus with alemtuzumab remains in the function of alemtuzumab to deplete mature and functional lymphocytes while tacrolimus attenuates activation of mature T lymphocytes in circulation. Recently, different investigators reported efficacy of alemtuzumab treatment in expansion of transitional B cells and regulatory B cells during kidney transplants.35,36 The proper mechanism of such repopulation of Breg and Treg cells after depletion of alloreactive cells is not clear and subject to in-

Table 1. Alemtuzumab Treatment Approach in Different Experimental and Clinical Transplant Studies

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<th>References</th>
<th>Study Details</th>
<th>Salient Findings</th>
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<tr>
<td>Weißenbacher et al. 2015</td>
<td>Single-center retrospective analysis of 225 consecutive kidney transplant patients treated with alemtuzumab and 205 recipients treated with basiliximab / Innsbruck, Austria</td>
<td>The mean lymphocyte counts (week 1 to 3 after treatment) were low in the alemtuzumab group compared with the basiliximab group. Delayed graft function, cytomegalovirus (CMV) status, and recipient age showed a significant correlation with lymphocyte counts in the alemtuzumab group.</td>
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<td>Tanriover et al. 2015</td>
<td>Renal transplant cohort from 2000 to 2012 was divided into two groups: steroid (n = 25,996) vs no-steroid (n = 10,157) - alemtuzumab in the no-steroid group / The Organ Procurement and Transplant Network registry (United States)</td>
<td>Odds of acute rejection with alemtuzumab were lower; however, overall allograft failure risk was higher.</td>
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<td>Willemsen et al. 2015</td>
<td>Cohort consisted of 148 children who underwent allogeneic hematopoietic stem cell transplantation for malignant and benign hematological disorders / Leiden, The Netherlands</td>
<td>Alemtuzumab significantly delayed the recovery of CD3(+) T cells and CD4(+) as well as CD8(+) T cell subsets (P ≤ 0.001) and natural killer (NK) cells compared with antithymocyte globulin (ATG). In both ATG- and globulin (ATG). In both ATG- and alemtuzumab-treated patients, shorter drug exposure led to significantly faster recovery of T cells. The overall survival and event-free survival risks were significantly lower for alemtuzumab-treated patients. Patients who received alemtuzumab showed a trend to lower risk of acute graft-versus-host disease, more human adenovirus, and less Epstein-Barr virus reactivations compared with ATG group.</td>
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<td>Mahadeo et al. 2015</td>
<td>Prospective pilot trial at 2 centers between 2006 and 2013 on 355 with blood and marrow transplant for nonmalignant genetic diseases / United States</td>
<td>Alemtuzumab-based reduced-toxicity regimen appeared to be promising with durable engraftment, effective cure of clinical disease, low rates of regimen-related toxicity, and no observed chronic graft-versus-host disease.</td>
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<td>Novelli et al. 2015</td>
<td>Six patients with Sézary syndrome (a rare leukemic variant of cutaneous T-cell lymphoma) / Barcelona, Spain</td>
<td>The median time of follow-up after alemtuzumab was 6 months. The overall response rate was 83.3% with 66.7% complete responses. The disease-free survival at 6 months was 33.3%</td>
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<td>Rogers et al. 2014</td>
<td>202 pancreas transplants over an 11.25 year period / North Carolina, United States</td>
<td>Lower rates of acute rejection and major infection were evidenced in patients receiving alemtuzumab induction therapy.</td>
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<td>Noureiddeen et al. 2014</td>
<td>Single-center retrospective study involving kidney transplant patients between 2009 - 2011 after receiving induction therapy with either alemtuzumab or rabbit-antithymocyte globulin (r-ATG) / Pennsylvania, United States</td>
<td>Higher incidence of antibody-mediated rejection (AMR), and similar incidence of acute cellular rejection. 1-year graft survival, patient survival, and allograft failure in recipients who underwent induction with alemtuzumab compared with those who received r-ATG. Inadequate B-cell suppression by alemtuzumab as well as altered phenotypic and functional properties of repopulating B cells could be contributing to heightened risk of AMR in these patients.</td>
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depth research. In particular, antigen specificity of such phenomena and regulation of memory cells is an important aspect in transplant procedures. The observations indicate a possibility of maturation and proliferation of lymphoid progenitor cells as part of reconstitution process in long run after alemtuzumab treatment. Likewise, more research must determine the effect of alemtuzumab on CD52 bearing dendritic cells and macrophages in the aspect of depletion and reconstitution in peripheral blood during transplant. The specific interaction between alemtuzumab and immunocompetent hosts is still under a careful analysis to improve graft acceptance with less adverse effects. The recent results on alemtuzumab mode of action on T cell repertoire, B cells, macrophages, and complement cascades are shown in the Table 2.

### Limitations of alemtuzumab treatment in transplant: clinicians’ perspectives

The selection of the proper dosage and duration of treatment are critical parameters in designing alemtuzumab-mediated therapeutic interventions for transplant and management of GVHD. Along with, the prevention of opportunistic infections is critical during posttransplant period. The preferred drug-induced immunocompromised conditions during transplant, thus, seek a continuous antimicrobial treatment regimen. The recent advancements in bone marrow and organ transplant put emphasis on use of vaccination and prophylaxis before set-up procedures.

### Conclusion and future perspectives

The lymphocyte depleting property of alemtuzumab leads the drug to induce a favorable condition for delaying rejection of allograft. In that aspect, the drug shows a promise for future treatment during transplant. The combination of antimicrobial treatment with alemtuzumab along with nonsteroidal compounds is a better approach for improvement of transplant therapy. Though, the treatment schedule is a matter of further research in transplant.

### References
