

REVIEW

# Immunomodulator alemtuzumab therapy in kidney transplantation

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Owing to an insufficient understanding of molecular mechanisms, currently the best treatment available for chronic kidney failure is transplantation. There is a heightened need for effective immunosuppressants to counteract rejection. Alemtuzumab, a humanized anti-CD52 antibody, is a powerful lymphocyte-depleting agent. Recently, it has been increasingly used as induction therapy in renal transplantation but its role is not yet fully defined. Indications that early withdrawal of corticosteroids in kidney transplant patients is associated with a better prognosis, has necessitated a hunt for an effective induction agent that supports early corticosteroid withdrawal. In this regard, alemtuzumab is an attractive agent because of its prolonged lymphocyte depleting properties. Long-term studies in kidney transplant patients are still needed for it to be considered as an effective induction agent. Trends in lower acute rejection rates in groups using alemtuzumab induction, particularly in association with tacrolimus maintenance therapy, have been noted and acute rejections were not as severe. Lymphocyte depletion is expected to be associated with an increased incidence of infection and any new immunosuppressive agents should be observed closely for development of infection. Initial studies have not established increased infection rates with alemtuzumab induction, possibly because of the preservation of function of the remaining T-lymphocytes other than CD4+ cells. Further randomized control trials with larger populations are needed to draft a protocol for alemtuzumab's more effective use in transplantation.

**Keywords:** Alemtuzumab; kidney transplantation; CD52; macrophage; lymphocyte

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## Introduction

Chronic kidney disease (CKD), a pre-dominantly non-communicable disease, involves the sustained but gradual loss of renal function over months to years. Decreasing kidney function often coexists with other chronic illnesses such as diabetes mellitus and hypertension and patients may present with vague, non-specific complaints which often go unrecognized. The progressive loss of renal

function may go undetected until it presents as End Stage Renal Failure/Disease (ESRD) requiring renal replacement therapy to sustain life. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) included ESRD in stage-5 chronic kidney failure, defined as less than 15% of normal renal function. It is assessed by an estimated glomerular filtration rate (eGFR) of less than 15 mL/min/1.73 m<sup>2</sup> (normal: 90-120 mL/min/1.73 m<sup>2</sup>); or those patients requiring dialysis irrespective of their glomerular

**Table 1. Stages of chronic kidney disease and complications that may prompt initiation of renal replacement therapy**

Stages of chronic kidney disease		
Stage	Description	Estimated GFR <sup>†</sup>
I	Kidney damage with normal or increased GFR	>90
II	Kidney damage with small decrease in GFR	60–89
III	Kidney damage with moderate decrease in GFR	30–59
IV	Kidney damage with large decrease in GFR	15–29
V	Kidney failure with need for dialysis (ESRD)	<15
Complications		
1.	Intractable ECV load	
2.	Electrolyte imbalance (hyperkalemia, hyperphosphatemia, hypercalcemia or hypocalcemia)	
3.	Neurological dysfunction like encephalopathy or neuropathy	
4.	Metabolic acidosis	
5.	Pleuritis or pericarditis	
6.	Unexpected decline in function and well being	
7.	Malnutrition	

For classify and staging kidney disease, glomerular filtration rate (GFR) is used. GFR (mL/min/1.73 m<sup>2</sup>) = 186 x [serum creatinine (μmol/L)/88.4] <sup>-1.154</sup> x age (years)<sup>-0.203</sup> x 0.742 if female and x 1.21 if African American.

filtration rate <sup>[1]</sup>. The kidney normally receives approximately 20% to 25% of the cardiac output per minute to filter and remove metabolic wastes including urea and other harmful toxins. With renal failure, the systemic effect is an accumulation of these toxic substances causing damage and disruption of normal homeostasis.

CKD represents an increasing global health problem (Table 1) requiring proper intervention. The recent and rapid increase in diabetes mellitus and hypertension appears to be driving the CKD epidemic. CKD arises from both communicable and non-communicable sources. The communicable diseases associated with kidney disease include hepatitis, HIV, malaria and schistosomiasis <sup>[2, 3]</sup>, while the non-communicable sources include glomerulonephritis, diabetes mellitus, hypertension, obstructive nephropathy, urological disease, and cystic kidney disease. Countries such as China and India that have high rates of diabetes mellitus and hypertension and resultant kidney disease have increasing rates of chronic renal failure. India's populations have risks as high as 40% of developing chronic renal disease <sup>[4, 5]</sup>. Chinese studies suggest approximately 12% (of the sample population) have evidence of CKD <sup>[6]</sup>.

The situation is equally dire in developed nations. In Europe, this uptick in incidence and prevalence of renal failure associated with poor outcomes and high treatment costs is creating profound challenges for western medicine in the 21<sup>st</sup> century <sup>[7, 8]</sup>. Coupled with increasing life expectancy, better health care facilities, and improvement in lifestyle modification risk factors, CKD has emerged as a major burden on the health systems. Research done in 2006 showed that CKD is the 12<sup>th</sup> highest cause of death and 17<sup>th</sup> highest cause of disability worldwide <sup>[9]</sup>. In the United Kingdom, the population prevalence is 774 per million, with

47,525 adult patients receiving renal replacement therapy (RRT) at the end of 2008 <sup>[10]</sup>. The Third National Health and Nutrition Examination Survey assessed the prevalence of CKD in the United States as close to 11% <sup>[8]</sup>. The data supports that the disease is increasing globally and that the need for proper intervention will be quite beneficial.

### Renal replacement therapy

The escalating trend of chronic illnesses such as diabetes and hypertension is predictive of increasing numbers of patients presenting with chronic renal failure in the future. As with any organ failure, CKD is associated with high morbidity and mortality. The treatment modalities available for CKD patients include conservative management of renal failure and renal replacement therapy including dialysis and transplantation. Conservative treatment includes measures to prevent further deterioration of renal function. Some interventions form an integral role in conservative chronic renal failure management and have been shown to retard the progression of kidney disease and these include dietary protein restriction, reduction in mean arterial blood pressure, correction of anemia, correction of hypocalcaemia and correction of acidosis <sup>[11, 12]</sup>.

Renal replacement therapy includes all currently available approaches to artificially support renal function. It covers a variety of intermittent and continuous therapies, traditional intermittent hemodialysis (IHD), peritoneal dialysis (PD) and renal transplantation <sup>[13]</sup>. The optimal therapy for kidney failure is organ transplantation which is cost-effective, increases patient survival and quality of life <sup>[14]</sup>. The Benefit-Risk ratio for a kidney transplant recipient is more favorable than those on dialysis <sup>[15]</sup>. Unfortunately, kidney transplantation is available to few patients due to organ shortages.

## Immunology of transplantation

Every year, thousands of transplants of organs, tissues, and cells are performed throughout the world. Kidney transplant is the best treatment for failing kidneys [16-19]. However, the major barrier to transplantation is our immune system, which generates a response against the graft and results in graft loss.

Our immune system consists of two main arms - innate and adaptive immunity. Both these arms are intertwined through the complement system and cytokines. The immune system's protective response is mounted with the assistance of cells and molecules that include antigen-recognizing lymphocytes (B-lymphocytes – humoral immunity and T-lymphocytes – cell mediated immunity), natural killer (NK) cells, granulocytes, macrophages, dendritic cells, and various cytokines. It is known that genetic polymorphism is the primary cause of tissue and organ rejection. Polymorphic gene products vary among different individuals of the same species (blood groups, MHC molecules) and represent the majority of transplantation antigens. Class I MHC molecules are expressed on all nucleated cells, whereas class II MHC molecules are expressed on the antigen-presenting cells (APCs). T-lymphocytes only recognize antigens presented to them complexed with MHC molecules. Class I MHC molecules present antigenic peptides (e.g. intracellular viral antigens, tumor antigens, self-antigens) from within the cell to CD8+ T-cells (cytotoxic T-cells); whereas, Class II molecules present extracellular antigens to CD4+ T-cells (helper T-cells). The combined immune responses from both cellular (acute and chronic rejection) and humoral immunity (hyperacute, acute and chronic) are responsible for graft rejection.

The central role in the cascade-like activation leading to graft rejection is played by T-cells. The rejection has two stages: in the sensitization stage, T-cells recognize and are activated by antigens expressed on the surface of the graft tissue through their T-cell receptors. There are at least two distinct pathways of allorecognition. The direct pathway is the dominant pathway and is involved in early alloimmune responses as T-cells recognize intact allo-MHC molecules on the surface of the donor cells (e.g. endothelial cells) [20]. The transplanted organ also contains some 'passenger' antigen-presenting cells (e.g. interstitial dendritic cells) which have a high density of allo-MHC molecules capable of stimulating the recipient's T-cells. In the indirect pathway, T-cells recognize antigens presented as self-APC peptides [21, 22]. Donor MHC molecules are constantly shed from the graft, taken up by the recipient APC, and then presented to the T-cells resulting in activation of CD4+ T cells, delayed-type hypersensitivity reaction and alloantibody

generation. It has been proposed that the indirect pathway is responsible for chronic allograft vasculopathy [23].

Regardless of the pathway, the effector stage follows the sensitization stage, wherein both direct and indirect pathways result in the graft destruction. Once activated, T-cells initiate macrophage activation; these macrophages then mount a delayed-type hypersensitivity response and facilitate B-cells for antibody production, leading to complement activation [24, 25]. Together these processes culminate in the beginning of apoptosis and destruction of the graft.

## Role of macrophages

In the kidney, the mononuclear phagocytes such as macrophages and dendritic cells probably play a significant role in both normal and disease conditions. Macrophages are innate immune effector cells, and dendritic cells induce adaptive immunity [26]. Macrophages can be classified into two major categories - M1 and M2. Classically-activated M1 (subsequent to exposure to IFN $\gamma$ ) perform pro-inflammatory antibacterial responses, whereas alternatively-activated M2 (subsequent to stimulation by IL-4) are involved in tissue repair and fibrosis. Macrophages have long been recognized within the renal graft in both acute and chronic rejection, as well as in ischemia-reperfusion injury (IRI) [27]. In experimental animal models, IRI has been reported to be associated with a strong influx of macrophages along with lymphocytes and neutrophils in response to the expression of pro-inflammatory cytokines and chemokines including IL-6, IL-8 and monocyte chemoattractant protein 1 (MCP-1) [28]. A study on biopsy samples of acute renal allograft rejection found 38% to 60% macrophages among all infiltrating cells [29]. Similarly, Kajiwara *et al.* [30] observed the significant role of macrophages in the process of acute renal allograft rejection. Furthermore, another study on acute rejection concluded that activated macrophages or their products were responsible for acute renal dysfunction associated with clinical rejection episodes [31]. Local production of macrophage colony-stimulating factor (M-CSF) by graft-infiltrating macrophages and resident cells has been reported to take part in a vicious circle promoting macrophage recruitment and proliferation, which may play a pathogenic role in acute rejection [32]. Interestingly, in the intimal arteritis of acute rejection renal allograft biopsies, the predominately infiltrating cells appeared to be macrophages [33].

Macrophage infiltration is evident in all forms of CKD including chronic allograft nephropathy [34]. Intriguingly, significant increases in macrophages were documented in the renal biopsy specimens in those patients who later developed chronic allograft rejection [35]. A recent study has noticed

**Table 2. Pharmacological mechanisms of four different immunosuppressive agent classes**

Corticosteroids	Inhibitor of Nucleotide Synthesis and Antimetabolites	Calcineurin Inhibitor (CNI)	Mammalian Target of Rapamycin (mTOR) Inhibitor
<p><b>Prednisolone</b> and <b>Methylprednisolone</b> have generalized effect acting on different phases of immune and inflammatory responses. Specifically, corticosteroids inhibit antigen presentation, cytokine production, and proliferation of lymphocytes.</p>	<p><b>Cyclophosphamide</b> and <b>Mycophenolate mofetil</b>:  <b>Cyclophosphamide</b> is an alkylating agent which is transformed into active alkylating metabolites (e.g. 4-hydroxycyclophosphamide, aldophosphamide, acrolein and phosphoramidate mustard) via hepatic enzymes resulting in prevention of cell division by cross-linking DNA and RNA strands.  <b>Mycophenolate mofetil</b> is a pro-drug of mycophenolic acid (MPA), an inhibitor of inosine monophosphate dehydrogenase, the rate-limiting enzyme in purine biosynthesis. B-cells and T-cells are dependent on this pathway and are therefore suppressed.  <b>Azathioprine</b> is converted into 6-mercaptopurine (6MP) which inhibits DNA and RNA synthesis leading to decreased immune cell proliferation.</p>	<p><b>Cyclosporine</b> and <b>Tacrolimus</b>:  These agents inhibit calcineurin (calcium/calmodulin-dependent phosphatase). Initially, cyclosporine and tacrolimus bind to cyclophilin and FKBP12 (FK binding protein or, FK506 binding protein), respectively. The competitive binding of cyclosporine-cyclophilin and tacrolimus-FKBP12 complexes to calcineurin inhibiting phosphatase activity of calcineurin. This inhibition suppresses IL-2 production and thus T-cell activation.</p>	<p><b>Sirolimus</b> and <b>Everolimus</b>:  The mTOR signaling pathway regulates cell proliferation, cell growth and angiogenesis. This class of drugs forms complexes with FKBP12 which then bind to mTOR preventing activation and resultant inhibition of cellular growth.</p>

major increases in populations of M2-macrophages in patients with chronic kidney allograft injury, and suggested that these M2-macrophages may promote the development of interstitial fibrosis [36]. Ozdemir *et al.* [37] reported an increased mean microvessel density occurring in parallel with increasing interstitial fibrosis in chronic rejection cases. They suggested that mononuclear cell infiltrates likely play an important role in the induction of angiogenesis. Mononuclear cells may potentiate interstitial fibrosis in vivo by stimulating neovascularization, leading to early fibrotic changes and poor outcomes.

### Immunosuppressive strategies in current practice

Immunosuppression in solid organ transplantation has evolved through several amazing incarnations. From the time of non-selective immunosuppression (irradiation and chemicals) to the development of monoclonal antibodies, the field of immunosuppressive drugs has changed dramatically. 6-mercaptopurine, azathioprine and corticosteroids were popular during 1940s and 1950s. After 1990s, corticosteroids were increasingly being combined with calcineurin-inhibitors (e.g. cyclosporine and tacrolimus) and antimetabolites (e.g. azathioprine) [25]. The 21<sup>st</sup> century marked the advent of the new immunosuppressants (e.g. mycophenolate mofetil/MMF and mycophenolate sodium), the mTOR inhibitors (e.g. sirolimus), antibody agents (e.g. antithymocyte globulin), and IL-2 receptor antibodies, (e.g. daclizumab and basiliximab). These advances led to increased post-transplant patient survival rates.

Unfortunately, the adverse effects of immunosuppression have evolved in parallel to these advancements. Non-immune toxicity to immunodeficiency complications (e.g. cancer) has

forced the need to find a balance between rigorous immunosuppression and adverse drug side effects. Effective modern immunosuppression requires blockade of one or more of the three stages in the life-cycle of lymphocytes to aid in increasing graft half-life by suppressing graft rejection [38]. The site of action defines the immunosuppressive therapy such as lymphocyte depletion, lymphocyte diversion, and lymphocyte-activation blockade. Immunosuppressive therapy is divided according to the site of the action. Apart from the corticosteroids, which have a generalized effect, all the other drugs block either of the signals discussed above (Table 2).

All the above-mentioned immunosuppressive drugs are used as maintenance immunosuppression given to host-patients in order to prevent acute rejection and subsequent graft loss. The optimal amount and combination of immunosuppressive drugs, which should be prescribed to limit the side effects, is not yet fully characterized. Every hospital has its own protocol. Research showed that the percentage of patients discharged after renal transplant in 2007 in the United States on different combination therapy maintenance immunosuppressive drugs were as follows: corticosteroids (66%), tacrolimus (85%), cyclosporine (12%), mycophenolate mofetil (75%), mycophenolate sodium (16%), azathioprine (0.6%), sirolimus (5%) and everolimus (0.4%) [25].

### Different induction therapies and their Role

It has been documented that the risk of graft rejection is highest in the first few weeks after transplantation and the acute rejection is predictive of subsequent graft function [39]. Induction therapy is used to prevent this early graft rejection,

reducing graft loss by 8% in deceased-donor transplant patients and by 13% in living-donor transplant patients [40]. Induction therapy is broadly classified into two groups:

#### *Lymphocyte-depleting agents*

These agents destroy both B-cells and T-cells and the immune system usually takes months to recover. These agents block many antigenic sites present on T-cells and the majority of the side effects are due to cytokine release [41]. Lymphocyte-depleting agents are further divided into 2 groups:

A. Polyclonal: includes thymoglobulin (r-anti-thymocyte globulin) produced in rabbits and ATGAM (lymphocyte immune globulin and anti-thymocyte globulin sterile solution), which is a purified gamma globulin solution produced in horses. Thymoglobulin is proposed to be used in those who are undergoing re-transplantation, having delayed graft function or those who are sensitized [42]. These antibodies produce reactions (e.g. chills, fever and hypotension) and risk of infections (e.g. lymphopenia and post-transplant lymphoproliferative disease).

B. Monoclonal: includes alemtuzumab (humanized anti-CD52 pan-lymphocytic monoclonal antibody), OKT-3 (mouse antibody directed against the CD3 antigen) and rituximab (blocks CD20 antigen on the surface of B-cells and selectively depletes B-cells).

#### *Non-lymphocyte-depleting agents*

After recognizing a graft antigen, T-cells are activated causing calcineurin-mediated production and the secretion of IL-2. IL-2 is a growth factor that acts in autocrine fashion inducing T-cell proliferation. Basiliximab and daclizumab are two IL-2 receptor antibodies used to block the CD25 subunit of receptor and thus prevent proliferation of activated T-cells. Only, basiliximab is available for commercial use. Their action is synergistic to calcineurin-inhibitors, which block T-cell receptor-mediated production of IL-2 [43]. These antibodies prevent acute rejection during first few days of transplant thereby reducing the initial immune system activity and condition the body for the graft. In 2009, Kidney Disease Outcomes Quality Initiative (KDOQI) recommended use of lymphocyte-depleting agents rather than IL-2 receptor antibodies in patients who have one or more risk factors for acute rejection [1], which includes: increased number of HLA mismatches between younger recipient and older donor age, African-American ethnicity (in the United States), panel-reactive antibody (PRA) greater than zero percent, the presence of a donor-specific antibody, blood group incompatibility, delayed onset of graft function, and a cold

ischemia time greater than 24 hours. The guidelines further recommend the use of IL-2 receptor antibodies in the patients who are not at high immunologic risk [44].

#### **Alemtuzumab - an induction agent**

Alemtuzumab is a humanized monoclonal antibody; it binds to the cell surface glycoprotein CD52 [1] which is present on the surface of B-lymphocytes, T-lymphocytes, most macrophages, monocytes, and NK cells. The CD52 is not present on stem cells, erythrocytes or platelets [45, 46].

#### *Development and history of alemtuzumab*

The search for improved lymphocyte suppression and development of a 'proper tolerance' has led to the development of alemtuzumab (Campath) by Herman Waldmann and colleagues at Cambridge University. They raised rat antibodies against human lymphocyte protein [46]. As a rat protein, it is antigenic to humans. Hence, in 1988, Greg Winter and his colleagues grafted campath-1 onto a human antibody framework known as Campath-1H, an IgG1 kappa antibody with a molecular weight 150 kD [47].

#### *Pharmacodynamics and pharmacokinetics*

Alemtuzumab binds to the peripheral blood mononuclear cells, bone marrow and malignant cells. It binds to essentially all T-lymphocytes and B-lymphocytes. After binding to these cells, alemtuzumab causes cytotoxicity primarily through three mechanisms: (1) complement system activation (2) antigen-antibody dependent cytotoxicity and (3) apoptosis [48]. Since entire CD52 antigen sites are blocked at high dosage, it obeys a non-linear kinetics and the margin for toxicity increases beyond a specific concentration of the drug [49]. Alemtuzumab is a large compound, which is primarily found on the cell membrane, in the plasma and in the interstitial space as molecules - this size does not easily cross bilipid membranes. Metabolism is through receptor-mediated clearance via internalization or antibody-dependent cytotoxicity [48].

Alemtuzumab is available in 30 mg/3 mL vials to be diluted in 5% dextrose solution. The preferred mode of administration is the intravenous route. It is given over 2 hours through slow intravenous infusion in order to prevent serious infusion reactions (pyrexia, chills, hypotension, urticaria, and dyspnea) which may be fatal. The occurrence of infusion reactions is greatest during the initial week of treatment and decreases with subsequent doses of alemtuzumab. Hence, it is advised to pre-treat all patients with antipyretics and antihistamines. Some patients may require glucocorticoid support due to the severity of the

reactions. In order to avoid infusion reactions, alemtuzumab may be given via subcutaneous routes; dosage is in escalating 3 mg, 10 mg and 30 mg or 30 mg three days in a week [50, 51].

The mean volume of distribution after intravenous infusion is 0.18L/kg. The mean half-life is 11 hours after the first 30 mg infusion lasting six days after the last dose. This prolongation of the half-life is due to a decrease in systemic clearance as receptor-mediated clearance (CD52 receptor) decreases with repeated dosages [51]. With drug concentrations continuing to increase during the first 48 hours and WBC counts decreasing [49], the exact estimation of the half-life cannot be estimated as the concentration of alemtuzumab in the body is related to the numbers of WBCs containing CD52 glycoprotein.

### Non-Renal use of alemtuzumab

As an immune cell-depleting antibody, alemtuzumab, has been tested in many immunological disorders (cutaneous scleroderma, Wegener's granulomatosis, autoimmune thrombocytopenic purpura and inflammatory arthritis) [52], but has not been approved for these conditions. The National Comprehensive Cancer Network Drug and Biologics Compendium (2010) recommended alemtuzumab for treatment of the following conditions: (1) Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). (2) Second-line therapy for individuals with stage III mycosis fungoides or Sezary syndrome that is refractory to or progressive following initial treatment options [53]. (3) Second-line therapy for relapsed or refractory angioimmunoblastic T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified, or anaplastic large cell lymphoma in non-candidates for high-dose therapy with autologous stem cell rescue. (4) Single agent salvage therapy for Waldenstrom's macroglobulinemia or lymphoplasmacytic lymphoma that does not respond to primary therapy or for progressive or relapsed disease [54].

Alemtuzumab continues to be considered an investigational and experimental drug for conditions such as multiple sclerosis [55], anti-neutrophil cytoplasmic antibody-associated vasculitides [56], graft versus host disease [57], sporadic inclusion-body myositis [58], aplastic anemia, pure red cell and pure white cell aplasia [59], refractory acute rejection (RAR) and bronchiolitis obliterans syndrome (BOS) [60].

### Alemtuzumab in renal transplantation

The first available evidence of alemtuzumab induction-agent use was in 1998 as the induction-agent for

renal transplantation together with a low dose of the maintenance-agent, cyclosporine. Calne and team in 1998 induced thirteen cadaveric renal allografts with two doses of 20 mg alemtuzumab given 24 hours apart [61]. Five of the thirteen cases were given the first dose just prior to surgery and the second dose 24 hours later; eight were given the first dose shortly post-operative and the second 24 hours later. All the grafts and patients survived until twelve months with two episodes of rejection. This was the ignition for further research in alemtuzumab as a novel immunosuppressive agent. However, to date no consensus has been reached regarding the safety and efficacy of an induction protocol using alemtuzumab.

Various studies show that an infusion of alemtuzumab results in marked depletion of NK cells, B-cells, T-lymphocytes, macrophages, and monocytes. With alemtuzumab use, cells such as NK cells, B-cells, and monocytes return to normal levels within 3 to 6 months. However, in one study by Isaac and his colleagues in 2001, rheumatoid arthritis patients who were given alemtuzumab, their CD4+ and CD8+ T cells were found to be persistently low even after a period of 84 months [62].

Lymphocyte depletion often leads to opportunistic infection. The majority of studies using alemtuzumab as an induction agent are either small, lack a comparator group, used different maintenance regimens, or lack randomization thus making it difficult to compare infection rates. In 2005 a randomized trial on kidney transplant patients who were induced with alemtuzumab and followed for the development of infections for six months was conducted. There was a 40% infection rate in the alemtuzumab group as compared to 30% in the comparator group [63]. A similar study followed patients for sixty months post-transplant and reported infection rates close to 30% as compared to 19% in the control group [64].

In solid organ transplantation, Peleg and his team in 2007 stated that dosing increased infection rates and the use of alemtuzumab as a treatment of rejection rather than induction was associated with a 3-fold increased risk of opportunistic infections [65]. Contrarily, many other studies have reported either no increase or the same infection rates with alemtuzumab when compared with different regimens [66, 67]. There was no difference in infection rates in patients induced with either alemtuzumab or basiliximab over a period of thirty-six months [68]. Similar results were also reported when alemtuzumab was compared with basiliximab as an induction agent [69]. The most common infections seen were viral (CMV, BK virus, Epstein-Barr virus), fungal (Candida), urinary tract infection, pneumonia and bacteremia (*Haemophilus influenzae*, *Chlamydomphila pneumoniae*,

*Mycoplasma pneumoniae*, *Legionella pneumophila*) [70]. One stand-alone observation from these studies should be noted; disseminated fungal infections (*Candida*) and CMV viremia were more severe.

A pilot study tentatively indicated that early withdrawal of corticosteroids in kidney transplant patients was associated with a better prognosis [71]. Thus, the hunt for an effective induction agent that supports early corticosteroid withdrawal is a priority for the pharmaceutical industry. From its early days, alemtuzumab has proven to be an attractive possibility because of its prolonged lymphocyte-depleting properties in one or two doses [72]. However, long-term studies in kidney transplant patients are needed before alemtuzumab will be considered as an effective induction agent.

A definitive conclusion regarding the effectiveness of alemtuzumab as an induction agent cannot yet be made because of the small sample size and limited numbers of randomized control trials. However, there appears to be a trend towards lower acute rejection rates in groups using alemtuzumab induction [66, 67, 73-77], particularly in association with tacrolimus maintenance therapy. The choice of calcineurin-inhibitor is also important when using monoclonal antibody for induction as acute rejections are temporally delayed [73, 78, 79]. It has been shown that a stable graft during the initial days results in better outcomes later [80], highlighting the potential importance of alemtuzumab. It was also noted from the trials that acute rejections were not as severe in the alemtuzumab group. The histological characteristics of the rejection episodes fell in BANFF I and BANFF II (moderate) in the alemtuzumab groups and BANFF III in control groups (The Banff Schema is described in the report of the Third Banff Conference, Banff, Canada [81]). Moreover, the acute rejections were reversible in the alemtuzumab group [73, 82]. Lymphocyte-depletion is expected to be associated with an increased incidence of infection and any new immunosuppressive agent should be observed closely for development of infection [83]. However, initial studies have not established increased infection rates with alemtuzumab induction [83-85], possibly because of the preservation of function of the remaining T-lymphocyte other than CD4+ cells [84]. Other studies mentioned that there was an increased incidence of CMV infection in alemtuzumab group [66, 73].

Kidney transplantation and the medications required to support the graft post-transplant are expensive affairs. Cost-effectiveness should be considered when any new immunosuppressant protocol is considered or selected. A study analyzed the cost-effectiveness of alemtuzumab, and according to the researchers, the cost of using alemtuzumab is three times less expensive when compared with rabbit

antithymocyte globulin (rATG) [85]. Furthermore, in the alemtuzumab group, the in-patient medication cost for transplant hospitalization is half.

## Conclusions

Since the latter part of the 21<sup>st</sup> century, following the rapid expansion of urban-based living in the western developed world as well as in the Indo-China region, kidney disease has become a major global health concern. At present, the best available treatment for chronic kidney failure is renal transplantation. To achieve optimal benefit for renal transplant patients, there is a heightened need for effective immunosuppressant agents to counteract graft rejection. Currently there are many ongoing investigations to address such issues. In this study, a small scale analysis has been carried out from publicly available data regarding the efficacy of alemtuzumab as an immunosuppressive induction agent. Among the existing drug therapies, alemtuzumab is proving to be one of the effective choices based on the evidence provided here. However, a cautious approach is justified as further large scale trials need to be conducted to establish the full potential of alemtuzumab as a therapeutic induction agent.

## Conflicting interests

The authors have declared that no conflict of interests exists.

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## Abbreviations

APC: antigen presenting cell (like macrophages and dendritic cells); CD: cluster of differentiation (surface receptor); CKD: chronic kidney disease; CMV: cytomegalovirus; ECV: extracellular volume; HIV: human immunodeficiency virus; HLA: human leukocyte antigen; IFN $\gamma$ : interferon gamma; IgG: immunoglobulin G; IL: interleukin; kD: kilodalton; MHC: major histocompatibility complex; mTOR: mechanistic/mammalian target of rapamycin (serine/threonine kinase); NK: natural killer; WBC: white blood cell.

## Author contributions

PE: Collection and assembly of data, critical revision of the article for important intellectual content. MB: Conception, collection and assembly of data, drafting of the

article. CO: Drafting of the article, critical revision of the article for important intellectual content. AR: Conception and design, analysis and interpretation of data, critical revision of the article for important intellectual content, final approval of the article.

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