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EDITORIAL

Effects of exercise in renal transplant recipients

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Abstract

Even after a successful renal transplantation, the renal transplant recipients (RTRs) keeps on suffering the consequences of the uremic sickness. Cardiovascular risk, work capacity, and quality of life do not improve according to expectations since biological and psychological problems are not completely solved by pharmacological treatment. Furthermore, post-transplant treatment, per se, induces additional problems (i.e., side effects of drugs). It becomes, indeed, very important to insert "non-pharmacological" therapies able to reverse this trend. Exercise may represent an important contribution in the solution of this problem. In fact, many studies have demonstrated, in the last two decades, that physical training is able both, to improve graft function, work capacity and quality of life, and to reduce cardiovascular risk. In conclusion, if the analysis of the available data suggests that an appropriate dose of physical training represent a useful, safe and non-pharmacologic contribution to RTR treatment, it becomes a kidney transplantologist responsibility to introduce exercise in the current therapy of RTRs.

Key words: Renal transplantation; Exercise; Working capacity; Quality of life; Cardiovascular risk; Renal function; Immunology

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BACKGROUND

Uremic patients' survival is conditioned by an increased cardiovascular risk. In spite of the decline of its incidence rate in the general population during the last three decades, cardiovascular events remain the major cause of death in nephropathic patients[1,2] with a mortality 10 to 20 higher than in the general population[3,4]. In 1998 the National Kidney Foundation Task Force in Cardiovascular Disease recommended to consider uremic patients as a group with very high risk for cardiovascular events[1]. The main cause of this raised risk is the accelerated atherosclerosis, which is now considered to be the expression of an inflammatory process[5,6]: pro-inflammatory cytokines are secreted by immune cells within the atherosclerotic plaque. These include interleukin (IL)-1, IL-2, IL-6, IL-8, IL-12, IL-10, tumor-necrosis factor, interferon-γ and platelet-derived growth factor[7]. The accelerated atherosclerosis is the most important late complication for all organ recipients too[8,9]. Over the years, various risk factors have been associated with the manifestation of atherosclerosis. Among these, elevated levels of plasma cholesterol (LDL in particular) are recognized as a major risk factor as well as hypertension, diabetes mellitus, smoking[10] and sedentary life style[11]. An increasing amount of data demonstrates that uremia,

per se, represents an inflammatory condition and that this inflammation remains unaffected by transplantation[12]. Also in nephropathic patients cardiovascular events are strictly related to inflammation[13,14] and they represent the main cause of death not only in predialysis[15] and in replacement therapy patients[16,17], but also in renal transplant recipients (RTRs)[12]. The immunosuppressive treatment itself contributes to increase cardiovascular complications in RTRs through the induction of hypertension and dislipidemia[18,19]. Moreover, it is important to consider that the tendency to sedentary lifestyle is favoured by both the depression and the reduced quality of life that affect not only dialysed patients[20,21] but also patients after a successful renal transplantation[22].

GOAL

On the basis of the above considerations, the question that arises is the following: Is it possible to reduce cardiovascular risk and to influence graft survival of RTRs other than pharmacologically? In our opinion physical activity could play an important role in this subset of patients. In fact, many studies have demonstrated that physical training is able to improve several factors involved in the increased cardiovascular risk of RTRs and may contribute to save renal function. In this review we will examine the existing evidences with respect to these topics.

EVIDENCE BASED RESULTS

Glomerular filtration rate

Greater physical activity is a statistically significant predictor of improved graft function over a 1-year period. The authors believe that physical activity leads to improved cardiovascular function, which, probably, improves perfusion and oxygen delivery to the kidney graft[23].

Arterial pressure

Exercise reduces the need for pharmacological therapy of hypertension both in lung[24] and kidney transplanted patients[22].

Homocysteine

It is a factor related to an higher prevalence of cardiovascular disease and poorer outcome[25-29]. It remains higher in RTRs with respect to general population but an exercise program may significantly decrease the levels of this aminoacid[30].

Work capacity

Patients with advanced chronic kidney disease have lower cardiorespiratory fitness (CF)[31,32] that remains reduced by 30% after transplantation in comparison with age and gender matched control subjects[33]. CF expresses the maximum capacity of aerobic activity. It is measured through the evaluation of the peak oxygen uptake (VO_2) obtained by expired gas analysis. It is important to note that CF is a well-validated predictor of cardiovascular outcome both in individuals with underlying cardiovascular disease and in normal individuals[34]. Exercise improves CF in RTRs[22,35-37]. The mechanisms behind this reduced work capacity are not known, but it could be simply due to the reduced activity level before transplantation[38]. Exercise enhances muscle strength too[37,39], while it does not modify the body composition (BC), evaluated through dual-energy X-ray absorptiometry[22,37]. The lack of difference in the BC is due to the fact that exercise alone is ineffective for weight loss, unless a careful dietary management is adopted[40].

Effects of exercise among elderly RTRs

Despite best practices, older patients are at increased risk for early graft loss and death[41]. It has been demonstrated that pre-transplant inactivity is a negative predictor of overall patients and graft survival in this subset of patients[42].

Exercise and immunology of kidney transplantation

An 8-wk aerobic exercise program enhances T-helper cell count, CD4+ to CD8+ ratio, natural killer cells activity and IgG and IgM levels without causing graft dysfunction in the short term[35].

Moreover, it has been widely demonstrated that IL-6 plays a significant role in the progression of mesangial proliferative glomerulonephritis[43] and that it is an important risk factor with respect to the relapse of IgA nephropathy in transplanted kidney[44]. Furthermore, IL-6 amplifies the inflammatory cascade also by promoting the development of Th17 and the synthesis of IL17 from naive T cells (along with TGFb1 and IL21), whereas the maturation of memory Th17[45] and IL17 induces the synthesis of IL6 by myoblasts thus creating a vicious cycle[46]. San Segundo *et al*[47] and Afzali *et al*[48] demonstrated that IL-17 serum levels were augmented in graft dysfunction (compared with end stage renal disease patients) and, in agreement with Afzali *et al*[48], hypothesized that an imbalance between T(H)17 and Tregs enhances immune inflammation among renal transplant patients. In addition, since elevated levels of Il-6 represent a trigger factor of inflammation, they may significantly contribute to the cardiovascular risk of RTRs. Increased basal levels of this cytokine have been measured in RTRs[49].

Castaneda *et al*[50] demonstrated that exercise reduces the levels of IL-6 in uremic patients and we recently showed that this happens in RTRs too[22].

It is interesting to note that IL-6 increase is actually indicated both as the effect of an overtraining syndrome[51] and as one of the main factors able to induce an "underperformance syndrome"[52]. In fact, during strenuous exercise, IL-6 increases[53] by greater amounts than any other cytokine[54-56]: an increment registered in behavioral changes during physical as well as psychological stress[57]. In agreement with Castaneda *et al*[50] our data[22] seem to demonstrate that there is a difference in the IL-6 production depending on the dose of physical training. This can lead to the conclusion that, if strenu-

ous exercise increases IL-6 production, a well regulated level of exercise will produce the opposite result (i.e., a reduction of IL-6 levels). The "appropriate level" of exercise, indicated in several studies regarding the effects of exercise in RTRs, consists of a 30-45 min/session of aerobic exercise (walking or cycling) three or more times per week[22,23,30,35,37,42,58]. Therefore data suggest that while the strong exercise is detrimental, the moderate exercise (appropriate level) is of great benefit because it improves, as shown by our experimental *in vivo* in RTR study[22], the physical strength while decreasing IL6 levels, thus clearly indicating that the net biological effect is overwhelmingly positive.

Anxiety and depression

The quality of life and the psychological status are impaired in patients on maintenance dialysis[20,21]. The most common psychological and psychosocial problems are depression, anxiety and social withdrawal[59-61]. Anxiety and depression are common in RTRs too[62] and contribute to increase cardiovascular risk[63,64].

We have recently demonstrated that physical activity is able to reduce anxiety and depression in RTRs[22].

Why kidney transplanted patients show low rates of exercise ?

Zhong *et al*[65] got to the bottom of this question: these authors believe it depends on the fear of injuring the transplanted graft[66,67], and/or on the transplant professionals' silence about the benefits of exercise[66]. The cause can sometimes be the protective attitude of the family members and friends[35]. Moreover, patients of diverse ethnic and cultural backgrounds may place differential values on exercise and self-care[68,69] or this lack of importance given to physical training can be the consequence of the absence of structural support[65].

CONCLUSION

For patients affected by end-stage renal disease, renal transplant represents a dramatic improvement of quality of life: the freedom from the dialytic treatment might be considered the starting of a second life. Nevertheless, also following a successful renal transplant, several previously taken drugs (i.e., antihypertensive drugs, allopurinol, statins), can't be stopped, whereas new treatments (i.e., immunosuppressive drugs), have to be started thus increasing per se the cardiovascular risk of RTRs (through drug-induced hypertension and dislipidemia). This massive drug administration and the need for a strict medical follow-up may justify both the persistence of depression and the interest in "non-pharmacological" therapies, which can improve psychical and physical health of RTRs.

The analysis of the available data allows to state that an appropriate dose of physical training is a useful, safe and non-pharmacological contribution to RTRs treatment through the reduction of the of the risks of cardiovascular disease, the improvement of the biology of transplantation, the increase of energetic metabolism, and allows for a better quality of life in these subtype of patients. The studies analysed in this review do not distinguish among different subgroups, such as different "age groups", of RTRs with respect to different physical exercise programs[22,23,30,35,37,42,58]. This non-distinction is a further confirmation that, regardless of the type, physical activity can always yield remarkable health benefits. Despite the positive effects of physical activity, most RTRs do not exercise adequately according to the routine practice recommended by the Surgeon General (3 times per week)[70].

It is now the moment to fill this gap, it is now the moment that kidney transplantologists consider exercise not as a luxury accessory, but as integral part in the complex treatment of RTRs

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GUIDELINES FOR CLINICAL PRACTICE

Current state of renal transplant immunosuppression: Present and future

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Abstract

For kidney transplant recipients, immunosuppression commonly consists of combination treatment with a calcineurin inhibitor, an antiproliferative agent and a corticosteroid. Many medical centers use a sequential immunosuppression regimen where an induction agent, either an anti-thymocyte globulin or interleukin-2 receptor antibody, is given at the time of transplantation to prevent early acute rejection which is then followed by a triple immunosuppressive maintenance regimen. Very low rejection rates have been achieved at many transplant centers using combinations of these agents in a variety of protocols. Yet, a large number of recipients suffer chronic allograft injury and adverse events associated with drug therapy. Regimens designed to limit or eliminate calcineurin inhibitors and/or corticosteroid use are actively being pursued. An ideal immunosuppressive regimen limits toxicity and prolongs the functional life of the graft. This article contains a critical analysis of clinical data on currently available immunosuppressive strategies and an overview of therapeutic moieties in development.

Key words: Review; Immunosuppression; Investigational agents; Renal/ kidney transplant

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INTRODUCTION

Advances in immunosuppressive strategies over the past decades have led to significant improvements in the field of renal transplantation. Cyclosporine revolutionized transplant practice by lowering acute rejection rates and improving short-term graft survival in the 1980s. Post-transplant outcomes improved further with tacrolimus and mycophenolic acid in the 1990s. Additionally, the use of induction immunosuppressive agents has lowered early acute rejection rates. Despite these advances, clear evidence for a beneficial effect on long-term graft survival is lacking as chronic allograft nephropathy continues to threaten the renal allograft. With newer immunosuppressive regimens, immunologic causes of early graft failure have become rare. However, late graft loss has remained virtually unchanged over the last few decades, because of the persistence of chronic allograft injury. The use of newer immunosuppressive agents and the use of mTOR inhibitors are evolving strategies that aspire to minimize lifelong exposure to calcineurin inhibitors and corticosteroids and improve long-term outcomes.

Currently available immunosuppressive agents can be classified into three categories: "induction agents", "maintenance therapy" and "treatment for rejection". Induction agents are typically polyclonal antibodies (anti-thymocyte globulins) and interleukin (IL)-2 receptor antagonists (basiliximab). New induction agents include alemtuzumab, efalizumab and alefacept. The four drug classes that comprise maintenance regimens include calcineurin inhibitors (cyclosporine and tacrolimus), mTOR inhibitors (sirolimus and everolimus), antiproliferative agents (azathioprine and mycophenolic acid), and corticosteroids (Tables 1 and 2). Potential improvements to the calcineurin inhibitor class include a prolonged release tacrolimus formulation and voclosporin, a cyclosporine analog. Three new maintenance agents with novel mechanisms of action include: sotrastaurin, a protein kinase C inhibitor; belatacept, a recently approved costimulation blocker; and tofacitinib, a JAK 3 inhibitor (Table 3). Transplant rejection can be easily divided into acute cellular rejection and acute humoral rejection. Treatment for mild cellular rejection involves corticosteroids whereas moderate to severe rejection is typically treated with anti-thymocyte globulins. Humoral rejection is more difficult to treat and typically is treated with intravenous immunoglobulin and plasmapheresis. Investigational treatments for antibody mediated rejection include bortezomib and eculizumab.The purpose of this review is to consolidate the published evidence of the effectiveness and safety of current immunosuppressive agents and explore potential new immunosuppressive agents.

INDUCTION AGENTS

Induction therapy is primarily used to avoid early acute rejection which is historically known to predict subsequent graft loss. There are currently three antibodies which are used for induction therapy - basiliximab; anti-thymocyte globulin; and alemtuzumab. Investigational agents with less published evidence include efalizumab and alefacept. A comprehensive review of the pharmacology and therapeutics of induction agents was recently published[1].

Basiliximab (Simulect®, Novartis)

It is an IL-2 receptor antagonist which is the only food and drug administration (FDA) approved induction agent in renal transplantation. Dosed at 20 mg and administered at the time of and 4 d following transplantation, basiliximab has few adverse reactions or drug interactions. Basiliximab has demonstrated a statistically significant reduction in the incidence of acute rejection in three clinical trials, two of which used a maintenance regimen of cyclosporine and corticosteroids without an antimetabolite[2,3]. The third trial included azathioprine in the maintenance regimen and had a 20.8% rejection rate in the basiliximab arm compared to a 34.9% rate in the placebo arm[4]. None of these trials demonstrated a significant difference in patient or graft survival. Using a more contemporary regimen, a recent trial comparing basiliximab to placebo (using cyclosporine, corticosteroids, and mycophenolate mofetil for maintenance) demonstrated a trend towards reduced incidence of acute rejection in the treatment group (15.3% *vs* 26.6%), although it did not reach statistical significance[5].

Rabbit anti-thymocyte globulin (Thymoglobulin®, Genzyme)

They are antibodies derived from rabbit sources which are commonly used induction agents although they are approved for corticosteroid resistant rejection. These antibodies are FDA approved for treatment of acute rejection at a dose of 1.5 mg/kg for 7-14 d, based on the results of a multi-center, double-blind randomized trial[6,7]. Although rabbit anti-thymocyte globulin (rATG) is not currently FDA approved as induction therapy for kidney transplantation, it is the most commonly administered agent for this purpose. Reported induction doses range from 1-6 mg/kg per dose over 1-10 d with a more typical regimen of 1.5 mg/kg for 3-5 d[7-16]. Common adverse events include cytokine release syndrome, leukopenia and thrombocytopenia. A comprehensive review on the use of anti-thymocyte globulins can be found in the literature[17].

rATG and basiliximab were compared in two multicenter induction trials in combination with cyclosporine, mycophenolate mofetil and corticosteroids. In the first trial, basiliximab (with early initiation of cyclosporine) compared to rATG (with delayed cyclosporine initiation), produced a similar incidence of acute rejection and similar patient and graft survival at 12 mo post transplantation in low risk patients[18]. There were fewer cytomegalovirus infections ($P = 0.005$) in the basiliximab group, but the percentage of clinically significant cytomegalovirus cases was not statistically different and cytomegalovirus prophylaxis was not used. In contrast, results of the larger second trial, using moderate to high-risk deceased donor recipients, demonstrated an improved combined endpoint for the incidence of rejection, graft loss, and patient death that favored rATG (19.1% *vs* 31.6%, $P = 0.01$)[19,20]. Most of the benefit in combined endpoints was attributed to the decreased incidence of acute rejection (14.2% *vs* 25%, $P = 0.013$).

Alemtuzumab (Campath®, Berlex Laboratories)

A recombinant DNA-derived humanized monoclonal antibody that is directed against CD52, is currently a FDA approved treatment for B-cell chronic lymphocytic leukemia. However, it has been used off label for induction therapy and in the treatment of acute rejection[21,22]. Infusion reactions may occur as it is given intravenously asa one-time dose of 30 mg. The subcutaneous route has also been studied, although this method of administration is not FDA approved[23].

The early use of alemtuzumab in renal transplant recipients was associated with intense and prolonged lymphocyte depletion, increased antibody-mediated graft

Table 1 Food and drug administration approved immunosuppressive medications used for transplantation

Drug	Dose	Side effects
Induction		
Basiliximab	20 mg IV × 2 doses	Hypersensitivity reactions
Anti-thymocyte globulin		
Rabbit	1.5 mg/kg IV × 3-14 d	Rash, fever, thrombocytopenia, leukopenia
Horse	15 mg/kg IV × 3-14 d	
Maintenance		
Prednisone	Maintenance: 2.5-10 mg/d Rejection: 250-1000 mg/d × 3 d IV	Mood disturbances, psychosis, cataracts, hypertension, fluid retention, peptic ulcers, osteoporosis, muscle weakness, impaired wound healing, glucose intolerance, weight gain
Cyclosporine	4-5 mg/kg po twice daily	Neurotoxicity, gingival hyperplasia, hirsutism, hypertension, hyperlipidemia, glucose intolerance, nephrotoxicity, electrolyte disturbances
Tacrolimus	0.05-0.075 mg/kg po twice daily	Neurotoxicity, alopecia, hypertension, hyperlipidemia, glucose intolerance, nephrotoxicity, electrolyte disturbances
Sirolimus	2-10 mg/d po daily	Hypertriglyceridemia, anemia, thrombocytopenia, mouth sores, hypercholesterolemia, gastrointestinal disturbances, bone marrow suppression, poor wound healing, edema
Everolimus	0.75 mg po twice daily	Hypertriglyceridemia, anemia, thrombocytopenia, mouth sores, hypercholesterolemia, gastrointestinal disturbances, bone marrow suppression, poor wound healing, edema
Azathioprine	1-2.5 mg/kg per day po daily	Leukopenia, thrombocytopenia, gastrointestinal disturbances, pancreatitis, hepatotoxicity
Mycophenolate mofetil	500-1500 mg po twice daily	Leukopenia, thrombocytopenia, gastrointestinal disturbances
Mycophenolate sodium	360-1080 mg po twice daily	Leukopenia, thrombocytopenia, gastrointestinal disturbances
Belatacept	10 mg/kg administered, prior to implantation, on day 5, and at the end of weeks 2, 4, 8, and 12, then 5 mg/kg every 4 wk (plus or minus 3 d)	

Table 2 Classification of immunosuppressive agents

Classification	Drug (Generic)	Drug (Trade)	Generic	Dosage form
Interleukin-2 receptor blockers	Basiliximab	Simulect®	No	Injection
Anti-T cell therapy	Antithymocyte globulin - horse	Atgam®	No	Injection
	Antithymocyte globulin - rabbit	Thymoglobulin®	No	Injection
Corticosteroids	Methylprednisolone	Solumedrol®	Yes	Injection, oral
	Prednisone	Deltasone®	Yes	Oral
Calcineurin inhibitors	Cyclosporine, CsA	Sandimmune®	Yes	Injection, oral
	Cyclosporine microemulsion	Neoral®	Yes	Injection, oral
	Tacrolimus, FK506	Prograf®	Yes	Oral
mTOR inhibitors	Sirolimus, rapamycin	Rapamune®	No	Oral
	Everolimus	Zortress®	No	Oral
Anti-proliferative	Azathioprine, AZA	Imuran®	Yes	Injection, oral
	Mycophenolate mofetil, MMF	Cellcept®	Yes	Injection, oral
	Mycophenolate sodium,EC-MPS	Myfortic®	No	Oral
Costimulation blockade	Belatacept	Nulojix®	No	Injection

rejection, and increased rates of serious infection[24-26], and until recently only a few, small, randomized trials have been published[27-29]. The largest, multicenter, randomized trial of alemtuzumab induction was stratified by risk: low-risk (alemtuzumab *vs* basiliximab, $n = 335$) or high risk patients (alemtuzumab *vs* rabbit antithymocyte globulin, $n = 139$)[30]. All patients received tacrolimus, mycophenolate mofetil and early steroid withdrawal. Expanded criteria donors and donors without a heartbeat were excluded. The rate of biopsy-confirmed acute rejection was significantly lower in the alemtuzumab group than in the conventional-therapy group (low and high risk combined) at 3 years of follow up (13% *vs* 20%, $P = 0.03$). However, this benefit did not translate to improved graft survival or improved renal function. The apparent superiority of alemtuzumab was restricted to patients at low risk for transplant rejection (acute rejection rates at 3 years: 10% *vs* 22%, $P = 0.003$). Among high-risk patients, alemtuzumab and rabbit antithymocyte globulin had similar efficacy. The lower acute rejection rates achieved in the conventional therapy group should be weighted with the risk of infection and cancer. The rate of serious adverse events related to cancer was higher in the conventional therapy group whereas the low risk alemtuzumab group suffered persistent leukopenia and a higher rate of serious infections.

Table 3 Non-food and drug administration approved/investigational agents and their mechanism

Name	Mechanism of action
Induction	
Alemtuzumab	Monoclonal antibody, CD52
Efaluzimab	Humanized antibody, CD11a/LFA-1
Alefacept	Costimulation inhibitor, CD2 LFA3
Maintenance	
Prolonged release tacrolimus	Calcineurin inhibitor
Voclosporin, ISA247	Calcineurin inhibitor
Mizoribine	Purine synthesis inhibitors
Sotrastaurin, AEB071	Protein kinase C inhibitor
Tofacitinib, CP-690550	JAK 3 inhibitor
Treatment of antibody medicated rejection	
Bortezomib	Proteasome inhibitor
Eculizumab	Monoclonal antibody, C5 complement protein

Efalizumab

A once weekly subcutaneous injection, works as an immunosuppressant by binding to the CD11a subunit of lymphocyte function-associated antigen 1 (LFA-1) and inhibiting white blood cell migration. Efalizumab (Raptiva®, Genentech) was indicated for the treatment of chronic moderate-to-severe plaque psoriasis, but has been associated with an increased risk for progressive multifocal leukoencephalopathy and was withdrawn from the market in April of 2009[31].

Clinical trials in renal transplant recipients have not been successful. Although patient survival, graft survival and acute rejection rates were equal in a trial of efalizumab (0.5 or 2 mg/kg administered weekly *via* subcutaneous route for 12 wk), cyclosporine, mycophenolate mofetil and steroids *vs* half-dose cyclosporine, sirolimus and prednisone (n = 38), 3 patients (8%) treated with the higher dose of efalizumab developed post-transplant lymphoproliferative disease[32]. A study that planned to replace the calcineurin inhibitors with efalizumab, soon after transplantation, in patients with mild impairment of renal function was also terminated.

Alefacept (Amevive®, Astellas Pharmaceuticals)

A CD2-LFA3 co-stimulation inhibitor[33,34], is FDA approved for treatment of moderate-to-severe chronic plague psoriasis in adults at a dose of 15 mg/wk intramuscularly for 12 wk. The most common adverse event is lymphopenia, therefore dosage adjustments are made by monitoring CD4+ lymphocyte counts. In a study of multiple courses of alefacept, no cumulative adverse effects were seen[35], although infections and malignancy may occur in patients treated with alefacept and liver function should be monitored.

Alefacept is currently being developed for use in conjunction with tacrolimus, mycophenolate mofetil and steroids for renal transplantation. A phase Ⅱ, multicenter, randomized, double-blinded, placebo controlled, parallel arm study in adult kidney transplant patients compared alefacept (n = 105) to placebo (n = 107)[36]. Exclusion criteria were HLA identical recipients, expanded criteria donors/donation after cardiac death, and recipients with panel reactive antibody greater than 20%. Alefacept treated patients received 7.5 mg of alefacept intravenously on days 0 and 3, 15 mg subcutaneously on day 7 and then weekly for a total of 12 wk. An abstract presented at the American Transplant Congress in 2011 reported that at 6 mo of follow-up, the incidence of delayed graft function, renal function, biopsy proven acute cellular rejection, patient survival and graft survival were similar[36]. The overall incidence of infection was similar although there appeared to be a higher rate of CMV in the alefacept arm (14.3% alefacept *vs* 7.5% placebo) and a lower incidence of BK infection (2.9% alefacept *vs* 9.4% placebo; no p values reported). The incidence of malignancy was higher in the alefacept arm (6.7% *vs* 0.9%, no P value reported). CD4+ and CD8+T memory cell subsets were lower in alefacept arm at 12 wk after transplant. A four arm study with calcineurin reduction, mycophenolic mofetil replacement, alternative alefacept dosing and control is ongoing.

It is now common practice in the transplant community to select induction therapy on the basis of risk-benefit considerations for each patient. The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines recommend including induction therapy with a biologic agent as part of the initial immunosuppressive regimen in kidney transplant recipients (Grade 1A Recommendation)[37]. They recommend that an IL-2 receptor antagonist be the first line induction therapy (Grade 1B Recommendation) and suggest the use a lymphocyte-depleting agent, rather than an IL-2 receptor antagonist, for recipients at high immunologic risk (Grade 2B Recommendation).

Despite these new recommendations, there are many unanswered questions relating to the use of potent induction agents. Induction agents have been associated with increased short-term costs and may contribute to an overall increased immunosuppressive state. Many centers are hesitant to use potent induction therapy because of the risks of infection or malignancy and lack of long-term data needed to determine a graft survival benefit. The choice of an induction agent remains debatable. However, basiliximab may be preferred for low-risk patients while rATG may be preferred for high-risk patients. Recently, alemtuzumab has also shown promise in low-risk patients, but a trial comparing basiliximab to alemtuzumab should be conducted to assess efficacy, the risk of cancer, and infection. Early results with efalizumab were disappointing but future results of alefacept trials are eagerly awaited.

MAINTENANCE THERAPY

Calcineurin inhibitors

Over the last two decades, calcineurin inhibitors have been extensively used in post-transplant immunosuppressive regimens and have secured a vital place in today's

solid organ post-transplant care for prevention of acute rejection and prolonging and graft survival. Cyclosporine (Neoral®, Novartis) and tacrolimus (Prograf®, Astellas) are calcineurin inhibitors that primarily suppress the activation of T lymphocytes by inhibiting the production of cytokines, specifically IL-2. Calcineurin inhibitors are associated with numerous toxicities that are often dose dependent. Hirsutism, gingival hypertrophy, hypertension and hyperlipidemia are more commonly encountered with cyclosporine treatment than with tacrolimus whereas neurotoxicity, alopecia, and potentially post-transplant diabetes are more commonly encountered with tacrolimus treatment than with cyclosporine. Potential drug interactions are important to recognize and vigilance is required when adding or adjusting any agent that may affect calcineurin inhibitors levels, usually by inducing or inhibiting the cytochrome P450 3A pathway. Both calcineurin inhibitors can be given intravenously or orally and are adjusted based on serum blood concentrations.

Several landmark trials have compared the available calcineurin inhibitors. The first two multicenter studies have compared tacrolimus to microemulsion cyclosporine using the combination of calcineurin inhibitors, azathioprine and corticosteroids[38,39] demonstrated a significant decrease in acute rejection with tacrolimus, but there was no difference in patient or graft survival post transplantation[38,39]. The next study randomized first deceased donor recipients to one of three immunosuppressive regimens (all included corticosteroids): (1) tacrolimus with azathioprine; (2) tacrolimus with mycophenolate mofetil; and (3) microemulsion cyclosporine and mycophenolate mofetil[40]. Acute rejection rates were similar in each group (≤ 20%) but the incidence of corticosteroid resistant rejection was lower in the tacrolimus arms. A 3-year follow-up found no statistically significant difference in renal function, patient or overall graft survival, but improved graft survival in recipients with delayed graft function in the tacrolimus arms[40]. In agreement with this data, ameta-analysis reported that for every 100 patients treated with tacrolimus rather than cyclosporine for the first year, 12 would be prevented from having acute rejection, 2 would be prevented from having graft failure, but 5 would develop new onset diabetes after transplantation[41]. In more recent evidence, the Elite Symphony trial demonstrated the low dose cyclosporine regimen to be not as effective as the low dose tacrolimus regimen[42]. As a result these trials, the KDIGO Clinical Practice Guidelines suggest that tacrolimus should be the first-line calcineurin inhibitor for renal transplant recipients (Level of recommendation 2A)[37].

Regardless of which agent is utilized, compliance is essential to prevent poor outcomes after transplantation. For this reason, a prolonged release tacrolimus formulation is being developed to improve adherence of the medication regimen in post-transplant patients. Prolonged release tacrolimus (Advagraf®, Astellas) has been approved for use in various European countries and Canada.

In a large, randomized, open label, phase Ⅲ study, 668 *de novo* kidney transplant recipients were studied for efficacy and safety of prolonged release-tacrolimus compared to tacrolimus and cyclosporine. Excellent patient and graft survival were achieved (> 93%) in all arms[43]. Silva *et al*[43] reported efficacy failure (death, graft failure, or acute rejection) of 14.0%, 15.1% and 17.0% in prolonged release-tacrolimus, tacrolimus and cyclosporine groups respectively; however, the study also reported that 10.3% of prolonged release tacrolimus patients had a biopsy proven acute rejection compared to 7.5% in tacrolimus and 13.7% in the cyclosporine groups. Krämer *et al*[44] also reported similar patient survival (97.5% *vs* 96.9%) and graft survival rates (92.8% *vs* 91.5%) among prolonged release tacrolimus and twice daily tacrolimus patients in a Phase Ⅲ trial. Table 4 summarizes the adverse event/side-effect profiles of prolonged release tacrolimus and tacrolimus[43].

Table 4 Comparative adverse effects of prolonged release Tacrolimus and Tacrolimus (%)

ADR	Prolonged released Tacrolimus	Tacrolimus twice daily
Gastrointestinal		
Diarrhea	45.3	44.3
Loose stools	5.1	7.1
Metabolism and nutritional		
Hyperlipidemia	16.4	17.5
Diabetes mellitus	14.0	11.3
Hyponatremia	2.8	0.9
Infections and infestations		
Sinusitis	7.0	3.3
Gastroenteritis	6.5	0.5
Peripheral edema	35.5	34.9
Nervous system		
Tremor	35.0	34.4
Paraesthesia	5.6	1.4
Vascular		
Orthostatasis	7.0	4.7
Lymphocele	0.5	0.9
Psychiatric		
Insomnia	25.7	30.2
Skin		
Alopecia	6.5	7.1

Various studies have suggested that the tacrolimus levels measured were slightly lower with prolonged release tacrolimus group compared to twice daily tacrolimus patients[45,46]. However, the efficacy measures were similar in both the groups. Serum creatinine, creatinine clearance and estimated glomerular filtration rate for both the formulations were very similar at 1 mo, 6 mo and 12 mo suggesting a non-inferior nephrotoxicity profile. As reported by various studies, there is a slightly increased incidence of biopsy proven acute rejection in the prolonged release tacrolimus groups[43,44] and therefore patients changing therapy should be monitored closely. Prolonged release tacrolimus has shown to have a non-inferior efficacy profile with the added benefit of a convenient daily dosing which is expected to improve patient compliance.

Over the last two decades there have been significant

improvements in transplantation, in large part due to the decreased incidence of acute rejection with the use of calcineurin inhibitors. This success has come at the expense of associated adverse side effects, including metabolic side effects that are risk factors for cardiovascular disease and cerebrovascular disease. Long-term use of these drugs has been associated with the development of chronic allograft nephropathy. New immunosuppressive agents that eliminate these issues are needed.

Voclosporin, (ISA 247, Isotechnika Pharma, Inc.) is a novel calcineurin inhibitor that is being studied in solid organ transplant and autoimmune disease[47-50]. Early animal studies demonstrated that voclosporin, a cyclosporine analogue, had a higher affinity and greater *in-vivo* potency[51,52]. PROMISE, a phase Ⅱb trial (completed in May 2008) of 334 renal transplant recipients compared low (0.4 mg/kg), medium (0.6 mg/kg) and high (0.8 mg/kg) dose voclosporin to tacrolimus (0.05 mg/kg), in combination with a standard immunosuppressive regimen and reported rejection rates of 11%, 9%, 2%, and 6% respectively with similar renal function at 6 mo after transplantation[47]. While most adverse reactions were similar, the incidence of new onset diabetes after transplantation was significantly lower in the low dose voclosporin group[53]. Voclosporin shows promise as an immunosuppressant in renal transplantation although Phase Ⅲ efficacy trials are warranted.

mTOR inhibitors

Although calcineurin inhibitors have significantly lowered acute rejection rates, they are direct nephrotoxins and exhibit several other side-effects. Calcineurin sparing regimens are an attractive immunosuppressive option that may minimize the risk of long-term graft loss while maintaining low rates of acute rejection. A potential alternative to the calcineurin inhibitor-based regimens are mTOR inhibitors (mammalian target of rapamycin). Two agents, sirolimus and everolimus, have been developed and FDA approved with the hopes of achieving this goal.

Sirolimus (Rapamune®, Pfizer) binds to FKBP-12, an intracellular protein, to form an immunosuppressive complex which inhibits the regulatory kinase, mTOR. This inhibition suppresses cytokine mediated T-cell proliferation, halting progression from the G1 to the S phase of the cell cycle. Sirolimus, dosed orally once daily, is associated with a number of adverse effects, including leukopenia, thrombocytopenia, anemia, mucositis, hypercholesterolemia, and hypertriglyceridemia. *De novo* use of sirolimus has been associated with delayed wound healing, lymphocele formation, and prolonged delayed graft function[54,55]. Dose adjustments are based on target trough levels of 5-15 ng/mL.

Sirolimus may have a favorable role in calcineurin inhibitor-free maintenance therapy[56,57], but caution is warranted in calcineurin inhibitor sparing regimens, as nephrotoxicity and rejection are still concerns. Several investigators have performed trials with mTOR inhibitors in hopes of attaining calcineurin sparing regimens. In the Spare-the-Nephron trial, a calcineurin free regimen of sirolimus and mycophenolate mofetil was compared to cyclosporine and mycophenolate mofetil. At 2 years of follow-up, renal function was not different[58]. The CONVERT trial studied 830 renal allograft recipients who were receiving cyclosporine or tacrolimus from 6 to 120 mo post-transplant. The participants were randomly assigned to continue calcineurin inhibitor (n = 275) or convert from calcineurin inhibitor to sirolimus (n = 555)[59]. Success with sirolimus was only observed in a subgroup of patients with a baseline glomerular filtration rate more than 40 mL/min and urine protein to urine creatinine ratio less than or equal to 0.11.ORION (Optimizing Renal Transplant Immunosuppression to Overcome Nephrotoxicity), another calcineurin sparing trial was recently halted because of high acute rejection rates in the elimination arm. The trial, only presented in abstract form[60], is a three-arm study of 450 *de novo* patients evaluating a sirolimus/mycophenolate mofetil/steroids combination, sirolimus/tacrolimus-elimination at 12 wk/steroid *vs* a standard regimen consisting of tacrolimus/mycophenolate/steroids. All patients in this study received daclizumab induction therapy. At 2 years, patient and graft survival and glomerular filtration rate were not different between groups. The urinary proteinuria to creatinine ratio was significantly higher in both sirolimus-containing arms when compared with the tacrolimus group.

Everolimus (Zortress®, Novartis) is a sirolimus-derivative with a much shorter half-life that recently received FDA approval for renal transplantation. Everolimus is also approved for treatment of advanced renal cell cancer subependymal giant cell astrocytoma and unresectable pancreatic neuroendocrine tumors (Afinitor®, Novartis). Everolimus, initially dosed at 0.75 mg orally twice daily followed by routine serum drug concentration monitoring, has an adverse events profile similar to sirolimus.

Efficacy of everolimus 1.5 mg/d *vs* 3 mg/d with steroids and low-exposure cyclosporine without induction (n = 237) or with induction (basiliximab, n = 256) has been studied[61]. In this study, the use of an induction agent eliminated the need for high dose everolimus. Six months biopsy-proven acute rejection occurred in 25.0% and 15.2% of patients (P = 0.073) in the 1.5 and 3 mg/d groups without induction, and 13.7% and 15.1% in the study groups with induction (P = 0.859). Calculated glomerular filtration rates (62-67 mL/min) and adverse events were similar in all arms.

Everolimus was compared to mycophenolate mofetil in a recent trial (n = 583)[62]. As part of triple-drug immunosuppression, everolimus (1.5 mg/d or 3 mg/d) was as efficacious as mycophenolate mofetil, although the side-effect profile featured increased adverse events. In combination with cyclosporine and corticosteroids, the incidences of primary efficacy failure at 36 mo (biopsy-proven acute rejection, graft loss, death, or loss to follow-up) were 33.7%, 34.0% and 31.1% for everolimus 1.5 mg/d, everolimus 3 mg/d, and mycophenolate mofetil, respectively (P = 0.810). Discontinuation of therapy due to adverse

events (hemolytic uremic syndrome, lymphoproliferative disease, and proteinuria, and higher serum creatinine) was more frequent in the everolimus arm compared to the mycophenolate mofetil arm.

Early elimination of calcineurin inhibitor by use of everolimus-based immunosuppression may improve renal function while maintaining efficacy and safety outcomes in selected patients. In a recent study, everolimus replaced calcineurin inhibitors at 4-5 mo after transplantation[63]. In this multicenter, European, open-label study (ZUES), 300low to moderate risk renal transplant patients initially received basiliximab induction, and cyclosporine, enteric-coated mycophenolate sodium, and corticosteroids for maintenance. They were randomly assigned in a 1:1 ratio to undergo calcineurin-inhibitor elimination (everolimus-based regimen that was based on trough concentrations (6-10 ng/mL) and enteric-coated mycophenolate sodium with corticosteroids), or continue standard cyclosporine-based treatment. At the time of conversion the mean glomerular filtration rate in both groups was above 60 mL/min. At 12 mo, the everolimus regimen was associated with a significant improvement in glomerular filtration rate in comparison to the cyclosporine regimen (mean difference +9.8 mL/min). Rates of biopsy-proven acute rejection were higher in the everolimus group than in the cyclosporine group after randomization (10% *vs* 3%, P = 0.036), but similar at the end of the study period (15% *vs* 15%). Compared with the cyclosporine regimen there were higher mean lipid concentrations, slightly increased urinary protein excretion, and lower hemoglobin concentrations noted with the everolimus regimen; thrombocytopenia, aphthous stomatitis, and diarrhea also occurred more often in the everolimus group.

The *de novo* use of sirolimus inhibitors has been proven to be comparable to calcineurin inhibitor, while it has been associated with early post-transplant adverse events including lymphoceles, prolonged delayed graft function and poor wound healing[56,57]. Likewise *de novo* us of everolimus in combination with induction has produced adequate rates of acute rejection, although adverse events were common[61,62]. It appears the sirolimus conversion is only successful in a subgroup of patients with a baseline glomerular filtration rate more than 40 mL/min and urine protein to urine creatinine ratio less than or equal to 0.11[59]. Likewise, the ZUES study demonstrated the everolimus conversion is possible in low to moderate risk patients with normal renal function, although this may come at the expense of a higher acute rejection rate. In summary, the best evidence for calcineurin withdrawal with mTOR inhibitors is in selected patients. Close monitoring of drug concentration levels and adverse events is warranted. Whether calcineurin inhibitor-free/sparing regimens using mTOR inhibitor maintenance therapy is efficacious in the long term remains unknown.

Antiproliferative agents

Antiproliferative agents are usually considered the "third agent" in triple immunosuppressive regimens, providing additive effects, but less essential than the calcineurin inhibitor or the corticosteroid component. Azathioprine and mycophenolic acid are the commonly used agents in this category. Currently there are two forms of mycophenolic acid available on the market, mycophenolate mofetil (MMF, CellCept®, Roche Laboratories) and mycophenolatesodium (EC-MPS, Myfortic®, Novartis Pharmaceuticals).

Azathioprine (Imuran®, GlaxoSmithKline) is a purine analog that inhibits DNA replication and suppresses B and T cell proliferation. Typical doses of azathioprine range from 1-2.5 mg/kg per day, adjusted for leukopenia. The primary adverse effects of azathioprine are dose-related bone marrow suppression and gastrointestinal disturbances. Other rare, but serious, adverse events like pancreatitis and elevations in liver function tests, paired with a potential serious drug interaction with allopurinol have limited the use of azathioprine.

Mycophenolic acid is an organic synthetic derivative of the natural fermentation product mycophenolic acid and causes noncompetitive reversible inhibition of inosine monophosphate dehydrogenases (IMPDH). This interferes with the *de novo* pathway of purine synthesis and DNA replication, producing cytostatic effects on T and B cells. Mycophenolate mofetil is rapidly converted to mycophenolic acid in the liver and enterohepatic recirculation of mycophenolic acid may occur. Typical doses of mycophenolate mofetil range from 500-1500 mg orally twice daily. Magnesium and zinc containing products should not be co-administered with mycophenolic acid. Common adverse effects of mycophenolate mofetil include nausea, diarrhea, leukopenia, and thrombocytopenia.

The efficacy of mycophenolate mofetil in renal transplantation has been reported in several trials. Mycophenolate mofetil-treatment groups demonstrated a reduced incidence and severity of early rejection episodes as compared to azathioprine-treated patients in treatment regimens consisting of tacrolimus plus corticosteroid as well as cyclosporine plus corticosteroids[64]. Follow-up of the Tri-continental mycophenolate mofetil study at 3 years found the decreased incidence of early rejection in the mycophenolate mofetil arm had not translated into a significant improvement in graft function or survival[65,66]. As a result of the summative evidence from these trials, the KDIGO Clinical Practice Guidelines suggest that mycophenolate be the first-line antiproliferative agent (Level 2B Recommendation)[37].

Mycophenolate mofetil is often associated with upper and lower gastrointestinal side effects that are dose related. Enteric-coated mycophenolate sodium has been developed to help circumvent the upper gastrointestinal side effects by facilitating release in the small intestine[67]. Two major clinical trials demonstrated that enteric coated mycophenolate sodium is therapeutically equivalent to mycophenolic mofetil, and that both drugs have a similar incidence and severity of side effects[68,69]. These trials did not demonstrate a statistically significant difference

in overall gastrointestinal symptoms when patients were given equivalent doses of mycophenolate mofetil or enteric-coated mycophenolate sodium (250 mg of mycophenolate mofetil is equivalent to180 mg of enteric coated mycophenolate sodium).

Other clinical trials that have been published since enteric coated mycophenolate sodium was approved have attempted to explore the gastrointestinal profiles of the two formulations of mycophenolic acid[70-72]. Many trials have proven a beneficial effect of enteric coated mycophenolate sodium[70-78] while others have not reported a difference in gastrointestinal related adverse effects between mycophenolate mofetil and enteric coated mycophenolate sodium[79-82]. In the myTIME, Progris and myGAIN[72,81,82] studies, patients reported improvement in their perception of change in GI symptom burden after conversion to enteric coated mycophenolate sodiumusing the self-administered GSRS questionnaire, overall treatment effect (OTE) scale for gastrointestinal symptoms and OTE scale for health-related quality of life questionnaires.

It is possible that gastrointestinal events are multifactorial (infectious etiology, related to gastroparesis or other concomitant medications) and enteric coated mycophenolate sodium may offer benefit to specific populations. If a patient fails mycophenolate mofetil because of the gastrointestinal side effects, then the patient may benefit if switched to enteric coated mycophenolate sodium. Also, if the patient is predisposed to gastrointestinal disorders, then enteric coated mycophenolate sodium may be a better initial choice for the patient. These perceived benefits should be weighed with the cost savings associated with generic mycophenolate mofetil.

Mizoribine is a purine analog that was identified and developed in Japan in the 1970s and has been used in Japan since 1984 as an immunosuppressive agent. It has been registered in Japan for the prevention of rejection in renal transplantation and for the treatment of lupus nephritis, rheumatoid arthritis and nephritic syndrome. Mizoribine selectively inhibits IMPDH and guanosine monophosphate synthetase. This prevents the synthesis of guanine nucleotides (GMP) from inosine monophosphate in activated leukocytes[83,84]. The deficiency of guanosine monophosphate (GMP) causes T-cell inactivity and therefore a deficiency of immune response upon antigen presentation. Mizoribine also affects the humoral response by directly inhibiting the proliferation of B-cells and cell-mediated immunity[84].

Mizoribine has been used only in Japan and a few other Asian countries; it has not been extensively used in other countries since there were alternative FDA approved antimetabolite immunosuppressants such as azathioprine and mycophenolic acid which have been shown to be efficacious. Mizoribine has been studied as an adjunct medication to standard calcineurin inhibitor immunosuppressive regimens to reduce the need for a higher dose of calcineurin inhibitors which may precipitate various adverse reactions such as nephrotoxicity, hyperlipidemia, diabetes, and osteoporosis apart from other less serious adverse events. Multiple clinical trials with 4906 cases receiving mizoribine for kidney transplantation and other disease states showed leukopenia, abnormal hepatic function, rash, increased levels of uric acid, and vomiting to be the most common adverse reactions. The incidence of adverse reactions was reported to be in about 0.5% of the mizoribine treated patients[85].

Historically mizoribine 1-3 mg/kg per day has been used as a substitute for azathioprine in combination with lower doses of cyclosporine and steroids. A clinical study comparing the cyclosporine/azathioprine and cyclosporine/mizoribine regimens showed the mizoribine group to be equally immunosuppressed with fewer side effects such as myelosuppression and liver dysfunction[86]. However a few clinical studies in the late 1980s showed the 1-3 mg/kg per day dose to be slightly less efficacious and have fewer adverse effects compared with azathioprine+ cyclosporine+ steroid therapy[87]. Due to this conflicting evidence, mizoribine was not well received in the western world. Akiyama *et al*[88] showed that a high dose (5 mg/kg per day) regimen has significantly higher rejection-free rates within 3 mo after transplantation (85%) compared with a 3 mg/kg per day low dose regimen (64.9%) and a 3-5 mg/kg per day intermediate dose regimen (65.1%). Tanabe *et al*[86] reported that the 10-year survival of cyclosporine/mizoribine was equivalent to cyclosporine/azathioprine. Tanabe *et al*[86] also showed mycophenolate mofetil and mizoribine based tacrolimus regimens to have similar rejection rates (24%)[89]. Considering various trials, mizoribine may have a place in the post-transplant care of patients who are not successful with the mycophenolic acid regimen for adequate immunosuppression.

Novel mechanisms

The protein kinase C inhibitor sotrastaurin (AEB071, Novartis) is an inhibitor of early T-cell activation *via* a calcineurin inhibitor independent pathway. Activation of the T-cell receptor plus CD28 results in T-cell activation *via* protein kinase C signaling and IL-2 production. It is in development for prevention of organ rejection after renal transplantation and treatment of psoriasis[90,91]. Sotrastaurin has shown to have a good tolerability profile with few adverse effects[92]. The most common adverse effects include nausea, vomiting and headache. Elevated liver function tests, tachycardia, serum creatinine elevation, hypertension and dyslipidemia were reported less frequently[92]. An important drug interaction between sotrastaurin and tacrolimus should be noted. In a phase Ⅱ trial, tacrolimus doses were 47% lower when combined with sotrastaurin *vs* with mycophenolic acid[93,94].

Initial phase Ⅱ trials evaluating the effectiveness of sotrastaurin were disappointing and were stopped early due to an increase in acute rejection in sotrastaurin treated groups[92]. In this trial patients were initially placed on sotrastaurin and steroids plus either standard exposure tacrolimus or reduced exposure tacrolimus. A control arm consisted of standard exposure tacrolimus,

mycophenolic acid and corticosteroids. Three-month follow-up indicated equivalent outcomes. At this phase of the trial (3 mo), patients in the sotrastaurin arms were eligible for conversion to mycophenolic acid in place of tacrolimus. After conversion, there was a significantly higher acute rejection rate in the sotrastaurin groups. The incidence of new-onset diabetes in the control group was 14.9% as compared to 6%-8% in the sotrastaurin groups. However, the median estimated glomerular filtration rate was not significantly different for the two study groups compared with the control group at any time point. A second phase Ⅱ study utilized a *de novo* calcineurin-free regimen of sotrastaurin, mycophenolic acid, and steroids and was compared with the control group of tacrolimus, mycophenolic acid, and steroids[95]. Again, a higher acute rejection rate was noted in the sotrastaurin group, and the trial was halted. A third phase Ⅱ trial studying sotrastaurin in combination with everolimus is ongoing.

Belatacept (Nulojix®, Bristol Myers Squibb) is a second generation co-stimulation blocker that received FDA approval for use in kidney transplantation in June of 2011. It is the first of a new immunosuppressant class of drugs that is as effective as cyclosporine and better at preserving kidney function. Belatacept is administered as a well-tolerated intravenous infusion over 30 min. The recommended dosing is 10 mg/kg administered, prior to transplantation, on day 5, and at the end of weeks 2, 4, 8, and 12, then 5 mg/kg every 4 wk (plus or minus 3 d).

Abatacept, the parent molecule of belatacept, was approved by the FDA for rheumatoid arthritis and juvenile idiopathic arthritis and was considered as a potential agent for solid organ transplantation due to its unique mechanism of action. However, abatacept showed poor efficacy in pre-clinical studies on primate renal transplant models and this was attributed to incomplete blocking of the co-stimulation pathway due to its uneven CD80 and CD86 antagonism (approximately 5:1) in the antigen presenting cells[96-98]. Belatacept was developed by altering two amino acids in the B7 ligand binding portion of the abatacept molecule. This resulted in a 4 fold increase in CD86 antagonism and 2 fold increase in CD80 antagonism making belatacept about 10 times more efficacious in blocking the co-stimulation pathway[96]. Due to concentration dependent antagonism of the B7 ligands, belatacept has a weight based dosing regimen. Intravenous dosing is also another key difference of belatacept compared to other conventional immunosuppressive regimens.

A summary of the clinical trials published to date can be found in Table 5. In the first 6-mo of a partially blinded, parallel group, phase 2 study, more intensive belatacept (11 infusions of 10 mg/kg over the first 6 mo, then 5 mg/kg infusions every 4-8 wk), less intensive belatacept (five infusions of 10 mg/kg over 3 mo, then 5 mg/kg infusions every 4-8 wk), and cyclosporine administrations were compared[99]. All patients received basiliximab, mycophenolate mofetil and corticosteroids (n = 218). Similar rates of acute rejection and graft loss occurred in each arms, while the glomerular filtration was statistically higher in each of the belatacept arms. The belatacept groups had less chronic allograft nephropathy, diabetes, hypertension and hyperlipidemia.

The efficacy and safety of belatacept in adult *de novo* kidney transplant patients were studied in two 3-year, phase 3, open-label, randomized, multicenter, active-controlled studies: Belatacept Evaluation of Nephroprotection and Efficacy as First-Line Immunoprotection Trial (BENEFIT) and BENEFIT Extended Criteria Donor (BENEFIT-EXT)[100-102]. In both trials, patients were randomized into three groups: more intensive belatacept, less intensive belatacept and cyclosporine. All patients received basiliximab, mycophenolate and corticosteroids. BENEFIT - EXT was designed similarly to the BENEFIT trial with the inclusion of expanded criteria donors. In the BENEFIT trial, despite the higher incidence of acute rejection in the belatacept arm, at the end of the first year renal function was statistically superior in the belatacept arms (more intensive 65 mL/min, less intensive 63 mL/min, and cyclosporine 50 mL/min). Two-year follow-up showed non-inferiority of two belatacept regimens when compared to a standard regimen of cyclosporine for the primary end-points of patient and graft survival in standard criteria kidney transplants and continued improvement in renal function (more intensive 65 mL/min, less intensive 68 mL/min, and cyclosporine 51 mL/min)[101]. In contrast in the BENEFIT-EXT trial, acute rejection rates were similar and renal function was statistically superior in the more intensive belatacept group, but not the less intensive group (more intensive 22%, less intensive 17%, and cyclosporine 7%)[102]. Three-year follow-up of these trials demonstrated persistent improvement in renal function (mean change +21 mL/min in the BENEFIT and +10 mL/min in the BENEFIT-EXT)[103]. A major concern that arose from these trials was the high incidence of post-transplant lymphoproliferative disease in the belatacept treated Ebstein-Barr virus seronegative recipient arms. Therefore the drug is contraindicated in patients that are Ebstein-Barr virus seronegative.

One limitation of the BENEFIT and BENEFIT-EXT trials is that cyclosporine, a less contemporary immunosuppressive, was utilized. More recently, a trial was reported that incorporated a more current immunosuppressive regimen. In a phase Ⅱ, 1 year randomized study, belatacept/mycophenolate mofetil, belatacept/sirolimus and tacrolimus/mycophenolate mofetil, in combination with rabbit antithymocyte globulin and without corticosteroids were compared (n = 89)[104]. Acute rejection was highest in the belatacept/mycophenolate mofetil arm, graft loss was lowest in the tacrolimus/mycophenolate arm and renal function was improved in the belatacept arms.

A conversion trial was recently conducted to test the hypothesis that belatacept-based regimens may provide a treatment option for calcineurin-based maintenance immunosuppression. Patients who were less than 6 mo but greater than 36 mo after transplantation with stable

Table 5 Summary of the Belatacept trials

Study		Phase Ⅱ			Benefit			Benefit-EXT	
Author		Vincenti			Vincenti			Durrback	
Induction		Basiliximab			Basiliximab			Basiliximab	
Study drug	MI β	LI β	CsA	MI β	LI β	CsA	MI β	LI β	CsA
Maintenance		MMF + steroids			MMF + steroids			MMF + steroids	
Demographics									
No. of patients	74	71	73	225	230	231	193	193	192
Age (yr)	47	42	46	44	43	44	57	56	56
Deceased donor (%)	69	73	78	42			100	100	100
Female (%)	27	32	33	31	35	25	35	26	37
Re-transplantation (%)	1	6	3	4	3	6		Not reported	
PRA > 20% (%)	1	3	1	11	13	8	0	1	3
African-American (%)	8	9	8	7	10	8	14	14	12
CIT (h)	20	20	18		16.3			Not reported	
CIT (> 24 h) (%)		Not reported			Not reported		39	43	44
Delayed graft function (%)		Not reported		16	14	18	47	47	49
Endpoints 6-12 mo		6 mo			12 mo			12 mo	
Acute rejection (%)	7	6	8	22	17	7	18	18	14
Acute Rejection (Grade Ⅱ) (%)	4	5	6	17	11	4	14	15	12
Measured GFR (mL/min)	66	62	54	65	63	50	52	50	45
NODAT (%)		Not reported		7	4	10	2	5	9
CAN (Stage Ⅱ or Ⅲ) (%)	8	9	9	4	6	7	10	12	4
Endpoints 12 mo									
Graft survival (%)	99	100	95	98	98	96	91	91	89
Patient survival (%)	96	99	97	97	98	97	96	98	96
Cancer	2	0	2	4	3	1	4	4	6
PTLD	2	0	0	1	1	0	3	3	0
Endpoints 2 yr									
Acute rejection				24	17	9	17	18	15
Measured GFR (mL/min)				65	68	51	52	50	45
Graft survival (%)				94	95	91	83	84	93
Patient survival (%)				97	97	94	93	94	94
Endpoints 3 yr									
Acute rejection (%)				24	17	10	18	19	16
Measured GFR (mL/min)				65	66	44	43	42	32
Patient/graft survival (%)				92	92	89	80	82	80

CsA: Cyclosporine; MI: More intensive; LI: Less intensive; PTLD: Post-transplant lymphoproliferative disorder; NODAT: New onset of diabetes mellitus after transplantation; CIT: Cold ischemia time; GFR: Glomerular filtration rate.

graft function (calculated glomerular filtration rate ⩾ 35 mL/min and ⩽ 75 mL/min) were randomized to either switch to belatacept (n = 84) or continue calcineurin inhibitor treatment (n = 89)[105]. At month 12, the mean change in calculated glomerular filtration rate from baseline was higher in the belatacept group *vs* the calcineurin inhibitor group. Six patients in the belatacept group had acute rejection episodes, all of them within the first 6 mo; all cases were resolved with no allograft loss. At month 24, mean calculated glomerular filtration rate was 62.0 mL/min in the belatacept arm *vs* 55.4 mL/min in the calcineurin inhibitor arm[106]. The mean change in calculated glomerular filtration rate from baseline was +8.8 mL/min in the belatacept arm and +0.3 mL/min in the calcineurin inhibitor arm. The relative renal benefit of belatacept was observed in patients switched from either cyclosporine (+7.8 mL/min) or tacrolimus (+8.9 mL/min), and was observed regardless of baseline renal function. Patient survival, graft survival and the overall safety profile was similar between groups.

Belatacept is the first immunosuppressive to demonstrate a renal benefit over a calcineurin inhibitor based regimen. The chronic intravenous administration of the belatacept remains controversial. It could be prove beneficial due to increased patient compliance with less frequent (monthly) administration as compared to other daily and twice daily oral regimens. In contrast, it may be perceived as a barrier to patients without social support that cannot readily access an infusion center. Administration and drug costs may also influence prescribing patterns and patient compliance. Another special consideration for belatacept is that it has a relatively long half-life and cannot be discontinued in cases of severe infection. Further trials are needed to explore the long-term outcomes, the impact of Epstein-Barr virus on post-transplant lymphoproliferative disease, and chronic allograft nephropathy. These trials should include more current immunosuppressive regimens.

Tofacitinib (CP-690550, Pfizer Inc.), previously called tascocitinib, is a kinase inhibitor with immunosuppressant properties and is being developed by Pfizer. Its novel mechanism of action, successful preclinical results in prevention of acute graft rejection, as well as its recent successful clinical trials using an oral dosage form (compared

to parenteral biologic alternatives) for autoimmune conditions such as rheumatoid arthritis and psoriasis make this a very promising agent for prophylaxis of acute rejection in solid organ transplant patients. In a normal immune response relating to the signal 3 cascade, cytokines bind and activate type- I and type- II cytokine receptors which in-turn activate the janus kinase (intracellular non-receptor tyrosine kinases) phosphorylation reactions[107]. JAK-1 and JAK-3 dependent activation of the STAT (signal transduction and activator of transcription) transcription factors leads to IL-2 driven T-cell proliferation whereas JAK-2 phosphorylation leads to GM-CSF-driven proliferation of HUO3 cells[108-110]. Tofacitinib is a small molecule agent which exhibits selective inhibition for the JAKs, with more specificity for JAK-1 and JAK-3. Therefore it primarily targets and inactivates the JAK/STAT dependent IL-2 induced T-cell proliferation.

Tofacitinib is being studied as a drug to be used in place of calcineurin inhibitors along with other anti-metabolite agents, primarily to take advantage of the specificity of the agent in immunosuppression and also for its expected low adverse effect profile owing to this specificity and novelty in the mechanism of action. In a small initial clinical study on *de novo* kidney allograft recipients comparing tofacitinib regimen at 15 mg *bid* (CP15) and 30 mg *bid* (CP30) with tacrolimus, researchers reported the 6-mo biopsy-proven acute rejection rates to be 1 of 20, 4 of 20 and 1 of 21 for CP15, CP30 and tacrolimus groups respectively and concluded the 15 mg *bid* regimen to be similar to the tacrolimus regimen[111]. In a subsequent phase-2 trial (n = 322), a standard cyclosporine regimen was compared with a 15 mg *bid* regimen of tofacitinib which is subsequently switched to 10 mg *bid* after 3 mo (less-intensity) and another 15 mg *bid* regimen of tofacitinib which is switched to 10 mg *bid* after 6 mo (more-intensity). The biopsy proven acute rejection at 6 mo with the low-dose group (12.4%) was lower than the more-intensity or cyclosporine groups (16.1% and 17.7%, respectively)[112]. In terms of glomerular filtration rate at 12 mo, the tofacitinib groups (less-intensity: 64.7 mL/min and more-intensity: 64.6 mL/min) showed a significant difference in preservation of renal function compared to the cyclosporine group (53.9 mL/min).In this study, the researchers have seen a lower incidence of chronic allograft nephropathy in the more intense and less intense groups (25% and 23.9% respectively) compared to the cyclosporine group (48.3%).

In a preliminary clinical study Busque *et al*[111] compared mycophenolate mofetil + tofacitinib regimens at 15 mg *bid* (CP15) and 30 mg *bid* (CP30) tofacitinib with mycophenolate mofetil plus tacrolimus and reported a high incidence of BK virus in the CP30 group (4/20) and similarly a higher 6 mo rate of CMV disease (4/20) compared to CP15 and tacrolimus (2/20 and 0/20 respectively). Some other common abnormalities noted with this agent were lipid elevations and a frequent anemia and neutropenia trending during the first 6 mo of the treatment. Gastrointestinal symptoms such as abdominal pain, diarrhea, dyspepsia and vomiting were some of the other common side effects reported with this agent[113]. In the phase 2 trial, there were also fewer cases of new-onset diabetes in the more-intense and less-intense groups (9.9% and 9.3% respectively) compared to cyclosporine (20.8%)[112]. The rate of serious infections, BK virus nephritis, post-transplant lymphoproliferative disorder and CMV disease was higher in the tofacitinib groups[112].

Tofacitinib, with its novel mechanism of action, less potential for nephrotoxicity and excellent graft survival data, is an important addition to the immunosuppressive arsenal. Quaedackers *et al*[114] reported the analysis of P-STAT5 as a potential monitoring parameter to measure the level of immunosuppression by tofacitinib; such markers could be vital in guiding dosage regimens of JAK inhibitors in transplant patients. About 43%-45% of tofacitinib treated patients have reported to discontinue the medication by the end of 12 mo compared to only 28% of the cyclosporine group. This could be due to the side-effect profile of the medication[112]. Although there have been promising results in the renal protective nature of this agent, there has to be a proper screening protocol and compliance programs associated with further phase 3 studies that should monitor post-transplant lymphoproliferative disorder and address compliance.

ANTIBODY MEDIATED REJECTION

Historically, antibody mediated rejection has been very difficult to reverse and has not been well studied. Acute antibody-mediated rejection is less responsive to conventional anti-rejection therapy and has a worse prognosis than acute cellular rejection. Treatment regimens may include one or more of the following: plasmapheresis, intravenous immunoglobulin (IVIG), and rituximab[115-121]. The first prospective randomized study comparing these strategies (plasmapheresis/IVIG/rituximab *s* IVIG alone) demonstrated improved graft survival in the combination group[121]. The KDIGO Clinical Practice Guidelines suggest treating antibody-mediated acute rejection with one or more of the following alternatives with or without corticosteroids: plasma exchange; intravenous immunoglobulin; anti-CD20 antibody; lymphocyte-depleting antibody (Grade 2CRecommendation)[37]. A review of antibody mediated rejection has recently been published[122].

Bortezomib (Velcade®, Millenium Pharmaceuticals) has demonstrated promise in the treatment of acute antibody mediated rejection. Seven years after the initial synthesis in May of 2003, bortezomib was approved in the United States for multiple myeloma. Bortezomib, the only proteasome inhibitor that was approved by FDA, inhibits the degradation of cell-cycle regulatory proteins resulting in cell-cycle death *via* apoptosis. It is metabolized *via* the cytochrome P450 system, a major substrate of 2C19 and 3A4 and inhibitor of 2C19. Ketoconazole causes a 35% increase in bortezomib area under the time concentration curve, and bortezomib may decrease concentration of the active metabolites of clopidogrel, a 2C19 substrate.

Table 6 Food and drug administration indications of immunosuppressive agents

Generic	Brand	FDA indication	Company
Basiliximab	Simulect	Prevention of acute rejection in kidney transplantatation	Novartis
Rabbit anti-thymocyte globulin	Thymoglobulin	Treatment of corticosteroid resistant rejection in kidney transplantation	Genzyme
Alemtuzumab	Campath	Treatment of B-cell chronic lymphocytic leukemia	Berlex Laboratories
Efaluzimab	No longer FDA approved Raptiva	Management of moderate to severe chronic plaque psoriasis in adults	Genentech-Merck
Alefacept	Amevive	Treatment of moderate-to-severe chronic plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	Astellas
Tacrolimus prolonged release	Advagraf (in Canada)	Not FDA approved	Astellas
Cyclosporine	Neoral	Prevention of acute rejection in renal transplant recipients	Novartis
Tacrolimus	Prograf	Prevention of acute rejection in renal transplant recipients	Astellas
Voclosporin		Not FDA approved	Isotechnika Pharma
Everolimus	Afinitor, Zortress	Treatment of advanced renal cell cancer (Afinitor®); treatment of subependymal giant cell astrocytom associated with tuberous sclerosis (Afinitor®); treatment of advanced, metastatic or unresectable pancreatic neuroendocrine tumors (Afinitor®); prophylaxis of organ rejection in patients at low-moderate immunologic risk receiving renal transplants (Zortress)	Novartis
Azathioprine	Imuran	Adjunctive therapy in prevention of rejection of kidney transplants; management of active rheumatoid arthritis	Glaxo-Smith-Kline
MMF	Cellcept	Prophylaxis of organ rejection concomitantly with cyclosporine and corticosteroids in patients receiving allogeneic renal cardiac, or hepatic transplants	Genentech
Mycophenolate sodium	Myfortic	Prophylaxis of organ rejection concomitantly with cyclosporine and corticosteroids in patients receiving allogeneic renal transplantation	Novartis
Mizoribine		Not FDA approved	Asahi Kasei Pharma
Sotrastaurin, AEB-071		Not FDA approved	Novartis
Belatacept, BMS224818	Nulojix	Prevention of acute rejection in renal transplant recipients	Bristol-Myers-Squibb
Tolfacitinib, formerly tasocitinib, CP-690550		Not FDA approved	Pfizer
Rituximab	Rituxan	Treatment of CD20-positive non-Hodgkin's lymphomas; Treatment of moderately- to severely-active rheumatoid arthritis in adult patients with inadequate response to one or more TNF antagonists; Treatment of Wegener's granulomatosis; Treatment of microscopic polyangiitis	Genentech
Bortezomib	Velcade	Treatment of multiple myeloma; treatment of relapsed or refractory mantle cell lymphoma	Millenium Pharmaceuticals
Eculizumab	Soliris	Treatment of paroxysmal nocturnal hemoglobinuria to reduce hemolysis	Alexion Pharmaceuticals

FDA: Food and drug administration.

Over the counter products like grapefruit juice may cause an increase in bortezomib levels, St. John's Wart may decrease bortezomib levels, and green tea and ascorbic acid supplements may diminish the therapeutic effects of bortezomib. Adverse events associated with bortezomib are neutropenia, thrombocytopenia, nausea, vomiting, diarrhea, constipation (up to 50%), reversible peripheral neuropathy (up to 30%), hypotension, QT prolongation, heart failure, pneumonitis and pneumonia.

Bortezomib's ability to cause cell cycle arrest and apoptosis has intrigued the transplant community. Case series have reported the use of bortezomib to remove HLA antibodies in live-donor transplant recipients with HLA alloantibodies[123,124] and to treat antibody and cell-mediated acute rejection[125-128]. A comprehensive review of bortezomib use in renal transplantation has recently been published[129]. Reported dosing of bortezomib is 1.3 mg/m^2 on days 1, 4, 8, 11. No adjustments are necessary for renal impairment, but the dosage should be reduced by one-half for moderate to severe hepatic impairment.

Eculizumab (Soliris®, Alexion Pharmaceuticals) is a humanized monoclonal IgG antibody that binds to complement protein C5, preventing cleavage into C5a and C5b. Blocking the formation of C5b inhibits the subsequent formation of terminal complex C5b-9 or membrane attack complex (MAC). Terminal complement-mediated intravascular hemolysis is a key clinical feature of paroxysmal nocturnal hemoglobinuria, the products FDA indication. Blocking the formation of membrane attack complex results in stabilization of hemoglobin and thereby a reduction in the need for red blood cell transfusions.

The currently approved dosing is 600 mg intravenously (infused over 35 min), every 7 d for the first 4 wk, followed by 900 mg 7 d later; then maintenance of 900 mg every 14 d thereafter. The risk for meningococcal *(Neisseria meningitides)* infections is increased with paroxysmal nocturnal hemoglobinuria and maybe further increased in patients receiving eculizumab. Vaccination with meningococcal vaccine at least 2 wk prior to initiation of treatment

is recommended. The most common side effects are headache, nausea, fatigue, back pain, cough and nasopharyngitis.

Several case studies in renal transplant recipients have reported success in treatment of atypical hemolytic uremic syndrome with eculizumab[130-134]. Eculizumab has also been successful in reducing antibodies in a highly sensitized patient prior to live donor transplant[135] and in prevention of antibody mediated rejection in patients with donor specific antibodies and positive flow cross-matches ($n = 4$)[136]. In a larger case-control study, patients with donor specific antibodies who received pre-transplant plasmapheresis and post-transplant eculizumab were compared to historical controls[137]. At a median follow up of 12 mo for the eculizumab group, antibody mediated rejection occurred in 7.7% (2/16) in the eculizumab group compared to 40% (20/51) in the control group ($P < 0.001$). Eculizumab 600 mg weekly for six doses with plasmapheresis has also been successful in reversing refractory, early (mean time 6.5 d), acute antibody mediated rejection in four transplant recipients[138]. Mean follow up time is 6.4 ± 5.7 mo, and while antibodies persisted in the majority of the patients, the allografts are functioning and infectious complications have not occurred.

Despite the small sample size and lack of randomized controls, these studies are encouraging, and although larger studies and long-term follow-up are needed, bortezomib and eculizumab may play a major role in antibody mediated therapy in the future. Their role in transplant desensitization may be better elucidated as more clinical data and well-designed clinical trials become available.

CONCLUSION

The past decade has brought about significant improvements to the immunosuppressive armamentarium. Evidenced based medicine has provided valuable information to manage post-transplant immunosuppression in the three categories of "induction", "maintenance" and "treatment of rejection". The FDA indications are listed in Table 6.

Two drug classes are used for "induction": polyclonal antibodies (anti-thymocyte globulins) and IL-2 receptor antagonist (basiliximab). Basiliximab may be preferred in low-risk patients and rATG in high risk patients. Recently, alemtuzumab has shown promise in low-risk patients. Future research is warranted with alefacept.

"Maintenance" immunosuppressives consist of calcineurin inhibitors, mTOR inhibitors, antimetabolites and corticosteroids. Today tacrolimus is the most commonly used calcineurin inhibitor. Prolonged release tacrolimus providesonce daily dosing of this product and hopefully will simplify a complex post-transplant immunosuppressive regimen. At this point in the clinical trials, voclosporin, a cyclosporine analog, has not shown superior efficacy outcomes, but perhaps improvement in the safety profile (namely new-onset diabetes after transplant) will secure its place in transplant immunotherapy. Although calcineurin inhibitors have significantly lowered acute rejection rates, they are direct nephrotoxins and chronic allograft nephrotoxicity still persists. A potential alternative to the calcineurin inhibitor-based regimens are mTOR-inhibitors, sirolimus and everolimus. The *de novo* use of mTOR inhibitors although promising has been associated with many adverse effects and it appears the mTOR conversion is only successful in a subgroup of patients. Whether calcineurin inhibitor-free/sparing regimens using mTOR-I maintenance therapy is efficacious in the long term remains unknown. Currently there are three antimetabolites on the market: azathioprine, mycophenolate mofetil, and mycophenolate sodium.It is still unclear whether enteric coated mycophenolate sodium has a gastrointestinal side effect benefit over mycophenolate mofetil. These perceived benefits should be weighed with the cost savings benefit associated with generic mycophenolate mofetil. Three maintenance agents with novel mechanisms of actionto watch include: sotrastaurin, a protein kinase C inhibitor; belatacept, a recently approved costimulation blocker; and tolfacitinib, a JAK 3 inhibitor. Belatacept, the first immunosuppressive to demonstrate a renal benefit over a calcineurin inhibitor based regimen, may prove beneficial to the immunosuppressive maintenance regimens.

Treatment regimens for humoral rejection may include one or more of the following: plasmapheresis, intravenous immunoglobulin, and rituximab. Investigations of bortezomib and eculizumab, have been hindered by small, non-randomized trial. Although results are encouraging, larger studies and long-term follow-up is needed.

While awaiting further advances in the immunosuppressive armamentarium, we should be able to improve the functional life of most renal allografts by tailoring our available agents for induction and maintenance therapy. The information gained through further study in these complex regimens should provide innovative strategies and new immunosuppressive agents that will serve to extend the functional life of allografts without toxicity or infection.

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Innsbruck, Austria

February 1 - 5, 2012
2012 BMT Tandem Meetings
American Society for Blood and Marrow Transplantation
Manchester Grand Hyatt,
San Diego, CA, United States

February 22 - 24, 2012
British Transplantation Society 15th Annual Congress
Glasgow, Scotland

February 23 - 25, 2012
2012 Canadian Society of Transplantation Annual Scientific Conference
Fairmont Château Frontenac,
Québec, Canada

March 8 - 10, 2012
3rd International Conference on Transplantomics and Biomarkers in Organ Transplantation
La Jolla/San Diego,
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April 18 - 21, 2012
The International Society for Heart and Lung Transplantation (ISHLT), 32nd Annual Meeting and Scientific Sessions
Prague, Czech Republic

April 25 - 27, 2012
United Network for Organ Sharing's 20th Annual Transplant Management Forum
Wyndham Rio Mar Beach Resort,
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June 2 - 6, 2012
2012 American Transplant Congress
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July 15 - 19, 2011
24th International Congress of the Transplantation Society
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ELITA - LICAGE LIVER MEETING and 4th ELITA Split-Liver Course
Ghent, Belgium

September 29 - 30, 2012
Advances in nephrology, dialysis, Kidney Transplantation
Odessa, Ukraine

October 5 - 7, 2012
V Congress of Transplantologists
Kharkiv, Ukraine

October 5 - 7, 2012
2012 European Organ Donation Congress, 24th ETCO-EDC
Dubrovnik, Croatia

October 12 - 14, 2012
ESOT and AST Joint Meeting - Transformational therapies and diagnostics in transplantation
Nice, France

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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