Current Concepts of Immunosuppression and Side Effects

2

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2.1 Introduction

The first successful human solid organ transplant was a renal transplant between two identical twin siblings, on 23 Dec 1954 [103]. Given the monozygosity, essentially no immunosuppression was used. The recipient never had a rejection episode but died 8 years later from recurrent glomerulonephritis. The introduction of immunosuppression with prednisone, azathioprine, and occasionally antilymphocyte globulin (ALG) in the 1960s allowed successful nonidentical living donor and deceased donor transplants. Through the 1970s and early 1980s, 1-year survival rates and acute rejection rates were around 60%. In the mid-1980s, cyclosporine was introduced and rejection rates decreased to 40–50% and 1-year survival rates increased to 75–85%. In the last 2 decades with the introduction of newer immunosuppressive induction agents such as basiliximab, daclizumab, and thymoglobulin and maintenance agents including tacrolimus, mycophenolate, and sirolimus, transplant patients are able to achieve 1 year graft survival rates in excess of 90% and acute rejection rates of 5–20%. Over the last several years, the focus of even newer immunosuppressive drugs regimens has included immunosuppression targeting the co-stimulatory pathways and avoiding toxicities associated with steroids and the calcineurin inhibitors cyclosporine and tacrolimus.

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Long-term allograft survival depends on controlling the allo-immune response and preventing toxicity. The allo-immune response is most intense after the placement of the allograft and initially requires broad and high levels of immunosuppression targeting multiple pathways to minimize the risk of rejection. These pathways have been reviewed previously (Chap. 1). In general solid organ transplant immunosuppression is divided into an induction phase and a maintenance phase of immunosuppression. For the purpose of this review "induction agents" will refer to those drugs used only during the initial few days or weeks after transplantation and usually refers to the use of lymphocyte depleting or lymphocyte targeted therapy. Maintenance immunosuppressive medications are often similar to those that are used during the induction phase but at lower doses when the recipient requires less immunosuppression to prevent rejection. Both induction and maintenance agents may be associated with side effects and allograft pathology.

2.2 Induction Drugs

Induction agents were used in less than 10% of renal transplants during most of the 1980s and mid 1990s and typically used for those recipients perceived to be at increased risk for rejection. Agents used during this period in the US were equine Minnesota antilymphocyte globulin (MALG), equine antithymocyte globulin (ATGAM), or monomuromab (OKT3), a mouse anti-human monoclonal agent that targets the CD3-complex. The use of induction agents has increased over the last decade [89]. As of 2003, approximately 70% of

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patients with renal transplant received induction immunosuppression therapy [68]. Of these, approximately 35% received rabbit ATG (thymoglobulin); 20% received basiliximab 15% received daclizumab; 4% received alemtuzumab (Campath), and OKT3 or ATGAM were used in <1%. A recent multivariate analysis showed that use of induction therapy over the last several years was associated with a reduced risk of rejection of 26% in deceased donors and 13% in living donor transplantation [20].

2.3 OKT 3

OKT 3 was the first agent approved by the FDA for induction therapy. It was approved in 1986 after decreased acute rejection rates were noted in comparison to no induction therapy.

2.3.1 Mechanism of Action

OKT 3 is a murine derived monoclonal antibody that targets the epsilon subunit of the CD3 complex. It causes an initial period of activation that is followed by subsequent inactivation of the T lymphocyte [68]. This initial period of activation causes a massive cytokine release which is responsible for the first dose effect associated with OKT3. T cells subsequently become ineffectual and are eventually opsonized and removed from the circulation. T cells usually appear in the circulation in about 3–5 days but lack CD3 and are immunologically incompetent [22]. The subsequent T cell paralysis helps prevent and treat acute rejection episodes.

2.3.2 Efficacy

OKT3 was initially used as an induction agent in renal transplantation. Its efficacy as an induction agent was highlighted by fewer rejection episodes and a longer time to initial rejection in comparison to placebo, along with maintenance regimen of prednisone, azathioprine and cyclosporine [3, 109]. The use of OKT3 as an induction agent has declined in the past few years because of it various side effects that have been described below. Its main role in transplantation is now restricted to the treatment of steroid resistant allograft rejections.

Dosage OKT3 is given as a dose of 5 mg intravenously, daily and peripherally for 7–14 days. Its efficacy on re-use is diminished because of the formation of antimurine antibodies which neutralize its effect. About 45–50% patients exposed to OKT3 develop anti OKT3 antibodies [56, 154]. These may be anti-isotypic or anti-idiotypic. Both of these antibodies differ in their capacity to neutralize the therapeutic effect of OKT3. Anti-idiotypic antibodies, which are directed toward the variable portion of OKT3, are more likely to limit efficacy than anti-isotypic antibodies, which are directed toward the murine component of the antibody [29]. In patients that do not develop anti-idiotypic antibodies, OKT3 can be used for retreatment.

2.3.3 Side Effects

The initial cytokine release is responsible for a major and sometimes life threatening "first dose effect" of this medication manifests as a flu-like syndrome with fever, tachycardia, diarrhea, nausea, myalgia and pulmonary edema and hypotension [68]. The package insert recommends that patients should be euvolemic prior to OKT3 to avoid serious pulmonary edema; however, this predisposes to acute tubular necrosis (ATN) (Fig. 2.1). Other

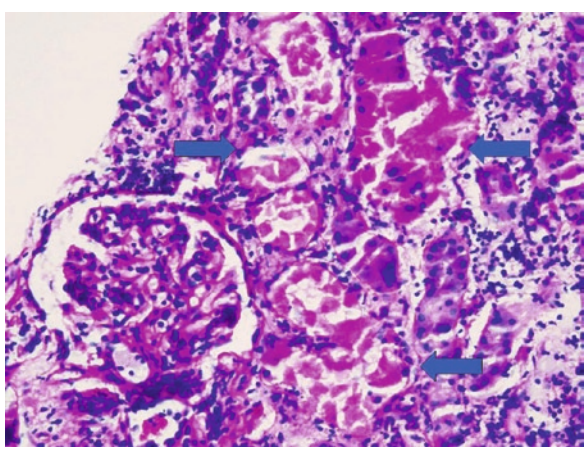

Fig. 2.1 Acute tubular necrosis. *Blue Arrows* show epithelial cell detachment from the tubular basement membrane

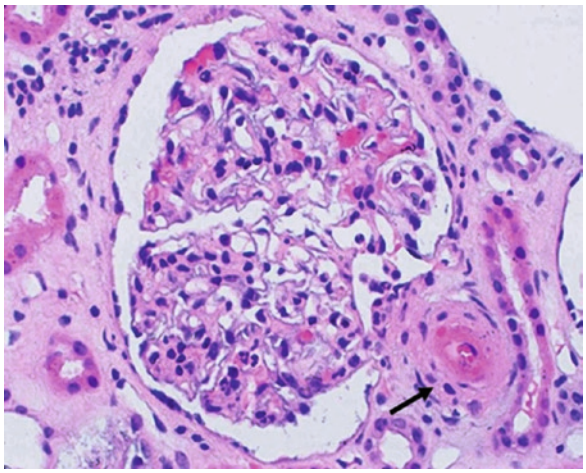

Fig. 2.2 Cyclosporine induced thrombotic microangiopathy. *Black Arrow* shows an arteriole occluded by fibrin deposition which is also apparent in the intraglomerular capillaries

side effects include nephrotoxicity which manifests as allograft thrombosis not only within the arteries and veins but also the glomerular capillaries with histology similar to thrombotic microangiopathy [4, 122] (Fig. 2.2). OKT3 can also be associated with neurotoxicity which manifests as aseptic meningitis, seizures and rarely akinetic mutism [117]. There is also an increased incidence of cytomegalovirus (CMV) infections after OKT3 therapy (see Chap. 3) and B cell lymphoma or post-transplant lymphoproliferative disease (PTLD). This is especially true among patients who have received multiple courses of OKT3 [21, 111]. Among all the induction agents currently in use, OKT3 carries the highest relative risk of PTLD [30]. In patients with liver transplantation, the use of OKT3 has been associated with early and severe recurrence of Hepatitis C [128].

2.4 IL-2 Receptor Antagonists (Anti CD25 Antibodies)

There are 2 IL-2 receptor antagonists available for use in organ transplantation- basiliximab and daclizumab. They are both chimeric, murine antibodies which have been humanized to decrease immunogenicity. Basiliximab is 75% human and daclizumab is 90% human [146].

2.4.1 Mechanism

IL-2 receptor antibodies bind to the alpha subunit of the IL-2R (CD25) which activates the intracellular kinases that promote T cell proliferation. The alpha subunit is expressed only on activated T cells, which are rare at the time of transplantation. Resting T cells do not express CD25 and are unaffected by IL-2R antagonists [110]. Basiliximab also impairs IL15 signaling through down regulation of the IL2γ/ IL15 receptor β chain [10, 27].

2.4.2 Dosage

Basiliximab is the more commonly used agent of the two drugs. It is given as a dose of 20 mg at days 0 and 4 and impairs the IL-2 receptor for a mean of 4–6 weeks [27, 110, 158]. The concomitant use of antimetabolites – azathioprine and mycophenolate mofetil (MMF) prolongs the duration of IL-2R alpha saturation [27]. The humanized content results in lower immunogenicity and longer half life of basiliximab in comparison to OKT3 [110].

A study of 339 patients using basiliximab as the induction agent found the incidence of anti-idiotype antibody formation to be 1%, which is much lower than OKT3 [27]. Daclizumab is the less commonly used IL-2 receptor antibody. It has not been studied as rigorously as basiliximab and has a more prolonged regimen for induction extending up to 8 weeks post transplant. Conventionally, it is given as 1 mg/kg on the day of the transplant and 4 doses subsequently 14 days apart. This regimen causes CD25 saturation for a mean period of 59 days [158]. An abbreviated regimen of 2 doses of 2 mg/kg daclizumab has also been compared to the conventional 5 dose regimen in patients with simultaneous kidney pancreas transplantation with favorable results [145].

2.4.3 Efficacy

Basiliximab has been compared to placebo in patients on maintenance therapy with cyclosporine, steroids

with/without azathioprine. It showed a lower rate of acute rejection with no difference in terms of overall graft and patient survival [62, 107, 108, 120, 159]. It has also been compared to placebo in combination with cyclosporine, mycophenolate and prednisone based triple immunotherapy regimens [77]. There was a 42.5% reduction in the rejection rate in comparison to placebo. Although it was not statistically significant, the study was not powered to detect a statistical difference between the two groups. In more recent studies, it has been used with prednisone, tacrolimus and mycophenolate based regimens [99]. The addition of basiliximab to the triple immunotherapy regimen was associated with a lower incidence of acute rejection in comparison to placebo and allowed for a lower dose of tacrolimus, thereby decreasing the risk of nephrotoxicity. Follow-up analyses showed improved acute rejection, graft loss and death in patients in the basiliximab group at 3 years that was not sustained at 5 years [62, 108]. Similar results have been obtained in another 5 year randomized controlled trial that demonstrated no significant long term benefit with basiliximab in comparison to placebo [134].

The data on daclizumab are not as extensive as basiliximab. In regimens using prednisone and cyclosporine, daclizumab has reduced the risk of early acute rejection and improved patient survival in comparison to placebo [107]. It has been compared with ALG in one small study where it showed better graft survival [121].

The two IL-2R antagonists have been compared head to head in limited trials and have shown mixed results [84, 114]. A modified two dose regimen of daclizumab was compared with the standard two dose regimen of basiliximab and found to be inferior in terms of preventing acute rejection episodes in one study [84]. However, another study found that modified two dose daclizumab was as effective as basiliximab, resulted in better renal function and was more cost effective [114]. A meta analysis of randomized trials using IL2 antagonists found that adding basiliximab to a double-drug or triple-drug therapy regimen had the same benefit as adding daclizumab in preventing acute rejection (at 6 months: basiliximab RR 0.67; CI 0.59–0.77 vs. daclizumab RR 0.66; CI 0.53–0.82) [171]. Both agents are felt to be equally efficacious despite the lack of randomized trials directly comparing the two agents.

Use of IL-2R antagonists to allow for steroid free and early steroid withdrawal has been studied in the FREEDOM and CARMEN trials. In the FREEDOM trial, the incidence of acute rejection at 3 months was 20.6% in the steroid avoidance group, 15.6% in early steroid withdrawal group and 5.9% in the steroid group [158, 165]. It was felt that 65–90% patients could be maintained on steroid free regimens using IL-2 receptor antagonists and early withdrawal of steroids is probably better than complete avoidance [165]. An initial pilot study using daclizumab induction followed by cyclosporine and mycophenolate was successful in avoiding steroids in about 65% of patients, especially with low immunologic risk [32]. In the CARMEN study group, the regimen of daclizumab/tacrolimus /mycophenolate was compared with prednisone/tacrolimus and mycophenolate. Eighty eight percent of patients in the daclizumab group were able to avoid steroids at the end of 6 months with similar rates of rejection, patient, and graft survival [129]. Basiliximab induction therapy along with tacrolimus and sirolimus therapy has enabled early withdrawal of steroid therapy (4 days post transplantation) in renal transplant patients with 79% patients staying off steroids and with 100% graft survival at the end of 1 year [173]. This study, however, excluded African American patients who generally suffer an unacceptably high rejection rate with steroid avoidance regimens [6].

Studies that have tried IL2 antagonists to enable complete avoidance of calcineurin inhibitors have been associated with unacceptable high rejection rates and this practice is not currently recommended.

2.4.4 Side Effects

The IL-2R antagonists are well tolerated and the incidence of side effects in studies has been reported to be similar to the placebo. The cytokine release syndrome does not occur although hypersensitivity reactions have been reported with both initial and re-exposure to both basiliximab and daclizumab [85]. The most frequent side effect is gastrointestinal upset [27]. The incidence of bacterial and viral infections and malignancies including PTLD are similar to placebo [27, 85, 111]. There do not seem to be any directly associated histopathologic side-effects of IL-2R antagonists.

2.5 Polyclonal Antibodies (Thymoglobulin and ATGAM)

Two preparations of polyclonal antibodies are currently available in the US – thymoglobulin and ATGAM. ATGAM is manufactured from immunization of human thymocytes in horses. Thymoglobulin is derived from rabbits [85].

2.5.1 Mechanism of Action

Both target multiple T-cell markers such as CD2, CD3, CD4, CD8, CD11a, CD18, CD25, CD44 and CD45, co-stimulatory and adhesion molecules on antigen presenting cells, T and B cells as well as MHC molecules and natural killer (NK) cells. The primary mechanism of action is felt to be lymphocyte-depletion [85, 136]. The duration of lymphopenia can be up to 1 year with the use of thymoglobulin while with the Equine ATG, the lymphopenia is much shorter, about 14 days [51]. Long term specific depletion of the CD4+ lymphocyte subset and the preferential generation of a CD8+, CD57+ immunomodulatory subset of T cells has been postulated to explain the long-term success of polyclonal immunosuppression [136]. Unlike the IL2 receptor antagonists, thymoglobulin leads to the generation of T-regulatory cells in vitro [86]. Even low concentrations of ATGs can induce a near complete disappearance of lymphocyte functioning antigen (LFA-1) on monocytes, granulocytes and lymphocytes and inhibit endothelial inflammatory and adhesion molecules [67]. Thus, they may be useful in ischemia reperfusion injury. Antibody affinity to CD 45 may also be important in controlling rejection and inducing tolerance [40, 85]. Binding to CD45RB alters the CD45 isoform expression on the T cells, which is associated with upregulation of CTLA 4 expression and induction of peripheral tolerance [40].

2.5.2 Dosage

The half life of thymoglobulin is 2–3 days and the usual dose is 1.5 mg/kg/day for 4–7 days. It is usually given by large central vein infusion because of its propensity to cause phlebitis although it has also been administered peripherally with heparin and hydrocortisone without significant thrombosis [93]. Data on bolus dose thymoglobulin are accumulating [5, 59, 105, 133, 176]. Three day bolus dose thymoglobulin (3 mg/kg intraoperatively followed by 1.5 mg/kg for 2 more days) has been shown to be as effective as the standard 7 day regimen in terms of preventing acute rejection, overall graft and patient survival [5]. Pretreatment with bolus dose anti lymphocyte therapy with thymoglobulin (5 mg/kg) can facilitate alloengraftment so that minimal immunosuppression is required for maintenance therapy in most patients [133].

2.5.3 Clinical Efficacy

Thymoglobulin has been shown to be more efficacious compared to ATGAM [17, 45, 85, 151]. Thymoglobulin causes a more profound depletion of lymphocytes, leads to less severe biopsy proven rejection, better event-free survival, less cytomegalovirus disease, and fewer serious adverse events [17, 45, 85, 151]. The short term effects of thymoglobulin vs. basiliximab induction therapy have been compared. In patients with high risk for delayed graft function or rejection, thymoglobulin was found to reduce the frequency of acute rejection in comparison to basiliximab [16]. There was no difference in the incidence of delayed graft function, graft loss and death between the two agents [16]. A higher incidence of bacterial and viral infections but a lower incidence of CMV disease was noted with thymoglobulin therapy [16]. In patients with low immunologic risk, thymoglobulin and basiliximab have shown comparable efficacy in terms of rates of rejection, allograft and patient survival [78, 102, 142].

2.5.4 Side Effects

Because of their xenogenic origin and significant antibody dose, polyclonal antibodies may cause allergic reactions or serum sickness. The most common adverse effects are urticaria and fever, chills, and rash especially after the first dose [85]. The cytokine release syndrome, more common with OKT3, can still occur

with the polyclonal antibodies, especially with bolus regimens. Polyclonal antibodies may cause phlebitis when administered peripherally and thus are most commonly given through a central vein to minimize the risk. Hypertension, diarrhea, and headache can be seen with therapy. Hypotension, leucopenia or thrombocytopenia may require slowing of the infusion rate or either a reduction in dose or termination of therapy.

There is an increased incidence of CMV infections with polyclonal antibodies after induction or treatment for rejection with intravenous anti-lymphocyte therapy. Use of polyclonal antibodies has also been implicated in the increased incidence of PTLD [21, 111]. The use of thymoglobulin increases the risk of PTLD by about fourfold. This risk increases further if anti rejection treatment is required [111].

2.6 Alemtuzumab

2.6.1 Mechanism of Action

Alemtuzumab (Campath 1H) is a monoclonal antibody directed against CD52 and approved for treatment of chronic lymphocytic leukemia (CLL) [168]. The CD 52 antigen is highly expressed on B and T cells and monocytes, macrophages, dendritic cells and NK cells and therefore alemtuzumab causes profound lymphocyte depletion [8, 124, 168]. Alemtuzumab complexes with CD52 and causes cell death through complement mediated killing or antibody dependent cellular toxicity [8]. The CD52 molecule may be involved in cell to cell adhesion and signal transduction [8]. Recent studies have shown that alemtuzumab causes activation of CD4+ regulatory T cells. These cells may suppress the polyclonal responses of both CD4+ and CD8+ T cells with polyclonal or allogeneic stimulation [8].

2.6.2 Dosage

After initial success in the treatment of CLL, Alemtuzumab is now being used as an induction agent for organ transplantation. The optimal dose for renal transplantation is unknown. Although the dose for treatment of CLL is 30 mg dose three times weekly, typical regimens for renal transplantation are 20 mg after surgery and repeated on day 1 [8, 170]. This reflects lower numbers of lymphocytes in a transplant patient compared to ten times higher numbers in patients with CLL [8].

2.6.3 Clinical Efficacy

A randomized control trial compared alemtuzumab to placebo for induction therapy [170]. It found no significant difference between the two groups in terms of delayed graft function, or patient and graft survival. The acute rejection rates were not different in the two groups although it occurred later in patients treated with alemtuzumab [170]. In this trial, patients that were treated with alemtuzumab were given lower doses of cyclosporine and steroids.

In a non-randomized, retrospective study with variable follow up, there was a significant reduction in the incidence of acute rejection episodes compared historically, with other induction therapies including thymoglobulin, basiliximab, daclizumab and OKT 3 [70]. There was no increase in the incidence of infections or malignancy in the alemtuzumab cohort. However, the duration of follow-up for the alemtuzumab group was about 1 year on average and 5–6 years for the other cohorts in the study. A 3 year prospective pilot study of Campath induction therapy followed by maintenance therapy with sirolimus as a single agent reported high incidence of early acute rejection, with a distinct predominance of humoral antibody mediated rejection [11].

2.6.4 Side Effects

Alemtuzumab for the treatment of CLL is associated with fever, chills and rigors and flu- like syndrome which require premedication and resolves with continued use [42]. Because of prolonged lymphopenia, patients can develop opportunistic infections like CMV, herpes zoster and herpes simplex infections among others [42]. When used as an induction agent for transplant, however, there was no reported increase in incidence of infectious complications in comparison to the control group. There was no increase in the incidence of PTLD with alemtuzumab [170]. However,

serious hematological toxicity has been reported with alemtuzumab. In 2005, the FDA issued a warning because of three cases of severe immune thrombocytopenic purpura (ITP) noted in a study on effectiveness of alemtuzumab with multiple sclerosis. Use of alemtuzumab has also been associated with development of autoimmune thyroiditis in multiple sclerosis patients and transplant recipients [32, 69].

2.7 Maintenance Drugs

2.7.1 Prednisone

Corticosteroids have been an important part of maintenance immunosuppression since the earliest days of transplantation. The many side effects associated with their use has led investigators to explore ways to eliminate or minimize their use recently.

2.7.1.1 Mechanism of Action

Corticosteroids are available in two formulations: prednisolone and prednisone. Prednisolone is primarily used in Europe and prednisone is used in North and South America. Prednisone is metabolized in the liver to prednisolone which is the active compound [149]. The bioavailability of prednisone is 80% of that of prednisolone. The efficacy of the two drugs is similar with a similar mechanism of action. Corticosteroids bind to glucocorticoid receptors in the cytoplasm. This complex then translocates into the nucleus and attaches to the glucocorticoid response elements (GREs) on the promoter sequence for various genes. Corticosteroids enhance the promoter enhanced transcription of I-kappa-B (IkB), interleukin (IL)-1 receptor-II (IL-1RII), lipocortin-1 (annexin I), IL-10, alpha-2-macroglobulin, and secretory leukocyte protease inhibitor, which are anti-inflammatory mediators and block the function of the transcription factors nuclear factor kappa B (NF-kB) and activator protein-1 (AP-1) that are required for transcription of proinflammatory mediators [149]. Corticosteroids also diminish the stability of mRNA encoding IL-1, IL-2, IL-6, IL-8, tumor necrosis factor (TNF), and granulocyte-macrophage-colony stimulating factor (GM-CSF). Corticosteroids exert general immunosuppressive side effects besides their effect on lymphocytes. They cause stabilization of the lysosomal membranes, suppression of prostaglandin synthesis, reduction of histamine and bradykinin release and impairment of monocyte/macrophage function.

2.7.1.2 Dosage

Steroids are usually administered as a "pulse" intraoperative dose of 5–10 mg/kg of methylprednisolone, which is followed by 1 mg/kg/day of prednisone. Steroids are currently tapered to approximately 0.1 mg/kg/day of prednisone by the end of 1 month to 6-months.

2.7.1.3 Clinical Efficacy

Corticosteroids were formerly used in very high doses previously until it was shown that when combined with azathioprine 2 mg/kg/day, lower doses were as effective as higher doses with less morbidity [36, 101]. However, the prolonged use of corticosteroids, even in low dose has been associated with significant side effects. The focus in the past few years has been to use immunosuppressive regimens that minimize or avoid the use of steroids. These regimens have varied from very low maintenance dose, early withdrawal to complete avoidance of steroids. The usual trend in most transplant centers has been to taper the steroids dose quickly to 5 mg/day and maintain it at this level unless acute rejection occurs. A meta-analysis of studies using early withdrawal of steroids found that this strategy was associated with an unacceptably high rejection rate [53]. A randomized, double-blind study comparing corticosteroid withdrawal to low dose prednisone showed that at 5-years there was no difference in the primary composite endpoint (death, graft loss, or moderate/severe rejection) or in any of the individual components of the primary endpoint. Renal function, assessed by serum creatinine or estimated glomerular filtration rate (eGFR), did not differ at any time-point out to 5-years. There were, however, higher rates of for cause biopsy-proven acute rejection (BPAR) in the withdrawal group and chronic allograft nephropathy (CAN) was more than twice as high in the withdrawal group [172].

Late withdrawal of steroids has yielded conflicting results [64, 112]. In a large prospective study, 1,110

cadaveric kidney recipients underwent slow glucocorticoid withdrawal after at least 6 months post transplantation. Seven year follow up noted improved graft, and patient survival in comparison to matched controls [112]. A meta-analysis of twenty glucocorticoid withdrawal studies, however, reported a higher relative risk of graft failure and increased risk of acute rejection with steroid withdrawal [64]. Various immunosuppressive combinations have been tried to enable steroid withdrawal without increasing the risk of rejection. Induction therapy with basiliximab, with maintenance regimen of sirolimus, mycophenolate and low dose tacrolimus was able successful in steroid withdrawal at 3 months without increasing the incidence of acute rejection [163, 164]. Similarly, induction therapy with thymoglobulin and maintenance therapy with mycophenolate and sirolimus has allowed for protocols with calcineurin minimization and early steroid withdrawal [55].

2.7.1.4 Side Effects

Corticosteroids have multiple adverse effects, including cushingoid habitus, susceptibility to infection, impaired wound healing, growth suppression in children, osteoporosis, aseptic necrosis of bone, cataracts, glucose intolerance, fluid retention, hypertension, emotional liability, insomnia, manic and depressive psychosis, gastric ulcers, hyperlipidemia, polyphagia, obesity, and acne [139, 149].

2.7.2 Calcineurin Inhibitors

The calcineurin inhibitors, first with the introduction of cyclosporine in the mid-1980s and then with and tacrolimus in the mid-1990s, have been the mainstay of immunosuppressive regimens for the past 25 years [16].

2.7.2.1 Mechanism of Action

Cyclosporine binds to cyclophilin which helps concentrate the cyclosporine in the cytoplasm. Tacrolimus binds to FK binding protein 12 (FKBP 12). Although they bind to different cytosolic proteins, both drugs exert similar effects downstream [16]. The drug – cytosolic protein complex binds to calcineurin, a calcium/calmodulin-activated protein phosphatase. Calcineurin dephosphorylates nuclear factor of activated T cells (NFAT) so that it can enter the nucleus and activate cytokine transcription genes. Binding of calcineurin by cyclosporine and tacrolimus causes failure of transcription of factors IL 2, IL3, IL 4, IL 5, CD 40 ligand, GM CSF, IFNγ and TNFα, which are activated by NFAT. An additional effect of tacrolimus is blockade of cytokine receptor expression and cytokine effects on target cells [130]. This may explain why tacrolimus is equally effective at preventing rejection despite less calcineurin inhibition compared to cyclosporine at clinically used doses and levels achieved [72].

2.7.2.2 Dosage

Historically doses of cyclosporine in transplantation were up to 17 mg/kg [119]. These high doses were associated with frequent side effects and poor tolerance. With further experience, it was realized that lower maintenance doses were as efficacious and less toxic. Tacrolimus achieves similar immunosuppression with 20–50 fold lower doses than cyclosporine [72]. Cyclosporine and tacrolimus doses are adjusted on blood levels. The dose of cyclosporine is adjusted to maintain 12 h trough levels of 200–300 ng/mL for the first 3 months post-transplant; after this period, trough levels of 50–150 ng/mL are generally adequate. For tacrolimus, doses are adjusted to attain target whole-blood trough concentrations of 8–10 ng/mL for the first 3 months, and 3–8 ng/mL after this period.

2.7.2.3 Clinical Efficacy

Cyclosporine alone or in combination with azathioprine and corticosteroids led to a dramatic lowering in acute rejection rates and marked improvement in 1-year graft survival compared to the use azathioprine and corticosteroids. Cyclosporine, however, is nephrotoxic and the reduced rate of acute rejection has not translated into improved long term graft survival [91, 119]. Over the last decade, tacrolimus has replaced cyclosporine as the calcineurin inhibitor of choice at most centers. Use of tacrolimus has been associated with less rejection, lower serum creatinines and fewer side-effects in comparison to cyclosporine in some studies. The combination of tacrolimus with azathioprine showed reduced rate of acute rejection in comparison to cyclosporine

and azathioprine combination [94, 116]. Further benefit of switching from cyclosporine to tacrolimus after the first episode of acute rejection was shown to reduce subsequent rejection episodes [18]. With the use of current induction regimens, use of mycophenolate as the antimetabolite, and conversion to modified cyclosporine, the graft and patient survival rates are not significantly different between tacrolimus and cyclosporine based-regimens [7, 58, 92]. The choice of calcineurin inhibitors at present is generally by center preference.

2.7.2.4 Side Effects

Both cyclosporine and tacrolimus have been associated with frequent side effects. Urinary tract infections are the most common infections and CMV infection is also seen frequently. The incidence of infections does not seem to differ among cyclosporine and tacrolimus [58, 92].

Nephrotoxicity, both acute and chronic, has been the major concern with calcineurin inhibitors. Cyclosporine and tacrolimus can cause acute nephrotoxicity because of intense arterial vasoconstriction that they produce. The vasoconstriction is associated with increased levels of endothelin1, decreased nitric oxide and increased TGF β [23, 157]. Acute CNI toxicity is usually a dose dependent phenomenon and resolves as the dose is decreased [119]. A variety of histopathological changes are noted with the use of cyclosporine. Isometric tubular vacuolization is a characteristic histopathologic change of acute calcineurin toxicity (Fig. 2.3). Cyclosporine can also cause arteriolopathy with nodular protein deposits in the arterial wall and mucinoid thickening of the intima (Fig. 2.4). This is only partially reversible with reduction in dose.

Long term cyclosporine use has been implicated in the development of CAN manifested as interstitial infiltrates, striped fibrosis, and arteriolar hyalinosis (Fig. 2.5). This CAN is irreversible. Similar nephrotoxicity has been noted with tacrolimus [98, 140]. Immunologic factors cause the initial tubulo-interstitial damage but calcineurin inhibitors are responsible for the major histological damage noted in CAN [106]. Calcineurin inhibitors may also cause hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP) or thrombotic microangiopathy (Fig. 2.2) [43]. This may be dose-related or idiosyncratic. Lower

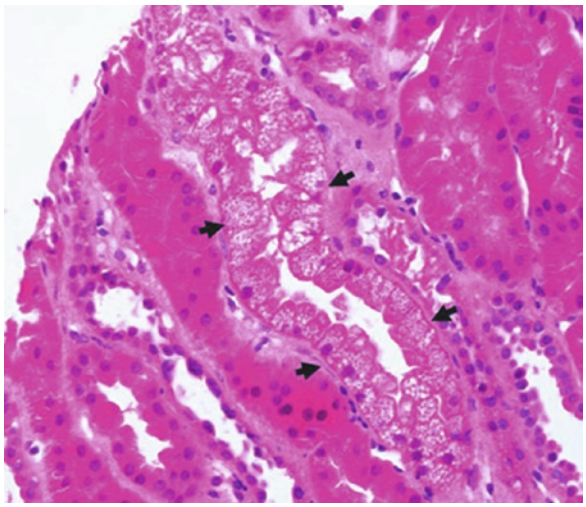

Fig. 2.3 *Black arrowheads* indicate cyclosporine induced isometric vacuolization

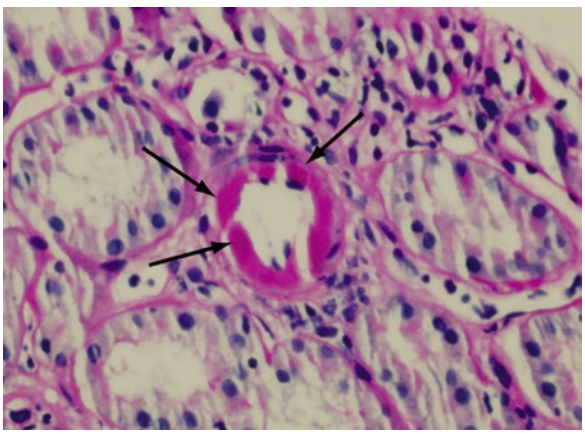

Fig. 2.4 *Black arrows* show arteriolar beaded hylanosis of chronic cyclosporine toxicity

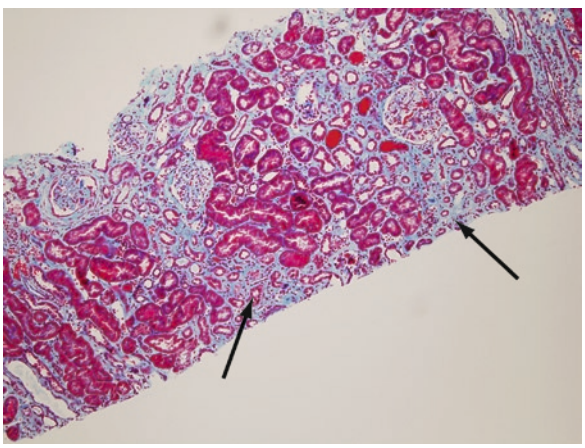

Fig. 2.5 *Black arrows* show striped interstitial fibrosis of chronic cyclosporine toxicity

doses of CNIs are currently used and the incidence appears to be decreasing from 3–14% in older literature to 0.8% in the current literature [127, 175].

Hypertension is also a known side effect of cyclosporine and tacrolimus therapy. It develops within a few weeks to months after therapy with calcineurin inhibitors. It seems to be independent of nephrotoxicity. In contrast to nephrotoxicity of the two drugs, which is comparable, the effects on blood pressure are more pronounced with the use of cyclosporine [24, 83]. The effect seems to more dependent on vasoconstriction than salt retention as demonstrated by hypertension present in an anuric transplant on cyclosporine [167].

Hyperlipidemia is a complication of the cyclosporine therapy. Patients treated with cyclosporine have higher LDL levels in comparison to tacrolimus based regimens, although triglyceride levels are similar [31, 57]. This may be related to binding of the LDL receptor or decreased lipoprotein lipase activity but the exact cause is not clear.

Post transplant diabetes mellitus is a significant side-effect of current immunosuppressive regimens. Steroids induce insulin resistance but the calcineurin inhibitors, especially tacrolimus, have detrimental effects on beta cell function. Tacrolimus causes beta cell damage and reduced insulin secretion [132]. The incidence of hyperglycemia has been previously reported to be as high as 24% at 36 months with the use of tacrolimus [65]. The risk of de novo diabetes mellitus has now decreased because of lower doses of steroid therapy and lower doses of tacrolimus that are currently used [148, 155]. Risk factors for the development of diabetes are the dose of tacrolimus, concomitant use of steroids and African American race. Cyclosporine can decrease beta cell volume and increase the risk of post transplant diabetes. The risk of diabetes is lower with cyclosporine than tacrolimus.

Both drugs are associated with neurological side effects: tremor, headache, neuralgia and peripheral neuropathy, with tremors more common with tacrolimus [116]. However, serious neurological complications can occur including seizures, encephalopathy, visual and auditory hallucinations, cerebellar ataxia, motor weakness and encephalopathy [12].

Other side effects include hirsutism, gingivitis and gum hyperplasia, which are more common with use of cyclosporine [116]. There is a 1–1.5% risk of malignancy with the use of the calcineurin inhibitors [94]. This risk may be reflective of the overall degree of immunosuppression rather than any specific drugs. Skin cancers and lymphomas are the most common cancers. Post transplant lymphoproliferative disorder is equally prevalent among adult patients with the use of cyclosporine and tacrolimus. The pediatric literature, however, suggests an increased incidence of PTLD with the use of tacrolimus [37].

Dose-dependent hyperkalemia due to tubular aldosterone resistance has been noted with cyclosporine [46, 147]. Cyclosporine also causes hyperuricemia and gout and hypomagnesemia because of its effects on tubular handling of uric acid and magnesium respectively. Tacrolimus causes these disorders as well but is reported less often.

2.7.3 Mycophenolate

Mycophenolate is an antimetabolite that is available in two formulations: mycophenolate mofetil (MMF, CellCept) and enteric coated mycophenolic acid (MPA, MyFortic). Both inhibit inosine monophosphate dehydrogenase (IMPDH).

2.7.3.1 Mechanism of Action

Lymphocytes require IMPDH for replicating genetic information during cell division. Other cells in the body may use alternate enzyme pathways when the IMPDH-dependent pathway is inhibited. MMF, introduced in 1995, is the morpholinoethyl ester of MPA, a selective antimetabolite that blocks de novo purine synthesis in lymphocytes. Because it is a stronger inhibitor of type II isoform of IMPDH, which is expressed preferentially in activated lymphocytes, it is useful for transplantation and treatment of autoimmune diseases. In addition, MPA inhibits recruitment of monocytes and macrophages and decreases TNF α and IL1 production which are essential in recruitment of fibroblasts [9]. This contrasts with the calcineurin inhibitors which increase TGF β expression in the grafted kidneys and promote fibrogenesis. Mycophenolate also strongly interferes with the adhesion of lymphocytes to the vascular endothelium [9].

2.7.3.2 Dosage

The dose of mycophenolate for renal transplantation is 1,000 mg twice daily when used with cyclosporine but lower doses are used with tacrolimus because tacrolimus, unlike cyclosporine, does not block P-glycoprotein and thus does not block enterohepatic circulation leading to higher drug exposure compared to concomitant use of cyclosporine [35]. Doses up to 3 g/day may be required in African American patients for adequate immunosuppression. MyFortic which is the enteric coated formulation is given as 720 mg twice daily dosage.

2.7.3.3 Clinical Efficacy

Compared to placebo or low dose azathioprine with a non-modified preparation of cyclosporine (Sandimmune), mycophenolate was shown to reduce acute rejection by about 50% [1, 104, 118, 141]. This prompted the increased use of mycophenolate in transplant centers and the gradual phasing out of azathioprine as the anti metabolite of choice. In long term studies, the reduced rejection rates have not translated into better allograft survival. A recent randomized-prospective study showed that when used with a modified cyclosporine preparation and standard azathioprine doses that rejection rates were similar at 1, 2, and 5 years as was graft survival even among those who had steroid withdrawal [125, 126].

2.7.3.4 Side Effects

Mycophenolate, unlike calcineurin inhibitors, has no direct cardiovascular, hemodynamic or renal side effects. It is also free of metabolic side effects. This along with its effects on reducing antidonor antibodies and TNF α and IL1 have been speculated to be the reason for decreasing CAN in transplant recipients [97, 153]. Its main side effects include gastrointestinal side effects including abdominal pain, nausea, diarrhea and hematological side effects including anemia, and leucopenia [169]. Patients with gastrointestinal complaints can be switched from MMF to Myfortic without loss of efficacy [19]. Mycophenolate may predispose to a slightly higher risk of CMV infections with higher doses (3 g/day) [25, 169]. There is a high incidence of occult-gastrointestinal CMV in the absence of viremia among patients with GI side-effects on mycophenolate [63]. Invasive CMV in the kidney may also be seen with very low or absent CMV viremia [82]. Mycophenolate is not associated with any increase in incidence of post-transplant malignancies and has a satisfactory safety profile for long term immunosuppression [169].

2.7.4 Rapamycin (Sirolimus)

Sirolimus is an inhibitor of mTOR (mammalian target of Rapamycin).

2.7.4.1 Mechanism of Action

Sirolimus binds to the FK binding proteins, similar to tacrolimus but this complex binds to the mTOR complex. It blocks the effect of mTOR and blocks the activation of IL-2 and inhibits the progression of the T cell from the G phase to the S phase. Besides its effects on IL-2 and IL4, sirolimus also affects IL7, IL12 and IL15 [39]. Sirolimus, but not cyclosporine has been shown to prevent the CD28 mediated down regulation of IkB. This causes persistent inhibition of NF-kB and prevents transcription of IL2 and other cytokines [73].

2.7.4.2 Dosage

The loading dose of sirolimus can vary from 6 to 15 mg. The maintenance dose is 2–5 mg and is adjusted based on sirolimus whole blood trough concentrations targeted to 5–15 ng/mL.

2.7.4.3 Clinical Efficacy

Studies have shown that in comparison with azathioprine, sirolimus is associated with a significant reduction of both the incidence and severity of biopsy proven rejection episodes [60, 61, 88]. When sirolimus was substituted for high-dose cyclosporine, there was an improvement in the graft function with no significant increase in the rejection rates [50, 52].

Sirolimus has antiproliferative effects, causes inhibition of vascular smooth muscle cells and intimal proliferation and thus has been utilized for drug coated coronary stents [48]. It has been used with promising results in the treatment of variety of tumors including small cell lung cancer, pancreatic cancer, leukemia, lymphoma, rhabdomyosarcoma, neuroblastoma and breast cancer [54].

2.7.4.4 Side Effects

Sirolimus is associated with increased incidence of delayed graft function [82, 95, 137, 143]. In a study of 144 patients with first cadaveric or living donor kidney allograft recipients, the incidence of delayed graft function was 25% with the use of sirolimus in comparison to 9% in those without [143]. A retrospective analysis of the cadaveric renal transplant patients in the USRDS system found that sirolimus was associated with a twofold increase in the incidence of delayed graft function although the graft and patient survival rate was unaffected [137].

Other side effects include increased incidence of lymphoceles, hernia, synergistic nephrotoxicity in combination with calcineurin inhibitors, hyperlipidemia, edema, anemia, proteinuria, thrombotic microangiopathy, thrombosis, and pneumonitis [2, 28, 47, 50, 100]. There has been a small case series of three patients who developed lymphedema after exposure to sirolimus [2].

Sirolimus has been associated with synergistic nephrotoxicity with calcineurin inhibitors. This may be in part related to the increased drug levels of cyclosporine and/or increased TGF β levels with the combination therapy [135]. Like the calcineurin inhibitors, it has metabolic side effects including hyperlipidemia. Hyperlipidemia usually starts at 1-month post transplant and peaks at 3-months [28, 61, 100]. This invariably requires lowered cholesterol intake and the use of statins. Other metabolic side effects include impaired glucose tolerance. Sirolimus is associated with insulin resistance with hyperglycemia and hyperinsulinemia [74]. In a study of peripheral blood mononuclear cells of 30 transplant patients on chronic sirolimus therapy, a marked decrease of basal and insulin-stimulated AKT phosphorylation was noted [38]. The combination of sirolimus with tacrolimus synergistically decreases islet cell size and increases islet cell apoptosis [74].

Sirolimus increases the de novo development of proteinuria. Non nephrotic and nephrotic range proteinuria have been noted when calcineurin inhibitors were withdrawn and sirolimus therapy was initiated. This may have been a consequence of calcineurin inhibitor withdrawal and subsequent hyper-filtration in the setting of impaired glomerular permeability and CAN [123]. However, convincing reports of focal segmental glomerulosclerosis related to sirolimus have now emerged [81]. Immunohistochemistry has shown diminished expression of the podocyte-specific epitopes synaptopodin and p57, reflecting dedifferentiation and podocyte dysregulation. Moreover, a decrease in vascular endothelial growth factor (VEGF) expression has been observed.

A variety of pulmonary effects have been attributed to the use of sirolimus. These have varied from lymphocytic alveolitis, lymphocytic interstitial pneumonitis, bronchoalveolar obliterans organizing pneumonia, focal fibrosis, pulmonary alveolar hemorrhage, or a combination thereof [115]. Sirolimus discontinuation or dose reduction resulted in clinical and radiologic improvement in all 15 patients in this series within 3 weeks.

Anemia is another side effect which has been seen with the use of sirolimus [100]. This side effect was notable when higher trough levels of sirolimus were targeted but with current trough levels of 5–12 ng/mL, the incidence of this side effect has decreased [41]. Microcytosis has been noted in some studies [44, 66, 100]. It may be related to decrease in levels of hepcidin, the key regulator of iron metabolism, although the exact mechanism is not clear [90].

Sirolimus has been associated with an increased incidence of herpes virus infection and pneumonia but not CMV infections [28].

The incidence of skin cancers may be less with use of sirolimus. Use of sirolimus in place of an antimetabolite has been associated with reduction in appearance of new lesions [152]. Other beneficial effects have included a decrease in BK viremia in one small study. However, it is unclear if both effects were related to conversion to sirolimus or reduction in the level of immunosuppression related to stopping the antimetabolite [80].

2.8 Newer Immunosuppressive Medications

2.8.1 Janus Kinase (JAK) 3 Inhibitors

JAK3 associates specifically with the common gamma chain of the interleukin-2 (IL-2) receptor and is found primarily on hematopoietic cells [174]. The genetic mutation of JAK3 causes abnormal lymphoid cell development and severe combined immunodeficiency [87, 174]. The association of JAK3 with the TcR/CD3 machinery as well as the IL-2R suggests a crucial role of this kinase in the regulation of both early T-cell activation and cytokine-driven cell growth [144, 150]. JAK 3 may also have a role in expression of eosinophilic airway inflammation [156].

JAK 3 inhibitors have had significant success in murine models of cardiac transplantation with prolongation of survival [71]. The most commonly tested JAK 3 inhibitor has been CP 690550. It produces a 20–100-fold more potent inhibition of JAK 3 in comparison to JAK 1 and 2 [26]. This compound is thus more immunosuppressive than other JAK inhibitors and carries a lower risk of hematological toxicity such as anemia and leucopenia. In *in vitro* studies, CP-690,550 caused a significant reduction of IL-2-enhanced IFN-gamma production by T-cells, T-cell surface expression of CD25 and T-cell proliferative capacity [113]. Similar results have been replicated in animals. In addition, transplanted animals displayed significant reduction of NK cell and CD8+ T cell numbers in a dose- and time-dependent manner [33]. Though CD4+ T cells were unaffected, their number increased significantly within 2 weeks of the last dose of CP-690550. CP-690550 also inhibited IL-15-induced CD69 expression in NK cells [33].

CP-690550 has been shown to reduce allograft rejection in nonhuman primates in combination with mycophenolate [15]. CP-690550 has also been shown to prevent allograft vasculopathy in a rodent model of aortic transplantation [131]. In preclinical and early clinical studies, the major side effects of CP 690550 have included reactivation of polyomavirus infection and anemia [14]. Subclinical pyelonephritis has also been noted along with one incidental lymphosarcoma [15]. There have been no cardiovascular or metabolic side effects noted thus far [26]. Its use in human patients is under investigation.

2.9 AEB-071

AEB-071 (AEB) is a novel, oral compound that inhibits protein kinase C (PKC). PKC is largely restricted to T lymphocytes and mediates activation NFkB, leading to downstream IL-2 production. AEB blocks early T-cell activation independent from the calcineurin pathway. This has prompted studies on the use of this agent in place of calcineurin inhibitors. AEB has been noted to have similar antiproliferative activity to MMF and retained its inhibitory effect on IL-2 production when combined with mycophenolate [138]. Preclinical studies have reported prolonged renal allograft survival in nonhuman primates with AEB at therapeutic doses or at non-therapeutic doses in combination with cyclosporine [166]. AEB in sub-therapeutic doses has been used in combination with everolimus, mycophenolic acid or FTY720 with prolonged graft survival [13]. It does not seem to have significant drug interactions with mycophenolate or everolimus. This has prompted two clinical trials using AEB 071 in place of calcineurin inhibitors in combination with steroids and basiliximab and everolimus or mycophenolate, and assesses the incidence of biopsy proven acute rejection and graft loss. No significant side effects related to this medication have been noted. In cynomolgus monkeys, AEB was well tolerated with normal blood chemistries and normal extra-renal histology at necropsy [13].

2.9.1 LEA 29Y (Belatacept)

Belatacept (LEA29Y) is an intravenously administered second-generation cytotoxic T lymphocyte antigen-4 immunoglobulin (CTLA-4Ig) that interferes with CD28 and CD 80/86 [75, 76]. CD28 is constitutively expressed by a majority of CD4+ T cells and approximately 50% of CD8+ cells [75]. CD28 helps lower the T-cell activation threshold and causes enhanced proliferation, T-cell differentiation into T helper (Th) cells, increased B-cell antibody production and increased

proliferation of previously activated T cell [161]. In contrast to CD28, CTLA-4, binds to CD80 and CD86, but with a 10–20-fold higher affinity and inhibits T cells.

Belatacept in low and intermediate doses was compared to high-dose cyclosporine and was found to have similar rates of study defined rejection in comparison to cyclosporine. Investigator treated rejection, however, was as much as twice as common in the belatacept arms compared to the cyclosporine arm (26, 32, and 16%, respectively), but there was a lower incidence of CAN and higher glomerular filtration rates in the no-cyclosporine belatacept groups compared to the high-dose cyclosporine group [160].

Similar blood pressure profiles and lipid profiles were seen with no difference in the side effect profiles of the two medications. Indication-biopsies were analyzed for infiltration of T regulatory cells [49]. Belatacept did not affect the infiltration of the grafts with T regulatory cells in comparison to cyclosporine. There was a 6% incidence of PTLD at 1-year in patients treated with intermediate-dose belatacept, but no PTLD was seen in the low-dose or cyclosporine-treated patients.

2.10 Efalizumab

Efalizumab is a humanized IgG1 version of a murine anti-CD11a monoclonal antibody with a noncovalently linked alpha chain (CD11a) and a beta chain (CD18). Lymphocyte functioning antigen-1 (LFA 1), CD11a/CD18, is a classic adhesion molecule. LFA1/intracellular adhesion molecule (ICAM) interactions are necessary for T cell activation, T cell and B cell responses. LFA 1 stabilizes the major histocompatibility (MHC)/T cell receptor complex and provides an important co-stimulatory signal. Efalizumab is approved for the treatment of moderate to severe psoriasis [34]. In a large trial for the treatment of psoriasis, Efalizumab was more effective than placebo, well tolerated with few side effects and safe with a 5% incidence of development of anti-Efalizumab antibodies [79].

Its role in renal transplantation is still being investigated. A Phase I/II open label multicenter trial comparing low dose (0.5 mg/kg/week) and high dose (2 mg/kg/week) with Efalizumab combined with half dose cyclosporine, prednisone and sirolimus or full dose cyclosporine, mycophenolate and prednisone regimens has been reported [162]. Complete saturation of the CD11a molecule occurred with the low dose as well as the high dose Efalizumab. There was no difference in acute rejection rates among groups and the mean GFR was similar. However, 30% of patients who received the higher dose Efalizumab combined with full dose cyclosporine regimen developed PTLD. Other drug related serious adverse events in this study included CMV infections, peritonitis and pancreatitis. No cases of PTLD were seen in trials of Efalizumab using the 1 mg/kg dose in patients with psoriasis [96].

2.11 Summary

A broad range of immunosuppressive agents are now available for use in renal transplantation. The last 2 decades have seen a remarkable increase in the introduction of new agents, both pharmacological and biological. The routine use of induction therapy along with maintenance immunosuppression with calcineurin inhibitors and mycophenolate has brought about an impressive reduction in the rates of acute rejection. One-year graft and patient survival rates now exceed 90% at most centers. This improved short term benefit has not translated into improved long term graft survival with most allografts being lost to CAN. Immunosuppressive drugs also have cardiovascular and metabolic side effects, and cardiovascular causes continue to be the leading cause of mortality for transplant patients. With an armamentarium of new immunosuppressive drugs now available, efforts are underway to combine immunosuppressive drugs with maximal efficacy, and avoid drugs with negative cardiovascular, renal and metabolic side effects or synergistic toxicity.

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