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Month/Year of Review: May 2013
PDL Classes: Oral Immunosuppressants

Date of Last Review: April 2010
Source Document: Provider Synergies

Current Status of PDL Class:

- Preferred Agents: AZATHIOPRINE, CYCLOSPORINE, EVEROLIMUS, MYCOPHENOLATE, SIROLIMUS, TACROLIMUS
- Non-Preferred Agents: NONE

Previous Recommendations:

1. Evidence does not support a difference in efficacy/effectiveness
2. Evidence does not support a difference in harm/adverse events
3. Recommend coverage of all entities
4. Recommend preference of generic products

Methods:

A Medline OVID search was conducted with the following search terms: azathioprine, cyclosporine, everolimus, mycophenolate, sirolimus, tacrolimus, oral immunosuppressants, transplantation, homologous transplantation, kidney transplantation, graft rejection, renal transplantation, organ transplantation, organ transplants, liver transplantation, graft rejection, heart transplantation, cardiac transplant, rheumatoid arthritis, inflammatory bowel diseases, myasthenia gravis, pancreas transplantation, Systemic Lupus Erythematosus, Takayasu's Disease, keratoconjunctivitis, Graft vs. Host Disease, lung transplantation, Ulcerative Colitis, Crohn's Disease, Sjogren's Syndrome, small intestine transplantation, and corneal transplantation. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to March week 4 2013.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Trials (Appendix 1):

A total of 1005 citations resulted from the initial MEDLINE search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, 18 relevant head-to-head clinical trials were identified and are discussed below. Seventeen studies were conducted in transplant patients and one trial in psoriasis patients. Because of the nature of the studied populations, these trials were of low quality; blinding, randomization, and allocation concealment were either not performed or not discussed. Please see Appendix 1 for the full abstracts.

Six studies focused on kidney transplant patients. Budde[1] et al conducted a multicenter open-label study in renal transplant patients (n=300) randomized to either cyclosporine or everolimus based regimens. The primary outcome was improved renal function; secondary outcomes included patient tolerance and organ rejection. At twelve months, everolimus patients showed significantly greater glomerular filtration rate (GFR) improvement (mean difference between groups: 9.8 mL/min, 95% CI -12.2 to -7.5). At the end of the trial reject rates were identical (15%) between the two groups. A follow-up study[2] was conducted at 3 years. At this time nearly 30% of everolimus patients had been reintroduced to cyclosporine or started on tacrolimus. The GFR was significantly higher with everolimus compared with cyclosporine (mean difference: 7.5 mL/min, 95% CI 3.6 to 11.4); however rejection rates were higher in the everolimus patients (13% versus 4.8%, p=0.015).

Dantal[3] et al conducted a multicenter open-label trial to measure the benefit of eliminating calcineurin inhibitors (CNI) on kidney function. Renal transplant patients were randomized to a regimen of everolimus and cyclosporine or everolimus and mycophenolate for twelve months. The primary outcome was mean difference in GFR and was not statistically significant between the two groups (p=0.059). The mycophenolate cohort did have an average improvement in GFR not seen in the CNI group; however, the two groups were not well matched at baseline and the CNI group had a much lower average GFR.

Guerra[4] et al looked at the long-term benefits of different immunosuppressant regimens post-renal transplant. Patients (n=150) were randomized in an open-label trial to tacrolimus and sirolimus, tacrolimus and mycophenolate, or cyclosporine and sirolimus. Acute rejection occurred less often (p=0.05) during the first 36 months among those treated with tacrolimus and mycophenolate (14%) than among those treated with tacrolimus and sirolimus (34%) or cyclosporine and sirolimus (31%). Average GFR was consistently higher in the tacrolimus and mycophenolate group (p= 0.008). There were no significant differences in survival between the groups at the end of eight years after transplant.
Mjörnstedt[5] et al also looked at the benefit for renal function of switching from a CNI to another immunosuppressant. Subjects (n=202) were randomized at week seven post-transplant to remain on cyclosporine or switch to everolimus. Improvement in GFR was measured at twelve months. Patients on everolimus saw improvement in average GFR (mean increase of 8.7 mL/min) compared with cyclosporine (mean decrease 0.4 ml/min, p<0.001). Acute rejection was higher for everolimus than cyclosporine (27.5% vs. 11.0%, p=0.004), although there was no difference in overall graft or patient survival.

Santos[6] et al conducted a trial comparing baseline low-dose cyclosporine paired with either everolimus or mycophenolate in kidney transplant patients. After two years patients were measured for differences in creatinine levels, acute rejection and survival rates. There was no significant difference between the everolimus and mycophenolate groups in mean serum creatinine (1.2 mg/dL vs 1.4 mg/dL, p=0.05), acute rejection (31% vs 40%, p=0.05), and patient or graft survival (100%).

Vacher[7] et al compared tacrolimus and mycophenolate with cyclosporine and azathioprine in a twelve month trial with a primary endpoint of acute organ rejection. Kidney transplant patients (n=289) were randomized to one of the two protocol groups. After one year, 14.4% of cyclosporine patients had an acute organ rejection versus 7.7% of tacrolimus patients, although this was nonsignificant (p=0.07). Overall rates of patient and graft survivals were also similar between the two groups.

Three trials focused on liver transplant patients. Abdelmarkel[8] et al looked at the possible benefits in renal function when switching liver transplant patients (n=607) from a CNI (tacrolimus or cyclosporine) to sirolimus. The primary endpoint was difference in GFR at twelve months. No statistical difference was seen in mean GFR between groups (p=0.34). In addition, no difference was seen between groups in rates of organ rejection or death.

Herlenius[9] et al also examined the effect on renal function when changing liver transplant patients from a CNI regimen to another immunosuppressant. Patients with preexisting chronic kidney disease (n=25) were randomized to either sirolimus or mycophenolate in this before and after trial. The average GFR at baseline was 31 mL/min. After three months the average GFR increased to 40 mL/min (p=0.0001) and at twelve months to 42 mL/min (p=0.0006). There was not a significant difference between the two study arms. No long-term outcomes were examined.

Schmeding[10] et al randomized liver transplant patients (n=150) to either standard CNI or mycophenolate treatment for a long-term safety trial. Patients were followed for five years to see if there was any difference in clinical outcomes. No significant difference regarding the incidence of acute rejection was detected and patient survival was identical in the two groups.

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De Simone et al conducted a 24-month, multinational, open-label, randomized trial in liver transplant patients starting 30 days post-transplant in 1,147 patients.[11] Prior to randomization, patients received tacrolimus and corticosteroids, with or without mycophenolate. At day 30, 719 patients were ranomidzed into one of three groups: everolimus initation with tacrolimus elimination, everolimus initation with reduced exposure tacrolimus, or standard-exposure tacrolimus. The first group (tacrolimus elimination) was discontinued early due to a higher incidence of acute rejection. The reduced tacrolimus group was non-inferior to the tacrolimus control group for the primary endpoint of acute rejection, graft loss, or death at 12 months post-transplant (6.7% vs. 9.7%, p<0.001).[11]

Five trials focused on heart transplant patients. Guethoff[12] et al randomized patients to either tacrolimus or cyclosporine and followed them for ten years. Primary efficacy outcomes included acute rejection and overall survival. Members on tacrolimus were significantly less likely to experience an acute rejection (21.7% vs. 65.5%, p<0.004). This did not translate to increases in overall survival for tacrolimus subjects; survival rates at one, five and ten years were 96.7%, 80.0%, and 66.7% for tacrolimus and 90.0%, 83.3%, and 80.0% for cyclosporine (p>0.05 for all years).

Sanchez-Lazero[13] et al examined the rate of cardiac allograft vasculopathy (CAV) in heart transplant patients taking different calcineurin inhibitors. CAV is a leading cause of death in this population. Patients (n=49) were randomized to either cyclosporine or tacrolimus. After one year, no significant difference was detected between the two groups development of CAV (cyclosporine 31.6% vs tacrolimus 38.9%, p=0 .642). Thirteen patients died within the study period; no distinction was made as to which medication regimen these patients were assigned to.

Vigano[14] et al examined the rate of cytomegalovirus (CMV) in heart transplant patients (n=176) randomized to either everolimus or mycophenolate. This twelve month multicenter, open-label study found that the everolimus patients had significantly lower incidence of CMV than the mycophenolate arm (8.8% vs. 32.5%, p<0.001).

Potena[15] et al compared long-term use of low-dose cyclosporine with everolimus or mycophenolate for reducing progression of renal dysfunction in heart transplant patients. Patients (n=34) were one to four years post-transplant with a creatinine clearance (CrCl) of 25 to 60 ml/min. Primary end point was improvement in CrCl after a follow-up of three years. CrCl improved in the mycophenolate group 20% from baseline (p=0.01) but the everolimus group did not have a significant change from baseline. Overall survival and organ rejection rates were not significantly different between the two groups.

Zuckerman[16] et al evaluated the effect on renal function of switching from a CNI to sirolimus in heart transplant patients. The primary outcome was change in GFR after one year. Patients (n=116) were randomized to remain on a CNI (tacrolimus or cyclosporine) or change to sirolimus; baseline GFR for all patients was between 40 and 90 mL/min. After one year, sirolimus patients had a significant increase in GFR compared with those on CNI medications (+3.0 vs.−1.4mL/min, p = 0.004). Acute rejection rates were not significantly different between treatment groups.

Two trials focused on lung transplant patients. Treede[17] et al examined any difference in the incidence of bronchiolitis obliterans syndrome (BOS) with CNI regimens in a multicenter, open-label trial. BOS is the primary cause of death in lung transplant patients. Patients (n=149) were randomized to either cyclosporine or tacrolimus and followed for three years. The rate of BOS, after three years was lower for tacrolimus patients (11.6% vs. 21.3%, p=0.037). Differences in acute rejection and overall survival rates were statistically nonsignificant.

Bhorade[18] et al compared the incidence of organ rejection in lung transplant patients placed on sirolimus. Patients (n=181) were randomized to either sirolimus or azathioprine in a twelve month open-label trial. After one year, there was no significant difference in organ rejection between the two study groups (p=0.82).

One trial focused on psoriasis patients. Akhyani[19] et al randomized patients (n=36) to either mycophenolate or methotrexate for twelve weeks to treat their chronic plaque psoriasis. Patients had a baseline Psoriasis Area and

Severity Index (PASI) score of 10 or greater and the average difference from baseline was the primary outcome. After 12 weeks of treatment, the mean score for the PASI decreased from 16.46 to 3.17 among methotrexate patients and from 17.43 to 3.97 in mycophenolate patients ($p>0.05$). Improvement seen three months after trial discontinuation was also statistically nonsignificant between treatment groups.

New drugs:
None

New Formulations/Indications:
Two new formulations of everolimus have been approved since the last oral immunosuppressant class review. Zortress[20] is an oral tablet indicated for the prophylaxis of organ transplant in adults. It was approved in April of 2010. In February of 2013, it was also approved for the prophylaxis of organ rejection in those receiving a liver transplant.

Afinitor[21] was approved in August of 2012. Afinitor Disperz is a tablet for oral suspension approved for the new indication[22] of treatment in pediatric and adult patients with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected. It is also indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole.

New FDA safety alerts:
In September of 2012, the FDA began a Risk Evaluation and Mitigation Strategy (REMS) for mycophenolate[23] to address the increased risk of miscarriage and birth defects if taken during pregnancy. The Mycophenolate REMS includes a Medication Guide, training for health care professionals, and the establishment of a pregnancy registry for women who become pregnant and agree to participate in the registry.

An FDA safety communication was released in April 2011 for azathioprine[24] informing the public that it has received reports of a rare cancer of white blood cells (known as Hepatosplenic T-Cell Lymphoma or HSTCL), primarily in adolescents and young adults being treated for Crohn's disease and ulcerative colitis with medicines known as tumor necrosis factor (TNF) blockers, as well as with azathioprine, and/or mercaptopurine. No labeling changes were associated with this communication. The FDA believes the risks and benefits of using these medications should be carefully weighed when prescribing these drugs to children and young adults.

New Systematic Reviews: (Appendix 2)
Five new systematic reviews were identified. Please see Appendix 2 for the full abstracts.
Asrani[25] et al conducted a systematic review to determine if using sirolimus improves renal function in liver transplant patients with baseline renal insufficiency. Three randomized control trials (RCT) and eight observational studies were included in the analysis. Patients with a glomerular filtration rate (GFR) of less than 60 mL/min were switched from a calcineurin inhibitor (CNI) to sirolimus from the time of transplantation to five years post-transplant. All three RCTs and four of the observational study (n=368) were included in the estimated change in renal function after 12 months (3.38 mL/min, 95% CI -2.93 to 9.69). Isolating the RCT (n=82), the pooled estimated renal function change was significant (10.35 mL/min, 95% CI 3.98 to 16.77), but the average baseline GFR was higher for this population. Sirolimus did not significantly decrease the risk of death (RR 1.12, 95% CI 0.66 to 1.88) or organ rejection (RR 0.8, 95% 0.45 to 1.41). Individual trial quality was poor with high risk of bias in all of the RCT due to lack of blinding, allocation concealment and randomization methodology.

A Cochrane Collaborative systematic review involving oral immunosuppressants was published in2012. Penninga[26] et al planned to examine the efficacy and safety of using low dose CNI (tacrolimus or cyclosporine) in liver transplant

patients. Trials that included a switch to another immunosuppressant were not eligible. No trials were found to meet the author's criteria for inclusion and the review was discontinued.

Sharif[27] et al also examined strategies to minimize the negative effects of CNI therapy. Their analysis focused on kidney transplant patients who had undergone CNI avoidance, CNI minimization, or CNI delayed introduction. Fifty-six studies were included with 11,337 subjects; the median trial length was twelve months. No difference was found in overall graft failure (OR 1.05, 95% CI 0.85 to 1.29) or death (OR 1.11, 95% CI 0.89 to 1.38) between standard versus reduced CNI exposure patients. Acute rejection was measured in 53 studies (n= 10,712) and increased rates of rejection were seen in the reduced CNI exposure group (OR 1.24, 95% 1.01 to 1.53). Breaking the data down for individual regimens, use of sirolimus or everolimus with mycophenolate (n=2688) was associated with an increase in graft failure (OR 0.61, 95% CI 0.39 to 0.96). Individual trial quality was considered fair to poor, with limited information available for allocation concealment and randomization practices. Also, most trials were not blinded.

Penninga[28] et al conducted a systematic review to compare the safety and efficacy of cyclosporine versus tacrolimus for heart transplant patients. Ten randomized control trials (n=956) were reviewed; trial duration was between six months and five years. Both cyclosporine and microemulsion cyclosporine formulations were included. Tacrolimus patients had a significantly lower risk than cyclosporine patients (either type) of experiencing hypertension (RR 0.8, 95% CI 0.69 to 0.93), hyperlipidemia (RR 0.57, 95% CI 0.44 to 0.74), hirsutism (RR 0.17, 95% CI 0.04 to 0.62), and gingival hyperplasia (RR 0.07, 95% CI 0.01 to 0.37). No significant difference was found between groups in rates of acute rejections. Tacrolimus patients also had significantly lower rates of mortality compared with microemulsion cyclosporine (RR 0.64, 95% CI 0.42 to 0.96). Trial quality was rated as poor by the authors for all of the included studies.

Guidelines:

The updated guideline[29] for ulcerative colitis from the American College of Gastroenterology was reviewed; as was the updated lupus nephritis[30] and rheumatoid arthritis[31] guidelines from the American College of Rheumatology. No changes regarding the use of oral immunosuppressants were found.

Similar to 2008, azathioprine, cyclosporine, and gold were not recommended for the treatment of rheumatoid arthritis based on their infrequent use and lack of new data.

Recommendations:

- No further research or review needed at this time.

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Appendix 1: Abstracts of Randomized Control Trials

Budde K, Becker T, Arns W, et al. Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial. *The Lancet*. 2011;377(9768):837–847. doi:10.1016/S0140-6736(10)62318-5.

Background Non-nephrotoxic immunosuppressive strategies that allow reduction of calcineurin-inhibitor exposure without compromising safety or efficacy remain a goal in kidney transplantation. Immunosuppression based on the mammalian-target-of-rapamycin inhibitor everolimus was assessed as a strategy for elimination of calcineurin-inhibitor exposure and optimisation of renal-graft function while maintaining efficacy. Methods In the ZEUS multicentre, open-label study, 503 patients (aged 18–65 years) who had received de-novo kidney transplants were enrolled. After initial treatment with ciclosporin, based on trough concentrations, and enteric-coated mycophenolate sodium (1440 mg/day, orally), corticosteroids (≥5 mg/day prednisolone or equivalent, orally), and basiliximab induction (20 mg, intravenously,

on day 0 [2 h before transplantation], and on day 4), 300 (60%) patients were randomly assigned at 4・5 months 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 [1440 mg/day] with corticosteroids), or continue standard ciclosporin-based treatment. Randomisation was done by use of a central, validated system that automated the random assignment of treatment groups to randomization numbers. The primary objective was to show better renal function (glomerular filtration rate [GFR]; Nankivell formula) with the calcineurin-inhibitor-free everolimus regimen at 12 months after transplantation. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00154310. Findings 118 (76%) of 155 everolimus-treated patients and 117 (81%) of 145 ciclosporin-treated patients completed treatment with study drug up to 12 months after transplantation. At this time point, the everolimus regimen was associated with a significant improvement in GFR versus the ciclosporin regimen (71・8 mL/min per 1・73 m2 *vs* 61・9 mL/ min per 1・73 m2, respectively; mean difference 9・8 mL/min per 1・73 m2, 95% CI −12・2 to −7・5). Rates of biopsy-proven acute rejection were higher in the everolimus group than in the ciclosporin group after randomisation (15 [10%] of 154 *vs* five [3%] of 146; p=0・036), but similar for the full study period (23 [15%] *vs* 22 [15%]). Compared with the ciclosporin regimen, higher mean lipid concentrations, slightly increased urinary protein excretion, and lower haemoglobin concentrations were noted with the everolimus regimen; thrombocytopenia, aphthous stomatitis, and diarrhoea also occurred more often in the everolimus group. A higher incidence of hyperuricaemia was noted with ciclosporin. Interpretation Early elimination of calcineurin inhibitor by use of everolimus-based immunosuppression improved renal function at 12 months while maintaining efficacy and safety, indicating that this strategy may facilitate improved long-term outcomes in selected patients.

Budde K, Lehner F, Sommerer C, et al. Conversion From Cyclosporine to Everolimus at 4.5 Months Posttransplant: 3-Year Results From the Randomized ZEUS Study. *American Journal of Transplantation*. 2012;12(6):1528–1540. doi:10.1111/j.1600-6143.2012.03994.x.
The long-term effect of conversion from calcineurin inhibitor (CNI) therapy to an mTOR inhibitor requires clarification. Following completion of the 12-month, open-label, multicenter ZEUS study, in which 300 kidney transplant recipients were randomized to continue cyclosporine (CsA) or convert to everolimus at 4.5 months post transplant, outcomes were assessed at month 36 (n = 284; 94.7%). CNI therapy was reintroduced in 28.4% of everolimus patients by month 36. The primary efficacy endpoint, estimated glomerular filtration rate (Nankivell, ANCOVA)was significantly higher with everolimus versus the CsA group at month 24 (7.6 mL/min/1.73 m2, 95%CI 4.3, 11.0 mL/min/1.73 m2; p < 0.001) and month 36 (7.5 mL/min/1.73 m2, 95%CI 3.6, 11.4 mL/min/1.73 m2; p < 0.001). The incidence of biopsy-proven acute rejection from randomization to month 36 was 13.0% in the everolimus arm and 4.8% in the CsA arm (p = 0.015). Patient and graft survival, as well as incidences of malignancy, severe infections and hospitalization, were similar between groups. Kidney transplant patients who are converted from CsA to everolimus at month 4.5 and who remain on everolimus thereafter may achieve a significant improvement in renal function that is maintained to 3 years. There was a significantly higher rate of rejection in the everolimus arm but this did not exert a deleterious effect by 3 years post transplant.

Abdelmalek MF, Humar A, Stickel F, et al. Sirolimus Conversion Regimen Versus Continued Calcineurin Inhibitors in Liver Allograft Recipients: A Randomized Trial. *American Journal of Transplantation*. 2012;12(3):694–705. doi:10.1111/j.1600-6143.2011.03919.x.
A large prospective, open-label, randomized trial evaluated conversion from calcineurin inhibitor (CNI)- to sirolimus (SRL)-based immunosuppression for preservation of renal function in liver transplantation patients. Eligible patients received liver allografts 6–144 months previously and maintenance immunosuppression with CNI (cyclosporine or tacrolimus) since early post transplantation. In total, 607 patients were randomized (2:1) to abrupt conversion (<24 h) from CNI to SRL (n = 393) or CNI continuation for up to 6 years (n=214). Between-group changes in baseline-adjusted mean Cockcroft–Gault GFR at month 12 (primary efficacy end point) were not significant. The primary safety end point, noninferiority of cumulative rate of graft loss or death at 12months,was not met (6.6% vs. 5.6% in the SRL and CNI groups, respectively). Rates of death at 12 months were not significantly different, and no true graft losses (e.g. liver transplantation) were observed during the 12-month period. At 52 weeks, SRL conversion was associated with higher rates of biopsy-confirmed acute rejection (p = 0.02) and discontinuations (p < 0.001), primarily for adverse events. Adverse events were consistent with known safety profiles. In conclusion, liver transplantation patients showed no demonstrable benefit 1 year after conversion from CNI- to SRL-based immunosuppression.

Akhyani M, Chams-Davatchi C, Hemami M, Fateh S. Efficacy and safety of mycophenolate mofetil vs. methotrexate for the treatment of chronic plaque psoriasis. *Journal of the European Academy of Dermatology and Venereology*. 2010;24(12):1447–1451. doi:10.1111/j.1468-3083.2010.03667.x.
Background Methotrexate (MTX) is a well-known systemic drug for moderate to severe chronic plaque psoriasis. Recently, mycophenolate mofetil (MMF) has been recommended for psoriasis. Objective To compare the efficacy and safety of MMF vs. MTX for the treatment of chronic plaque psoriasis. Methods Thirty-eight consecutive patients with Psoriasis Area and Severity Index (PASI) >10 were randomly assigned for 12 weeks of treatment with either MTX (18 patients; initial dose, 7.5 mg/ week) or MMF (20 patients; dose; 2 g/ day) and were followed for 12 weeks after discontinuing the treatment. The differences between the two groups were analysed at the end of treatment and follow-up comparing with baseline values. Results After 12 weeks of treatment, the mean ± SD score for the PASI decreased from 16.46 ± 5.29 at baseline to 3.17 ± 2.35 among 15 patients treated with MTX, whereas the score decreased from 17.43 ± 7.42 to 3.97 ± 5.95 among 17 patients treated with MMF (P > 0.05). Twelve weeks after discontinuing the treatment, the scores were 4.77 ± 3.52 and 5.94 ± 4.27, respectively (P > 0.05). PASI -75 were achieved in 58.8% of patients in MMF group and 73.3% in MTX group (P > 0.05). Three months after discontinuing the treatment, PASI-75 remained in 33.3% of patients in MMF and 53.3% of MTX group (P > 0.05). Both drugs were well tolerated and side-effects were minor and transient. Conclusions No significant differences in efficacy were found between MTX and MMF groups. MMF may represent a good alternative for the treatment of psoriasis in patients who are unable to take MTX or other available drugs due to contraindication or toxicity.

Dantal J. Conversion from everolimus with low-exposure cyclosporine to everolimus with mycophenolate sodium maintenance therapy in kidney transplant recipients: A randomized, open-label multicenter study. *Annals of Transplantation*. 2012;17(1):58–67. doi:10.12659/AOT.882637.
Background: Data in kidney transplant recipients regarding elimination of calcineurin inhibitor (CNI) therapy from a *de novo* regimen based on low CNI exposure and an mTOR inhibitor are sparse, and restricted to CNI elimination within the first six months post-transplant. Material/Methods: In a 12-month, randomized, multicenter, open-label study, kidney transplant patients who had received everolimus, low-exposure cyclosporine and corticosteroids from transplantation to month 12 (with proteinuria <1 g/24 h at month 12) were randomized to convert from cyclosporine to mycophenolate sodium 720 mg/day with increased everolimus exposure (6–10 ng/mL [CNI-free group], n=15) or continue unchanged (everolimus 3–8 ng/mL [CNI group], n=15). Results: Median (range) baseline mGFR was 54 (21–87) mL/min and 37 (range 18–69) mL/min (p=0.053) in the CNI-free and CNI groups, respectively, compared to 56 (18–126) mL/min and 32 (12–63) mL/min at month 12 (p=0.007). The between group difference in change in mGFR from baseline to month 12 post-conversion (the primary endpoint) was –14.4 mL/min (95% CI –29.3 to 0.6 mL/min, p=0.059 [least squares mean]). Changes in serum creatinine and estimated GFR to month 12 were significantly in favor of CNI-free patients. One CNI patient experienced biopsy-proven acute rejection. Study drug was discontinued due to adverse events in one CNI-free patient (7%) and three CNI-treated patients (20.0%). Conclusions: Elimination of CNI from a *de novo* regimen of everolimus with low-exposure CNI at one year post-transplant maintained efficacy and led to a non-significant but clinically relevant improvement in renal function, although patients numbers were low (n=30). Findings from this small study require confirmation in a larger controlled trial.

Date: May 2013

Bhorade S, Ahya VN, Baz MA, et al. Comparison of Sirolimus with Azathioprine in a Tacrolimus-based Immunosuppressive Regimen in Lung Transplantation. *American Journal of Respiratory and Critical Care Medicine*. 2011;183(3):379–387. doi:10.1164/rccm.201005-0775OC.
Rationale: Lung transplantation has evolved into a life-saving therapy for select patients with end-stage lung diseases. However, long-term survival remains limited because of chronic rejection. Sirolimus is beneficial in preventing cardiac rejection and may decrease rejection after lung transplantation. Objectives: To determine the potential benefit versus risk of sirolimus in lung transplantation. Methods: We conducted a multicenter randomized, open label controlled trial comparing sirolimus (SIR) with azathioprine (AZA) in a tacrolimus-based immunosuppressive regimen in lung transplantation. The primary end point was the incidence of acute rejection at 1 year after transplantation between the two study groups. Measurements and Main Results: One hundred eighty-one patients were randomized to be included in this study. At 1 year after transplantation, there was no significant difference in the incidence of grade A acute rejection between the two study groups. Similarly, the incidence of chronic rejection and graft survival was no different between the two study groups. Cytomegalovirus infection was decreased in the SIR arm compared with the AZA arm (relative risk, 0.67 [95%confidence interval, 0.55, 0.82]; P , 0.01). There was a higher rate of adverse events leading to early discontinuation of SIR (64%) compared with AZA (49%) during the course of this study. Conclusions: Sirolimus, an mTOR inhibitor, did not decrease the incidence of acute rejection at 1 year compared with azathioprine in lung transplantation. These results differ from previous results in cardiac and renal transplantation and emphasize the need for multicenter randomized controlled trials in lung transplantation.

Guerra G, Ciancio G, Gaynor JJ, et al. Randomized Trial of Immunosuppressive Regimens in Renal Transplantation. *Journal of the American Society of Nephrology*. 2011;22(9):1758–1768. doi:10.1681/ASN.2011010006.
The optimal long-term regimen for immunosuppression for kidney transplant recipients is unknown. We conducted a randomized trial involving 150 kidney transplant recipients to compare tacrolimus/sirolimus, tacrolimus/mycophenolate mofetil (MMF), and cyclosporine/sirolimus. All patients received daclizumab induction and maintenance corticosteroids. Median follow-up was 8 yr. post-transplant. Acute rejection (AR) occurred significantly less often among those treated with tacrolimus/MMF (12%) than among those treated with tacrolimus/sirolimus (30%) or cyclosporine/sirolimus (28%). Mean estimated GFR was consistently higher in the tacrolimus/MMF arm, especially after controlling for donor age in a multivariable model during the first 36 mo. (*P* _ 0.008). The rate of dying with a functioning graft was significantly higher among those treated with tacrolimus/sirolimus (26%) than among those treated with tacrolimus/MMF (12%) or cyclosporine/sirolimus (4%). We did not observe significant differences in actuarial graft survival at 8 yr. post-transplant between the groups. Patient noncompliance seemed responsible for 45% (13/29) of observed graft failures, with 11 of these occurring after 36 mo. Significantly more viral infections, protocol violations, and need for antilipid therapy occurred among patients receiving sirolimus, but we did not observe differences between the groups with regard to infections requiring hospitalization or new-onset diabetes. Taken together, these results suggest that maintenance therapy with tacrolimus/MMF is more favorable than either tacrolimus/sirolimus or cyclosporine/sirolimus.

Guethoff S, Meiser BM, Groetzner J, et al. Ten-year results of a randomized trial comparing tacrolimus versus cyclosporine a in combination with mycophenolate mofetil after heart transplantation. *Transplantation*. 2013;95(4):629–634. doi:10.1097/TP.0b013e318277e378.
Background. Long-term results of prospective randomized trials comparing triple immunosuppressive strategies combining tacrolimus (TAC) or cyclosporine A (CsA) with mycophenolate mofetil (MMF) and steroids after heart transplantation (HTX) are rarely published. Therefore, we collected long-term follow-up data of an intervention cohort 10 years after randomization. Methods. Ten-year follow-up data of 60 patients included in a prospective, randomized trial between 1998 and 2000 were analyzed as intention-to-treat (TAC-MMF n=30; CsA-MMF n=30). Baseline characteristics were well balanced. Cardiac allograft vasculopathy (CAV) was graduated in accordance with the new ISHLT classification. Results. Survival at 1, 5, and 10 years was 96.7%, 80.0%, and 66.7% for TAC-MMF and 90.0%, 83.3%, and 80.0% for CsA-MMF (P=ns). Freedom from acute rejection (AR) was significantly higher in TAC-MMF versus CsA-MMF (65.5% vs. 21.7%, log-rank 8.3, P=0.004). Freedom from ISHLTQCAV1 after 5 and 10 years was in TAC-MMF 64.0% and 45.8%, and in CsA-MMF 36.0% (log-rank 3.0, P=0.085) and 8.0% (log-rank 9.0, P=0.003). No difference in long-term results for freedom from coronary angioplasty or stenting, renal dysfunction, diabetes mellitus, CMV infection, or malignancy was detected.
Conclusion. Cross-over effects because of treatment switch may result in impairment of significance between the groups. The long-term analysis resulted in a significant difference in manifestation of CAV between the groups after 10 years. Less rejection in the TAC-group might have contributed to the lower incidence of CAV. Superior freedom from AR and CAV in the TAC-MMF group did not result in better long-term survival.

Herlenius G, Felldin M, Nordén G, et al. Conversion From Calcineurin Inhibitor to Either Mycophenolate Mofetil or Sirolimus Improves Renal Function in Liver Transplant Recipients With Chronic Kidney Disease: Results of a Prospective Randomized Trial. *Transplantation Proceedings*. 2010;42(10):4441–4448. doi:10.1016/j.transproceed.2010.09.113.
Background. Chronic kidney disease (CKD) has emerged as a significant cause of morbidity and a risk factor for mortality after orthotopic liver transplantation (OLT). The use of calcineurin inhibitor (CNI)-based immunosuppression is an important etiologic factor for developing CKD. CNI discontinuation or minimization protocols with replacement of the CNI with non-nephrotoxic drugs, such as mycophenolate mofetil (MMF) or sirolimus (SRL), may have the potential to preserve or recover renal function. Patients and Methods. In this prospective, randomized, single-center study with CNI discontinuation, OLT recipients with CKD (measured glomerular filtration rate [GFRm] 15–45 mL/min/1.73 m2) were randomized to either SRL or MMF-based immunosuppression. The main objective was to study the effect of CNI discontinuation on renal function. Secondary aims were to assess the frequency of biopsy-proven acute rejection episodes (BPAR) and adverse events (AE). Renal function was followed with GFRm using 51-Chromium EDTA clearance at baseline, 3 months, and 1 year. Patients were stratified according to baseline GFRm _ versus _30 mL/min/1.73 m2. The 25 patients were enrolled for MMF (n _ 13) or SRL (n _ 12). The median age at inclusion was 59 years (range, 25–66) and the median number of years after OLT was 4.4 (range, 1–13). Twenty-two patients were followed up for a year; MMF (n _ 12) and SRL (n _ 10). Results. Mean GFRm for the whole cohort (n _ 25) was 31_/_8 mL/min/1.73 m2 at baseline. After 3 months the GFRm (n _ 23) increased to 40_/_10 mL/min/1.73 m2 (*P* _.0001) and at 1 year 42 _/_ 11 mL/min/1.73 m2 (n _ 22). There was no significant difference between the MMF and the SRL study arms. The cohort (n _ 8) with baseline GFRm _30 mL showed a 63% (*P* _ .003) increased filtration after 1 year. There was no significant difference in the frequency or severity of AE between the study arms with the exception of oral ulcerations and persistent hypertriglyceridemia in the SRL group. Two deaths occurred, 1 in each study arm, both probably unrelated to the change in immunosuppression. There were no BPAR episodes. Conclusion. CNI discontinuation and replacement with either MMF or SRL resulted in a significant improvement in renal function even in those patients with severe CKD. The protocol was effective with no acute rejection episodes. The SRL arm showed a higher frequency of oral aphthous ulcerations and hypertriglyceridemia. Future studies addressing long-term renal function after CNI discontinuations are needed.

Mjörnstedt L, Sørensen SS, von zur Mühlen B, et al. Improved Renal Function After Early Conversion From a Calcineurin Inhibitor to Everolimus: a Randomized Trial in Kidney Transplantation. *American Journal of Transplantation*. 2012;12(10):2744–2753. doi:10.1111/j.1600-6143.2012.04162.x.
In an open-label, multicenter trial, *de novo* kidney transplant recipients at low to medium immunological risk were randomized at week 7 post transplant to remain on CsA (n = 100, controls) or convert to everolimus (n = 102), both with enteric-coated mycophenolate sodium and corticosteroids. The primary endpoint, change in

measured GFR (mGFR) from week 7 to month 12, was significantly greater with everolimus than controls: 4.9 (11.8) mL/min versus 0.0 (12.9) mL/min (p = 0.012; analysis of covariance [ANCOVA]). Per protocol analysis demonstrated more marked difference: an increase of 8.7 (11.2) mL/min with everolimus versus a decrease of 0.4 (12.0) mL/min in controls (p < 0.001; ANCOVA). There were no differences in graft or patient survival. The 12-month incidence of biopsy-proven acute rejection (BPAR) was 27.5% (n = 28) with everolimus and 11.0% (n = 11) in controls (p = 0.004). All but two episodes of BPAR in each group were mild. Adverse events occurred in 95.1% of everolimus patients and 90.0% controls (p = 0.19), with serious adverse events in 53.9% and 38.0%, respectively (p = 0.025). Discontinuation because of adverse events was more frequent with everolimus (25.5%) than controls (3.0%; p = 0.030). In conclusion, conversion from CsA to everolimus at week 7 after kidney transplantation was associated with a greater improvement in mGFR at month 12 versus CNI treated controls but discontinuations and BPAR were more frequent.

Potena L, Prestinenzi P, Bianchi IG, et al. Cyclosporine lowering with everolimus versus mycophenolate mofetil in heart transplant recipients: Long-term follow-up of the SHIRAKISS randomized, prospective study. *The Journal of Heart and Lung Transplantation*. 2012;31(6):565–570. doi:10.1016/j.healun.2012.01.002.
BACKGROUND: Cyclosporine nephrotoxicity negatively impacts long-term outcome after heart transplantation (HT). We previously reported 1-year results from a randomized study showing that cyclosporine-lowering strategies based on everolimus or mycophenolate mofetil (MMF) are equally effective for reducing progression of renal dysfunction. It is unknown whether this efficacy could be maintained over the long term. METHODS: Thirty-four recipients 1 to 4 years after HT and with 25 to 60 ml/min of creatinine clearance (CrCl) were randomized to everolimus with a very low dose (C0: 50 to 90 ng/ml, *n* _ 17) or MMF with low dose of cyclosporine (C0: 100 to 150 ng/ml, *n* _ 17). Follow-up was prolonged up to 3 years, and calculated CrCl was the main efficacy measure. RESULTS: Cyclosporine was maintained at 70% and 30% lower than baseline in the everolimus and MMF arms, respectively, throughout the 3-year study period. CrCl remained stable in the everolimus patients (_7% from baseline; *p* _ 0.7), but improved in the MMF patients (_20% from baseline; *p* _0.01), with a trend toward improved values compared with everolimus patients (46 _ 12 vs 56 _ 15 ml/min; *p* _ 0.06). Subgroup analysis revealed that baseline proteinuria markedly influenced the renal function response to everolimus: whereas in patients with baseline proteinuria CrCl significantly worsened (_20%; *p* _ 0.04), it improved in those without (_15%; *p* _ 0.03). Safety was comparable between the two study arms. CONCLUSIONS: Cyclosporine nephrotoxicity improved after a prolonged dose reduction in patients receiving MMF. The everolimus-based strategy provided a similar benefit only to patients without baseline proteinuria. While raising caution against the universal use of everolimus for kidney protection, our long-term results support the need for customized approaches in the management of drug toxicities in maintenance HT recipients.

Sánchez-Lázaro IJ, Almenar-Bonet L, Martínez-Dolz L, et al. Preliminary Results of a Prospective Randomized Study of Cyclosporine Versus Tacrolimus in the Development of Cardiac Allograft Vasculopathy at 1 Year After Heart Transplantation. *Transplantation Proceedings*. 2010;42(8):3199–3200. doi:10.1016/j.transproceed.2010.05.055.
Introduction and aims. Cardiac allograft vasculopathy (CAV) is the leading cause of death after the first year post– heart transplantation (HT). Numerous factors have been implicated in the development of CAV. The aim of this prospective randomized study was to assess the impact of cyclosporine (CsA) and tacrolimus (Tac) on the development of CAV. Materials and methods. From November 2006 to October 2008, 49 HT patients in our center were randomized to receive CsA or Tac. The additional treatment for all patients consisted of daclizumab induction and maintenance treatment with mycophenolate mofetil (1 g/12 hours) and steroids (withdrawal was not attempted). Thirteen patients died before coronary arteriography plus intravascular ultrasound of the left anterior descending artery was performed at 1 year after HT. Hence, the final number of patients included was 36 (18 per group). We considered significant CAV to be the presence of intimal proliferation _1 mm and/or _0.5 mm in 180°. The statistical methods were Student *t* and chi-square tests. Results. There were no differences in baseline characteristics between the two groups. Nor were there significant differences in maximum intimal proliferation between the groups (CsA 0.65 _ 0.29 vs Tac 0.82 _ 0.51 mm; *P* _ .292) or in the development of significant CAV when both criteria were combined (CsA 31.6% vs Tac 38.9%; *P* _ .642). Conclusions. One year after HT, no differences were detected in the development of significant CAV according to the type of calcineurin inhibitor used when combined with daclizumab induction and maintenance treatment with mycophenolate mofetil and steroids.

Santos SM, Carlos CM, Cabanayan-Casasola CB, Danguilan RA. Everolimus with Reduced-dose Cyclosporine Versus Full-dose Cyclosporine and Mycophenolate in De Novo Renal Transplant Patients: A 2-Year Single-Center Experience. *Transplantation Proceedings*. 2012;44(1):154–160. doi:10.1016/j.transproceed.2011.11.055.
background. Although calcineurin inhibitors (CNIs) have improved short-term graft survival, long-term function remains a challenge. CNIs have been implicated in the development of chronic allograft failure. Low-dose cyclosporine with everolimus may mitigate CNI nephrotoxicity and prolong graft survival. We compared the efficacy and safety of de novo everolimus with low-dose cyclosporine and prednisone versus cyclosporine, mycophenolate, and prednisone among kidney transplant patients up to 24 months after transplantation. Methods. Kidney transplant patients given low-dose cyclosporine, everolimus, and prednisone were compared with patients given cyclosporine, mycophenolate, and prednisone from December 2006 to December 2008. All had living donors, panel reactive antibody _15%, and follow-up for 2 years after transplantation. Continuous variables using mean and standard deviation, *t* test and test for proportions were used to determine significant differences between the baseline characteristics of the 2 treatment groups. Generalized linear regression and logistic regression were used to measure the effect of treatment on outcomes. Results. Demographic characteristics were similar in both groups except for age, length of time awaiting kidney transplantation, type of renal replacement therapy, follow-up time, sex distribution, and number of HLA mismatches. These independent variables were used in the generalized linear regression model. There was no significant difference between the everolimus and mycophenolate groups up to 2 years in mean serum creatinine (1.2 mg/dL vs 1.4 mg/dL-, respectively *P* _ .05), acute rejection (12 months: 20% vs 31%; 24 months: 31% vs 40%; *P* _ .05), patient survival (98%), and graft survival (100%). Likewise, there were no significant differences in surgical, infectious, metabolic, and gastrointestinal side effects between the 2 groups. Conclusions. Everolimus with low-dose cyclosporine and prednisone in de novo kidney transplant recipients was similar in efficacy and safety to cyclosporine, mycophenolate, and prednisone. Longer follow-up is needed to see whether everolimus with low-dose cyclosporine will result in improved kidney function.

Schmeding M, Kiessling A, Neuhaus R, et al. Mycophenolate mofetil monotherapy in liver transplantation: 5-year follow-up of a prospective randomized trial. *Transplantation*. 2011;92(8):923–929. doi:10.1097/TP.0b013e31822d880d.
Background. Calcineurin inhibitors (CNIs) play the key role in immunosuppressive protocols yet are often associated with numerous side effects. Renal insufficiency, hypertension, hyperglycemia, and increased risk of secondary malignancy are major problems in short- and long-term follow-up of liver transplant patients. Mycophenolate mofetil (MMF) has proved to be a potent immunosuppressive agent free of the CNI-associated side effects. Patients and Methods. One hundred fifty patients who received liver transplantation at our institution (1998 –2003) were prospectively randomized: 75 patients continued CNI standard therapy, 75 patients were switched to MMF monotherapy, and follow-up was 5 years. Incidence of rejection, renal complication, cardiovascular, neurological and gastrointestinal adverse effects, and diabetes and malignancy development was recorded. Graft biopsies were performed every 2 to 3 years. Results. No significant difference regarding the incidence of acute rejection was detected. A trend to higher rejection frequency was apparent in the MMF monotherapy group. Chronic rejection was absent; organ and patient survival were identical in the two groups. No significant difference occurred concerning the incidence of cardiovascular, gastrointestinal or neurological adverse effects, or the development of malignancies. Renal function improved significantly in patients with renal insufficiency when patients treated with CNI were

switched to MMF monotherapy. Conclusion. MMF monotherapy may serve as safe long-term immunosuppression after liver transplantation for a subgroup of patients. Especially for patients with renal insufficiency MMF offers immunosuppression without the risk of nephrotoxicity.

Treede H, Glanville AR, Klepetko W, et al. Tacrolimus and cyclosporine have differential effects on the risk of development of bronchiolitis obliterans syndrome: results of a prospective, randomized international trial in lung transplantation. *J. Heart Lung Transplant.* 2012;31(8):797–804. doi:10.1016/j.healun.2012.03.008.
BACKGROUND: Chronic lung allograft dysfunction, which manifests as bronchiolitis obliterans syndrome (BOS), is recognized as the primary cause of morbidity and mortality after lung transplantation. In this study we assessed the efficacy and safety of two de novo immunosuppression protocols to Prevent BOS. METHODS: Our study approach was a multicenter, prospective, randomized (1:1) open-label superiority Investigation of de novo tacrolimus vs cyclosporine, with both study arms given Mycophenolate Mofetil and prednisolone after lung transplantation. Cytolytic induction therapy was not employed. Patients were stratified at entry for cystic fibrosis. Primary outcome was incidence of BOS 3 years after Transplant (intention-to-treat analysis). Secondary outcomes were survival and incidence of acute Rejection, infection and other adverse events. RESULTS: Group demographic data were well matched: 110 of 124 tacrolimus vs 74 of 125 cyclosporine Patients were treated per protocol (*p* _ 0.01 by chi-square test). Cumulative incidence of BOS Grade _1 at 3 years was 11.6% (tacrolimus) vs 21.3% (cyclosporine) (cumulative incidence curves, *P* _ 0.037 by Gray's test, pooled over strata). Univariate proportional sub-distribution hazards Regression confirmed cyclosporine as a risk for BOS (HR 1.97, 95% CI 1.04 to 3.77, *p* _ 0.039). Three-year cumulative incidence of acute rejection was 67.4% (tacrolimus) vs 74.9% (cyclosporine) (*p* _ 0.118 by Gray's test). One- and 3-year survival rates were 84.6% and 78.7% (tacrolimus) vs 88.6% and 82.8% (cyclosporine) (*p* _ 0.382 by log-rank test). Cumulative infection rates were similar (*p* _ 0.91), but there was a trend toward new-onset renal failure with tacrolimus (*p* _ 0.09).

Vacher-Coponat H, Moal V, Indreies M, et al. A randomized trial with steroids and antithymocyte globulins comparing cyclosporine/azathioprine versus tacrolimus/mycophenolate mofetil (CATM2) in renal transplantation. *Transplantation*. 2012;93(4):437–443. doi:10.1097/TP.0b013e31824215b7.
Background. The best immunosuppressive regimen in benefit-risk ratio in renal transplantation is debated. Nowadays, tacrolimus (Tac) and mycophenolate mofetil (MMF) are considered more efficient than cyclosporine A (CsA) and MMF, but recent studies have challenged this assumption. Methods. We conducted a monocentric, prospective, open-labeled, randomized, and controlled trial comparing CsA/azathioprine (Aza) versus Tac/MMF in 289 kidney transplant recipients treated with antithymocyte globulins and prednisone. Primary outcome was the number of patients with clinically suspected acute rejection at 1 year. Secondary outcomes were the number of patients with biopsy-proven acute rejection (BPAR), estimated glomerular filtration rate (eGFR), patient and graft survivals, and adverse events at 1 and 3 years. Results. During the first year, 21 patients had clinically suspected acute rejection with CsA/Aza (14.4%) vs. 11 (7.7%) with Tac/MMF (*P*_0.07). BPAR, including borderline, was more frequent in the CsA/Aza group (14.4%) than in the Tac/MMF group (5.6%; *P*_0.013). At 1 year, patient and graft survivals were not different, and eGFR was 48_1 in the CsA/Aza group and 53_1 mL/min/1.73 m2 in the Tac/MMF group (*P*_0.007). There was no significant difference in diabetes after transplantation (16.8% and 18.8%, respectively). Conclusions. With antithymocyte globulins and steroids, clinically suspected acute rejections did not differ between CsA/Aza and Tac/MMF arms. Analysis of secondary endpoints showed a lower rate of BPAR, including border line, and a higher eGFR in the Tac/MMF group. CsA/Aza allowed a low acute rejection rate, but Tac/MMF seemed as a better regimen regarding severe secondary outcomes.

Viganò M, Dengler T, Mattei MF, et al. Lower incidence of cytomegalovirus infection with everolimus versus mycophenolate mofetil in de novo cardiac transplant recipients: a randomized, multicenter study. *Transplant Infectious Disease*. 2010;12(1):23–30. doi:10.1111/j.1399-3062.2009.00448.x.
Abstract: Cytomegalovirus (CMV) is a major cause of infectious complications following cardiac transplantation, severely affecting short- and long-term outcomes. A 12-month, multicenter, randomized, open-label study in de novo cardiac transplant patients was undertaken to compare the efficacy, renal function, and safety of everolimus plus reduced cyclosporine versus mycophenolate mofetil (MMF) plus standard cyclosporine (ClinicalTrials.gov NCT00150046). CMV specific data was prospectively collected on infections, laboratory evidence, CMV syndrome, and CMV disease. In total, 176 patients were randomized (everolimus 92; MMF 84). Use of CMV prophylaxis was similar between groups (everolimus 20.8%; MMF 24.0%). Patients in the everolimus arm had a significantly lower incidence of any CMV event (8.8% versus 32.5%with MMF, Po0.001), CMV infection as an adverse event (4.4%versus 16.9%, P50.011), laboratory evidence of CMV (antigenemia 7.7%versus 7.7%, Po0.001; polymerase chain reaction assay 2.2% versus 12.0%, P50.015), and CMV syndrome (1.1%versus 8.4%, P50.028). In the donor (D)1/recipient (R)1and D _/R1 subgroups, even after adjusting for use of prophylaxis, the CMV event rate remained significantly lower with everolimus than with MMF (P50.0015 and P50.0381, respectively). In conclusion, de novo cardiac transplant recipients experienced lower rates of CMV infection, CMV syndrome, or organ involvement on an everolimus-based immunosuppressant regimen compared with MMF.

Zuckermann A, Keogh A, Crespo-Leiro MG, et al. Randomized Controlled Trial of Sirolimus Conversion in Cardiac Transplant Recipients With Renal Insufficiency. *American Journal of Transplantation*. 2012;12(9):2487–2497. doi:10.1111/j.1600-6143.2012.04131.x.
This randomized, comparative, multinational phase 3b/4 study of patients 1–8 years post cardiac transplantation (mean 3.9 years) evaluated the effect of conversion from a calcineurin inhibitor (CNI) to sirolimus on renal function in patients with renal insufficiency. In total, 116 patients on CNI therapy with GFR 40–90 mL/min/1.73m2 were randomized (1:1) to sirolimus (n = 57) or CNI (n = 59). Intent-to-treat analysis showed the 1-year adjusted mean change from baseline in creatinine clearance (Cockcroft-Gault) was significantly higher with sirolimus versus CNI treatment (+3.0 vs.−1.4mL/min/1.73m2, respectively; p = 0.004). By on-therapy analysis, values were +4.7 and –2.1, respectively (p < 0.001). Acute rejection (AR) rates were numerically higher in the sirolimus group; 1 AR with hemodynamic compromise occurred in each group. A significantly higher treatment discontinuation rate due to adverse events (AEs; 33.3% vs. 0%; p < 0.001) occurred in the sirolimus group. Most common treatment-emergent AEs significantly higher in the sirolimus group were diarrhea (28.1%), rash (28.1%) and infection (47.4%). Conversion to sirolimus from CNI therapy improved renal function in cardiac transplant recipients with renal impairment, but was associated with an attendant AR risk and higher discontinuation rate attributable to AEs.

Appendix 2: Abstracts of Meta Analyses

Asrani SK, Leise MD, West CP, et al. Use of sirolimus in liver transplant recipients with renal insufficiency: A systematic review and meta-analysis. *Hepatology*. 2010;52(4):1360–1370. doi:10.1002/hep.23835.
Sirolimus is used in patients with renal insufficiency after liver transplantation (LT) and especially in those with calcineurin inhibitor (CNI)–associated nephrotoxicity. We conducted a systematic review of all randomized controlled trials and observational studies to test the hypothesis that the use of sirolimus is associated with an improvement in renal function at 1 year in LT recipients with renal insufficiency [glomerular filtration rate (GFR) < 60 mL/minute or creatinine level ‡ 1.5 mg/dL]. We performed a search of all major databases, conference proceedings, and relevant journals through December 2009 and contacted content experts, corresponding authors, and the pharmaceutical manufacturer. A random effects model was used to determine the pooled estimate of the change in renal function and pooled risk

estimates of adverse events that may be associated with sirolimus-based therapy at 1 year. Eleven studies (three randomized controlled trials and eight observational studies) met the final inclusion criteria. A nonsignificant improvement of 3.38 mL/minute [95% confidence interval (CI)522.93 to 9.69] was observed in methodologically sound observational studies and controlled trials reporting the primary outcome. In controlled trials, baseline GFR >50 mL/min sirolimus use was associated with an improvement of 10.35 mL/minute (95% CI 5 3.98-16.77) in GFR or creatinine clearance. Sirolimus was not significantly associated with death [relative risk (RR) 5 1.12, 95% CI 5 0.66-1.88] or graft failure (RR 5 0.80, 95% CI 5 0.45-1.41), although reporting was incomplete. It was associated with a statistically significant risk of infection (RR 5 2.47, 95% CI 5 1.14-5.36), rash (RR 5 7.57, 95% CI 5 1.75-32.70), ulcers (RR 5 7.44, 95% CI 5 2.03-27.28), and discontinuation of therapy (RR 5 3.61, 95% CI 5 1.32-9.89). Conclusion: Conversion to sirolimus from CNIs is associated with a nonsignificant improvement in renal function in LT recipients with renal insufficiency, although the results are limited by heterogeneity, a risk of bias, and a lack of standardized reporting.

McDonald JW, Tsoulis DJ, MacDonald JK, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. In: The Cochrane Collaboration, McDonald JW, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: http://doi.wiley.com/10.1002/14651858.CD003459.pub3. Accessed April 22, 2013.

Background Although corticosteroids are effective for induction of remission of Crohn's disease, many patients relapse when steroids are withdrawn or become steroid dependent. Furthermore, corticosteroids exhibit significant adverse effects. The success of methotrexate as a treatment for rheumatoid arthritis led to its evaluation in patients with refractory Crohn's disease. Methotrexate has been studied for induction of remission of refractory Crohn's disease and has become the principal alternative to azathioprine or 6-mercaptopurine therapy. This systematic review is an update of a previously published Cochrane review.
Objectives The primary objective was to assess the efficacy and safety of methotrexate for induction of remission in patients with active Crohn's disease in the presence or absence of concomitant steroid therapy. Search methods We searched MEDLINE, EMBASE, CENTRAL and the Cochrane IBD/FBD group specialized register from inception to June 27, 2012 for relevant studies. Conference proceedings and reference lists were also searched to identify additional studies.
Selection criteria Randomized controlled trials of methotrexate compared to placebo or an active comparator for treatment of active refractory Crohn's disease in adult patients (> 17 years) were considered for inclusion. Data collection and analysis The primary outcome was failure to failure to enter remission and withdrawal from steroids. Secondary outcomes included adverse events, withdrawal due to adverse events, serious adverse events and quality of life. We calculated the relative risk (RR) and 95% confidence intervals (95% CI) for each outcome. Data were analyzed on an intention to treat basis. The Cochrane risk of bias tool was used to assess the methodological quality of included studies. The GRADE approach was used to assess the overall quality of evidence supporting the primary outcome. Main results Seven studies (495 patients) were included. Four studies were rated as low risk of bias. Three studies were rated as high risk of bias due to open label or single-blind designs. The seven studies differed with respect to participants, intervention, and outcomes to the extent that it was considered to be inappropriate to pool the data for meta-analysis. Three small studies which employed low doses of oral methotrexate showed no statistically significant difference in failure to induce remission between methotrexate and placebo or between methotrexate and 6-mercaptopurine. For the study using 15 mg/week of oral methotrexate 33% (5/15) of methotrexate patients failed to enter remission compared to 11% (2/18) of placebo patients (RR 3.00, 95% CI 0.68 to 13.31). For the study using 12.5 mg/week of oral methotrexate 81% (21/26) of methotrexate patients failed to enter remission compared to 77% (20/26) of placebo patients (RR 1.05, 95% CI 0.79 to 1.39). This study also had an active comparator arm, 81% (21/26) o^{24}f methotrexate patients failed to enter remission compared to 59% (19/32) of 6-mercaptopurine patients (RR 1.36, 95% CI 0.97 to 1.92). For the active comparator study using 15 mg/week oral methotrexate, 20% (3/15) of methotrexate patients failed to enter remission compared to 6% of 6-mercaptopurine patients (RR 3.20, 95% CI 0.37 to 27.49). This study also had a 5-ASA arm and found that methotrexate patients were significantly more likely to enter remission than 5-ASA patients. Twenty per cent (3/15) of methotrexate patients failed to enter remission compared to 86% (6/7) of 5-ASA patients (RR 0.23, 95% CI 0.08 to 0.67). One small study which used a higher dose of intravenous or oral methotrexate (25 mg/week) showed no statistically significant difference between methotrexate and azathioprine. Forty-four per cent (12/27) of methotrexate patients failed to enter remission compared to 37% of azathioprine patients (RR 1.20, 95% CI 0.63 to 2.29). Two studies found no statistically significant difference in failure to enter remission between the combination of infliximab and methotrexate and infliximab monotherapy. One small study utilized intravenous methotrexate (20 mg/week) for 5 weeks and then switched to oral (20 mg/week). Forty-five per cent (5/11) of patients in the combination group failed to enter remission compared to 62% of infliximab patients (RR 0.73, 95% CI 0.31 to 1.69) The other study assessing combination therapy utilized subcutaneous methotrexate (maximum dose 25 mg/week). Twenty-four per cent (15/63) of patients in the combination group failed to enter remission compared to 22% (14/63) of infliximab patients (RR 1.07, 95% CI 0.57 to 2.03). A large placebo-controlled study which employed a high dose of methotrexate intramuscularly showed a statistically significant benefit relative to placebo. Sixty-one per cent of methotrexate patients failed to enter remission compared to 81% of placebo patients (RR 0.75, 95% CI 0.61 to 0.93; number needed to treat, NNT=5). Withdrawals due to adverse events were significantly more common in methotrexate patients than placebo in this study. Seventeen per cent of methotrexate patients withdrew due to adverse events compared to 2% of placebo patients (RR 8.00, 95% CI 1.09 to 58.51). The incidence of adverse events was significantly more common in methotrexate patients (63%, 17/27) than azathioprine patients (26%, 7/27) in one small study (RR 2.42, 95%CI 1.21 to 4.89). No other statistically significant differences in adverse events, withdrawals due to adverse events or serious adverse events were reported in any of the other placebo-controlled or active comparator studies. Common adverse events included nausea and vomiting, abdominal pain, diarrhea, skin rash and headache. Authors' conclusions There is evidence from a single large randomized trial which suggests that intramuscular methotrexate (25 mg/week) provides a benefit for induction of remission and complete withdrawal from steroids in patients with refractory Crohn's disease. Lower dose oral methotrexate does not appear to provide any significant benefit relative to placebo or active comparator. However, these trials were small and further studies of oral methotrexate may be justified. Comparative studies of methotrexate to drugs such as azathioprine or 6-mercaptopurine would require the randomization of large numbers of patients. The addition of methotrexate to infliximab therapy does not appear to provide any additional benefit over infliximab monotherapy. However these studies were relatively small and further research is needed to determine the role of methotrexate when used in conjunction with infliximab or other biological therapies

Penninga L, Møller CH, Gustafsson F, Steinbrüchel DA, Gluud C. Tacrolimus versus cyclosporine as primary immunosuppression after heart transplantation: systematic review with meta-analyses and trial sequential analyses of randomised trials. *European Journal of Clinical Pharmacology*. 2010;66(12):1177–1187. doi:10.1007/s00228-010-0902-6.

Purpose We conducted a systematic review of randomized trials to compare the benefits and harms of tacrolimus versus cyclosporine as primary immunosuppression after heart transplantation. Methods and results We searched electronic databases and bibliographies up to April 2010. Our review followed the Cochrane and PRISMA guidelines. The meta-analysis included 10 randomized trials with 952 patients. Tacrolimus was significantly superior to cyclosporine (both formula combined) with regard to hypertension (relative risk [RR] 0.8; 95% confidence interval [CI] 0.69–0.93, p=0.003), hyperlipidaemia (RR 0.57; 95% CI 0.44–0.74, p<0.0001), hirsutism (RR 0.17 95% CI 0.04–0.62, p=0.008), and gingival hyperplasia (RR 0.07 95% CI 0.01–0.37, p=0.002). No significant differences between the two calcineurin inhibitors were found with regard to acute rejections causing haemodynamic instability, diabetes, renal dysfunction, infection, malignancy, or neurotoxicity. Tacrolimus was significantly superior to microemulsion cyclosporine with regard to mortality (RR 0.64; 95% CI 0.42–0.96, p=0.03), acute severe biopsy-proven rejection (RR 0.71; 95% CI 0.56–0.90, p=0.004), hyperlipidaemia (RR 0.57; 95% CI 0.41–0.79, p=0.0009), hirsutism (RR 0.17 95% CI 0.04–0.62, p=0.008), and gingival hyperplasia (RR 0.07; 95% CI 0.01–0.37, p=0.002). Tacrolimus was significantly superior to oil-based cyclosporine with regard to hypertension (RR 0.66; 95% CI 0.54–0.80, p<0.0001), and Hyperlipidaemia (RR 0.57; 95% CI 0.38–0.87, p=0.009). Conclusion Tacrolimus seems to be superior to cyclosporine in heart transplant patients with regard to

hypertension, hyperlipidaemia, gingival hyperplasia and hirsutism. In addition, tacrolimus seems to be superior to microemulsion cyclosporine in heart transplant patients with regard to a number of outcomes, including death. More trials with a low risk of bias are needed to determine if the results of the present meta-analysis can be confirmed.

Penninga L, Wettergren A, Chan A-W, Steinbrüchel DA, Gluud C. Calcineurin inhibitor minimisation versus continuation of calcineurin inhibitor treatment for liver transplant recipients. In: The Cochrane Collaboration, Penninga L, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: http://doi.wiley.com/10.1002/14651858.CD008852.pub2. Accessed April 29, 2013.

Background The therapeutic success of liver transplantation has been largely attributable to the development of effective immunosuppressive treatment regimens. In particular, calcineurin inhibitors were essential in reducing acute rejection and improving early survival. Currently, more than 90% of all liver transplant recipients are treated with the calcineurin inhibitor cyclosporine or tacrolimus. Unfortunately, calcineurin inhibitors cause adverse events, such as nephrotoxicity, and because of this, minimisation (reduction and withdrawal) regimens of calcineurin inhibitor have been developed and studied. However, the benefits and harms of these minimisation regimens are unclear. Objectives To assess the benefits and harms of calcineurin inhibitor minimisation for liver transplant recipients without substitution by another immunosuppressive agent. Search methods We searched The Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Central Register of Controlled Clinical Trials (CENTRAL) in *The Cochrane Library,* MEDLINE (OvidSP), EMBASE (OvidSP), Science Citation Index Expanded and the World Health Organization (WHO) international clinical trials registry platform (www.who.int/ictrp) until August 2011. In addition, we searched bibliographies of relevant articles as well as US Food and Drug Administration (FDA) and European Medicines Agency (EMA) drug approval reviews for additional trials. Selection criteria We planned to select all randomised clinical trials investigating calcineurin inhibitor reduction or withdrawal in liver transplant recipients, irrespective of blinding, publication status, or language. Quasi-randomised clinical studies and cohort studies that were obtained through the searches were considered only for the reporting of harms. Trials investigating substitution of one calcineurin inhibitor by another calcineurin inhibitor were excluded. Trials investigating calcineurin inhibitor withdrawal concurrently with switching over to a mammalian target of rapamycin (mTOR) inhibitor-based regimen (everolimus or sirolimus) or mycophenolate mofetil-based regimen are the subject of a separate review. Data collection and analysis Search strategies were used to obtain titles and abstracts of studies that were relevant for the review. Two authors independently scanned the references and assessed trial eligibility. Main results A total of 1299 references were identified by the searches. After removal of duplicates, 794 references were left. Out of these, two abstract reports of one ongoing randomised trial fulfilled the inclusion criteria of the review. This ongoing trial studies total withdrawal of immunosuppression in patients who receive a calcineurin inhibitor (cyclosporine or tacrolimus) or mycophenolate mofetil as the only immunosuppressive agent. The trial compares withdrawal of calcineurin inhibitor or mycophenolate mofetil with continuation of calcineurin inhibitor or mycophenolate mofetil. However, no trial results on the outcomes of interest to this review were available. Authors' conclusions This review shows that strategies regarding calcineurin inhibitor minimisation, that is, reduction or withdrawal, without substitution versus continuation of calcineurin inhibitor treatment lack evidence from randomised trials. More research with calcineurin inhibitor reduction and withdrawal regimens is needed to optimise dosing and timing of calcineurin inhibitor treatment in order to achieve optimal patient and graft survival with a minimum of adverse events. Specifically regarding calcineurin inhibitor reduction versus no reduction, we recommend that randomised trials evaluating calcineurin inhibitor reduction versus continuation of calcineurin inhibitor treatment are conducted. Regarding calcineurin inhibitor withdrawal, we recommend that mechanisms for tolerance and 'graft acceptance' are clarified, and patient groups likely to tolerate calcineurin inhibitor withdrawal are identified in order to select the right patients for total withdrawal of calcineurin inhibitors without substitution with another immunosuppressive drug. The randomised trials should only be performed in highly selected patients.

Sharif A, Shabir S, Chand S, Cockwell P, Ball S, Borrows R. Meta-Analysis of Calcineurin-Inhibitor-Sparing Regimens in Kidney Transplantation. *Journal of the American Society of Nephrology*. 2011;22(11):2107–2118. doi:10.1681/ASN.2010111160.

Calcineurin-inhibitor-sparing strategies in kidney transplantation may spare patients the adverse effects of these drugs, but the efficacy of these strategies is unknown. Here, we conduct a meta-analysis to assess outcomes associated with reducing calcineurin inhibitor exposure from the time of transplantation. We search Medline, Embase, and Cochrane Register of Controlled Trials for randomized controlled trials published between 1966 and 2010 that compared *de novo* calcineurin-inhibitor-sparing regimens to calcineurin-inhibitor-based regimens. In this analysis, we include 56 studies comprising data from 11337 renal transplant recipients. Use of the contemporary agents belatacept or tofacitinib, in combination with mycophenolate, decreased the odds of overall graft failure (OR 0.61; 95% CI 0.39–0.96; *P* _0.03). Similarly, minimization of calcineurin inhibitors in combination with various induction and adjunctive agents reduces the odds of graft failure (OR 0.73; 95% CI 0.58–0.92; *P* _ 0.009). Conversely, the use of inhibitors of mammalian target of rapamycin (mTOR), in combination with mycophenolate, increases the odds of graft failure (OR 1.43; 95% CI 1.08–1.90; *P* _ 0.01). Calcineurin-inhibitor-sparing strategies are associated with less delayed graft function (OR 0.89; 95% CI 0.80–0.98; *P* _ 0.02), improved graft function, and less new-onset diabetes. The more contemporary protocols did not seem to increase rates of acute rejection. In conclusion, this meta-analysis suggests that reducing exposure to calcineurin inhibitors immediately after kidney transplantation may improve clinical outcomes.