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Literature Scan: Immunosuppressants

Date of Review: November 2015

Date of Last Review: May 2013
Literature Search: January 2013 to October 2015

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:
- There is low quality evidence of no difference between tacrolimus and cyclosporine in mortality or acute rejection in lung transplant recipients. Tacrolimus may be result in less harms compared to cyclosporine for certain adverse event outcomes such as the incidence of bronchiolitis obliterans syndrome (Relative Risk [RR] 0.46; 95%, CI 0.29 to 0.74). [1]
- There are insufficient data to assess the effects of immunosuppressant drugs in preventing rejection following lung transplantation in patients with Cystic Fibrosis. [2]
- Adequate immunosuppression is needed to support graft function following organ transplant and needs to be balanced against the risk of potential adverse effects from the medications. Although there is no standard of care for dose and regimen, calcineurin inhibitors remain the primary treatment to prevent rejection following transplantation. Monitoring of adequate immunosuppression levels and graft function remains essential.
- There is insufficient evidence for a difference in efficacy/effectiveness or harms between agents. Agents are often used concomitantly. Side effect profile, monitoring requirements and patient specific factors determine therapy of choice.

Recommendations:
- No changes to the PDL recommended at this time.

Previous Conclusions and Recommendations:
- Evidence does not support a difference in efficacy/effectiveness.
- Evidence does not support a difference in harms/adverse events.
- Recommend coverage of all entities.
- Recommend preference of generic products.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project,

Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

A Cochrane Collaboration systematic review compared the benefits and harms of tacrolimus versus cyclosporine for primary immunosuppression in lung transplant recipients.[1] Three studies (n=413) that compared tacrolimus with cyclosporine were included; all of which had a high risk of bias. Tacrolimus was significantly better than cyclosporine regarding the incidence of bronchiolitis obliterans syndrome (RR 0.46; 95% CI 0.29 to 0.74), lymphocytic bronchitis score (mean difference [MD] -0.60; 95% CI -1.04 to -0.16), treatment withdrawal (RR 0.27; 95% CI 0.16 to 0.46), and arterial hypertension (RR 0.67; 95% CI 0.50 to 0.89). The finding for arterial hypertension was not confirmed using the random-effects model. Diabetes mellitus occurred more frequently in the tacrolimus group compared with cyclosporine (RR 4.24; 95% CI 1.58 to 11.40), but no difference was seen when the random-effects model was used for the analysis. There was low quality evidence of no significant difference between the two groups in mortality, acute rejection, infections, cancer, kidney failure, neurotoxicity, and hyperlipidemia. Trial sequential analysis showed the required information thresholds were not reached for any of the outcome measures. Overall, the authors concluded that tacrolimus may be superior to cyclosporine for certain adverse event outcomes. However, there were few studies comparing these agents after lung transplantation, the included studies were at a high risk of bias, and more RCTS are needed to assess the results of the review.

Another systematic review from the Cochrane Collaboration assessed the effects of immunosuppressant drugs in preventing rejection following lung transplantation in patients with Cystic Fibrosis (CF).[2] Only two RCTs were identified in the literature search and because they did not report any information specific to patients with CF, the authors decided not to include them in the systematic review. Therefore, there was insufficient evidence to make conclusions about the comparative efficacy and safety of the various immunosuppressive drugs among patients with CF following lung transplantation.

A third systematic review from the Cochrane Collaboration aimed to compare mycophenolate versus methotrexate for prevention of acute graft-versus-host disease (GVHD) in people undergoing an allogeneic hematopoietic stem cell transplantation (allo-HCT).[3] A literature search for RCTs identified 3 trials (n=177); two trials included background therapy with cyclosporine and one with tacrolimus. There was low quality evidence of no difference seen between mycophenolate and methotrexate for the incidence of acute GVHD (RR 1.25; 95% CI 0.75 to 2.09), overall survival (HR 0.73; 95% CI 0.45 to 1.17), and incidence of chronic GVHD (RR 0.92; 95% CI 0.65 to 1.30). There was low quality evidence that mycophenolate was associated with decreased incidence of severe mucositis, use of parenteral nutrition, and medication for pain control. There was insufficient evidence to evaluate quality of life. The authors concluded that mycophenolate compared with methotrexate (in combination with a calcineurin inhibitor) appears to be associated with a more favorable toxicity profile, without an apparent compromise on disease relapse, transplant-associated mortality, or overall survival. However, the overall quality of the evidence was low and there remains a need for high quality studies evaluating the best approach to prevention of GVHD. [3]

A high-quality systematic review by Su, et al. evaluated everolimus-based calcineurin-inhibitor sparing regimens for kidney transplant recipients.[4] Seven RCTs (n=2067) were identified and included in the meta-analysis. Six of the seven trials included cyclosporine as the calcineurin inhibitor; only one used tacrolimus.

There was no significant difference in death or graft-loss (RR 1.07; 95% CI 0.73-1.58) between everolimus-based calcineurin inhibitor sparing and the standard calcineurin group. However, elimination of calcineurin inhibitor was associated with more acute rejection compared to the standard group (RR 2.51; 95% CI 1.63 to 3.87) while there was no difference between calcinerin inhibitor minimization. Lastly, patients on everolimus-based regimens had more discontinuations (RR 1.69; 95% CI 1.44 to 1.99).

New Guidelines:
2013 guidelines for the long-term medical management of the pediatric patient after liver transplantation were released by the American Association for the Study of Liver Diseases (AASLD) and the American Society of Transplantation.[5] Recommendations are focused on the prevention of acute rejection and management of side effects and complications. There are no recommendations or conclusions on the comparative efficacy or safety on different oral immunosuppressant and no specific therapy recommendations are provided.

New FDA Drug Approvals:
None identified.

New Formulations/Indications:
Tacrolimus extended-release (Astagraf XL) was approved by the FDA in July 2013.[6] This formulation was developed with interest in possible improvement in immunosuppressive medication adherence.

Pharmacokinetic trials demonstrated bioequivalence of the XL product with the immediate-release tacrolimus with a delayed time to maximum concentration. Many trials have been published regarding the conversion of immediate-release to extended-release tacrolimus in renal, liver and heart transplant patients. Four of the trials demonstrated bioequivalence of the products, but this was not duplicated in all clinical trials.[7–14] Trials in stable transplant patients showed statistically significant decreases in maximal plasma concentrations, requiring dose increases to maintain therapeutic blood levels (1:1.25). Data demonstrates a continued need to monitor drug levels while transitioning between formulations.

A systematic review evaluated 6 RCTs and 15 observational studies that compared daily versus twice-daily tacrolimus in patients with kidney transplant.[15] Overall, there was no difference in acute rejection (RR 1.24; 95% CI 0.93-1.65), patient survival (RR 0.99; 95% CI 0.97-1/02), and graft survival (RR 0.99; 95% CI 0.97-1.02) between the two formulations. Mean trough levels among those who received extended-release tacrolimus was at least 40% lower than patients on immediate-release tacrolimus. The additional dose required to achieve therapeutic targets varied between 10-25%. Additional observational and randomized trials have studied the conversion from immediate-release to extended-release tacrolimus; overall, studies demonstrated the conversion was safe and effective as long as appropriate therapeutic drug monitoring was provided, patients are educated about the conversion and that the same pharmaceutical manufacturer is utilized after conversion.[16]

Tacrolimus extended-release is indicated for the prophylaxis of acute organ rejection in patients receiving a kidney transplant with mycophenolate mofetil and corticosteroids, with or without basiliximab induction. [6] Limitations of use include: 1) it is not interchangeable with tacrolimus immediate-release and 2) it should not be used simultaneously with cyclosporine.

New FDA Safety Alerts:
None identified.

Author: Megan Herink, Pharm.D. Date: January 2016

References:

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2. Saldanha IJ, Akinyede O, McKoy NA, Robinson KA. Immunosuppressive drug therapy for preventing rejection following lung transplantation in cystic fibrosis. *Cochrane Database Syst Rev*. 2013;12:CD009421. doi:10.1002/14651858.CD009421.pub2.

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17. Cutler C, Logan B, Nakamura R, et al. Tacrolimus/sirolimus vs tacrolimus/methotrexate as GVHD prophylaxis after matched, related donor allogeneic HCT. *Blood*. 2014;124(8):1372-1377. doi:10.1182/blood-2014-04-567164.

18. Levy G, Villamil FG, Nevens F, et al. REFINE: a randomized trial comparing cyclosporine A and tacrolimus on fibrosis after liver transplantation for hepatitis C. *Am J Transplant*. 2014;14(3):635-646. doi:10.1111/ajt.12620.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAPSULE	CELLCEPT	MYCOPHENOLATE MOFETIL	Y
ORAL	CAPSULE	CYCLOSPORINE	CYCLOSPORINE	Y
ORAL	CAPSULE	CYCLOSPORINE MODIFIED	CYCLOSPORINE, MODIFIED	Y
ORAL	CAPSULE	GENGRAF	CYCLOSPORINE, MODIFIED	Y
ORAL	CAPSULE	MYCOPHENOLATE MOFETIL	MYCOPHENOLATE MOFETIL	Y
ORAL	CAPSULE	NEORAL	CYCLOSPORINE, MODIFIED	Y
ORAL	CAPSULE	PROGRAF	TACROLIMUS	Y
ORAL	CAPSULE	SANDIMMUNE	CYCLOSPORINE	Y
ORAL	CAPSULE	TACROLIMUS	TACROLIMUS	Y
ORAL	SOLUTION	CYCLOSPORINE	CYCLOSPORINE, MODIFIED	Y
ORAL	SOLUTION	GENGRAF	CYCLOSPORINE, MODIFIED	Y
ORAL	SOLUTION	NEORAL	CYCLOSPORINE, MODIFIED	Y
ORAL	SOLUTION	RAPAMUNE	SIROLIMUS	Y
ORAL	SOLUTION	SANDIMMUNE	CYCLOSPORINE	Y
ORAL	SUSP RECON	CELLCEPT	MYCOPHENOLATE MOFETIL	Y
ORAL	SUSP RECON	MYCOPHENOLATE MOFETIL	MYCOPHENOLATE MOFETIL	Y
ORAL	TABLET	AZATHIOPRINE	AZATHIOPRINE	Y
ORAL	TABLET	CELLCEPT	MYCOPHENOLATE MOFETIL	Y
ORAL	TABLET	IMURAN	AZATHIOPRINE	Y
ORAL	TABLET	MYCOPHENOLATE MOFETIL	MYCOPHENOLATE MOFETIL	Y
ORAL	TABLET	RAPAMUNE	SIROLIMUS	Y
ORAL	TABLET	SIROLIMUS	SIROLIMUS	Y
ORAL	TABLET	ZORTRESS	EVEROLIMUS	Y
ORAL	TABLET DR	MYCOPHENOLIC ACID	MYCOPHENOLATE SODIUM	Y
ORAL	TABLET DR	MYFORTIC	MYCOPHENOLATE SODIUM	Y
ORAL	CAP ER 24H	ASTAGRAF XL	TACROLIMUS	N
ORAL	TABLET	AZASAN	AZATHIOPRINE	N

Appendix 2: New Clinical Trials

A total of 45 citations were manually reviewed from the literature search. After further review, 43 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 2 trials are briefly described in the table below. Full abstracts are included in Appendix 3.

Table 1: Description of Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Cutler, et al.[17]	Tacrolimus + Sirolimus (T/S) vs. Tacrolimus + methotrexate (T/M)	<60 y/o undergoing transplantation for acute leukemia, myelodysplastic disorder, or chronic myeloid leukemia (n=304)	Day 144 acute GVHD-free survival	GVHD-free surivival: T/S: 67% (95% CI 59-74) T/M: 62% (95% CI 54-70) P=0.38
REFINE[18]	Cyclosporine vs. tacrolimus	HCV-positive adult recipients of a first liver transplant (n=356)	Rate of fibrosis stage ≥2 by 12 months after liver transplantation	Fibrosis score ≥2 Cyc: 63/88 (71.6%) Tac: 62/77 (67.5%) P=0.759 OR 1.11 (95% CI 0.56-2021)

Appendix 3: Abstracts of Clinical Trials

1. Cutler C et al. Tacrolimus/sirolimus vs tacrolimus/methotrexate as GVHD prophylaxis after matched, related donor allogeneic HCT. *Blood.* 2014 Aug 21;124(8):1372-7. doi: 10.1182/blood-2014-04-567164. Epub 2014 Jun 30.

Abstract
Grades 2-4 acute graft-versus-host disease (GVHD) occurs in approximately 35% of matched, related donor (MRD) allogeneic hematopoietic cell transplantation (HCT) recipients. We sought to determine if the combination of tacrolimus and sirolimus (Tac/Sir) was more effective than tacrolimus and methotrexate (Tac/Mtx) in preventing acute GVHD and early mortality after allogeneic MRD HCT in a phase 3, multicenter trial. The primary end point of the trial was to compare 114-day grades 2-4 acute GVHD-free survival using an intention-to-treat analysis of 304 randomized subjects. There was no difference in the probability of day 114 grades 2-4 acute GVHD-free survival (67% vs 62%, P = .38). Grades 2-4 GVHD was similar in the Tac/Sir and Tac/Mtx arms (26% vs 34%, P = .48). Neutrophil and platelet engraftment were more rapid in the Tac/Sir arm (14 vs 16 days, P < .001; 16 vs 19 days, P = .03). Oropharyngeal mucositis was less severe in the Tac/Sir arm (peak Oral Mucositis Assessment Scale score 0.70 vs 0.96, P < .001), but otherwise toxicity was similar. Chronic GVHD, relapse-free survival, and overall survival at 2 years were no different between study arms (53% vs 45%, P = .06; 53% vs 54%, P = .77; and 59% vs 63%, P = .36). Based on similar long-term outcomes, more rapid engraftment, and less oropharyngeal mucositis, the combination of Tac/Sir is an acceptable alternative to Tac/Mtx after MRD HCT. This study was funded by the National Heart, Lung, and Blood Institute and the National Cancer Institute; and the trial was registered at www.clinicaltrials.gov as #NCT00406393.

2. Levy G, et al. REFINE: a ramdonimized trial comparing cyclosporine A and tacrolimus after liver transplantation for Hepatitis C. *Am J Transplant.* 2014 Mar 14(3):635-46.

Abstract
REFINE was a 12-month, prospective, open-label study in 356 patients receiving de novo liver transplantation for hepatitis C virus (HCV) cirrhosis, randomized to cyclosporine A (CsA) or tacrolimus with (i) no steroids, IL-2 receptor antibody induction and mycophenolic acid, or (ii) slow steroid tapering. The primary analysis population based on availability of liver biopsies comprised 165 patients (88 CsA, 77 tacrolimus). There was no difference in the primary endpoint, fibrosis stage ≥2 at 12 months, which occurred in 63/88 CsA-treated patients (71.6%) and 52/77 tacrolimus-treated patients (67.5%) (odds ratio [OR] 1.11; 95% CI 0.56, 2.21; p = 0.759). Similarly, no significant between-group difference occurred at month 24 (OR 1.15; 95% CI 0.47, 2.80; p = 0.767). Among steroid-free patients, fibrosis score ≥2 was significantly less frequent with CsA versus tacrolimus at month 12 (7/37 [18.9%] vs. 16/38 [42.1%]; p = 0.029). HCV viral load was similar in both the tacrolimus- and CsA-treated cohorts. Mean blood glucose was significantly higher with tacrolimus from day 15 onward. Biopsy-proven acute rejection, graft loss and death were similar. These results showed no differences in post-transplant HCV-induced liver fibrosis between patients treated with CsA or tacrolimus in steroid-containing regimens, whereas CsA in steroid-free protocols was associated with reduced severity of fibrosis progression at 1 year post-transplant.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to October Week 3 2015, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 10, 2014
1 exp azaioprine.mp 9460
2 cyclosporine.mp or Cyclosporine/ 27272
3 everolimus.mp 3210
4 sirolimus.mp or Sirolimus/ 14682
5 mycophenolate.mp. 8571
6 immunosuppressive agents.mp or Immunosuppressive Agents/ 65117
7 tacrolimus.mp or Tacrolimus/ 16378
8 Graft Rejection/ or Lung Transplantation/ or transplantation.mp 37558
9 organ transplantation.mp or Organ Transplantation/ 14741
10 rheumatoid arthritis.mp or Arthritis, Rheumatoid/ 53500
11 inflammatory bowel disease.mp or Inflammatory Bowel Diseases/ 23618
12 ulcerative colitis.mp or Colitis, Ulcerative/ 19151
13 Graft vs. Host Disease/ or graft versus host.mp 17129
14 Crohn's disease.mp or Crohn Disease 24560
15 1 or 2 or 3 or 4 or 5 or 6 or 7 92720
16 8 or 9 or 10 or 11 or 12 or 13 or 14 164421
17 15 and 16 23834
18 limit 17 to (english language and yr="2013 -Current") and ((clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) 263

After initial review for appropriate study design, study comparators, and outcomes, 45 trials remained for further review.