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Drug Class Literature Scan: Immunosuppressants

Date of Review: February 2020

Date of Last Review: January 2016
Literature Search: 10/01/15 – 10/31/19

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

Conclusions:
- Two high quality systematic reviews, 4 clinical practice guidelines, one randomized controlled trial (RCT), 2 new indications and one safety alert were identified after literature review to update the evidence for this class.
- A Cochrane review in patients with Crohn's disease found clinical remission more effective in patients treated with infliximab compared to azathioprine (AZA) based on moderate strength of evidence, with an absolute risk reduction (ARR) of 16%. Combination therapy with AZA + infliximab was more effective compared to infliximab alone at inducing remission, with an ARR of 12%, based on moderate strength of evidence.[1]
- High quality evidence from a Cochrane review in patients undergoing kidney transplant found mycophenolate mofetil (MMF) to be more effective at preserving graft survival (ARR of 2.4%/number needed to treat [NNT] 42) and prevention of acute rejection (ARR 5.5%/NNT 18) compared to AZA; however, cytomegalovirus (CMV) was more common (approximately 1.7-fold increase) with MMF therapy.[2]
- High quality guidelines support the Oregon Health Plan (OHP) fee-for-service (FFS) preferred drug placement for the treatment of Crohn's disease, kidney transplant and ulcerative colitis.[3-6]
- Everolimus (Afinitor®) received an approval for the use as adjunctive treatment for adult and pediatric patients aged 2 years and older with tuberous sclerosis complex (TSC)-associated partial-onset seizures and for use in adults with renal angiomyolipoma and TSC not requiring immediate surgery.[4]
- Tacrolimus (Astagraf XL®) was approved for the use in pediatric patients in November of 2018.
- Caution should be used with everolimus (Afinitor®/Zortress) in patients of reproductive age due to evidence of fetal harm.[4,5]

Recommendations:
- No additional research is needed.
- No changes to the preferred drug list (PLD) are recommended based on the evidence. Consider making all therapies preferred due to high approval percentage of current prior authorization (PA) requests.
- After evaluation of costs in executive session, all medications in this class were made PDL preferred.

Summary of Prior Reviews and Current Policy
- Previous review of immunosuppressants found no differences between cyclosporine or tacrolimus for the outcomes of acute rejection or morality in patients who had undergone a lung transplant. Adverse events were lower with tacrolimus.

Author:

- There is insufficient evidence to suggest differences in efficacy or harms between the immunosuppressants. Calcineurin inhibitors are used most commonly to prevent rejection after transplant.
- There were no changes made to the PDL after review of the evidence presented for this class in January of 2016.
- All therapies in the class are preferred with the exception of: azathioprine (Azasan), tacrolimus (Prograf), and tacrolimus extended release (Envarsus XR). Non-preferred therapies are subject to the non-preferred agent PA criteria. There are approximately 40-50 requests for non-preferred therapies each quarter, resulting in an approval rate of almost 100%.
- The immunosuppressant class is not a large portion of OHP medication expenditures. There was approximately 100% utilization of preferred immunosuppressant therapies.

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), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, 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.

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:

<u>Cochrane – Azathioprine or 6-mercaptopurine for Induction of Remission in Crohn's Disease</u>
A 2016 Cochrane report reviewed the efficacy and safety of AZA or 6-mercaptopurine (6-MP) compared to placebo or active treatment in adult patients with active (acute) Crohn's Disease.[1] Thirteen trials were included in the analysis: 9 placebo-controlled and 6 active treatment comparisons. Most trials were found to be at low risk of bias. Placebo-controlled trial durations ranged from 12-17 weeks and active treatment comparisons lasted up to 26 weeks. The main outcome studied was the proportion of patients with clinical remission, measured by a validated outcome (e.g., Crohn's Disease Activity Index score less than 150 points or a Harvey-Bradshaw Index score less than 3). Clinical improvement, remission, glucocorticoids (GCS) reduction (or not needed) and mucosal healing were important secondary outcomes. Results with high to moderate evidence will be discussed.

There was moderate strength of evidence, from placebo-controlled trials (n=5), of no difference in clinical remission rates between AZA or 6-MP and placebo, 458/1000 patients versus 372/1000 patients (RR 1.23; 95% CI, 0.97 to 1.55).[1] There were similar findings for the comparison of AZA or 6-MP to placebo for the outcome of clinical remission or improvement, based on moderate evidence, 452/1000 patients versus 359/1000 patients (RR 1.26; 95% CI, 0.98 to 1.62).[1] These findings are limited by the fact that GCS were allowed in the placebo group, therefore confounding the effect of AZA or 6-MP. Additionally, the authors felt that some of the study durations may not have been long enough to adequately represent treatment efficacy, suggesting a minimum of 17 weeks is needed for an immunosuppressant effect to be realized. There was a GCS sparing (prednisone dose less than 10 mg/day while maintaining remission) effect of AZA compared

to placebo, 64% versus 46% (RR 1.34; 95% CI, 1.02 to 1.77; moderate evidence).[1] Serious adverse events occurred in 14% of patients treated with AZA compared to 4% placebo.[1]

In active treatment comparisons, AZA was compared to infliximab for induction of remission in Crohn's disease. Azathioprine induced remission in 32% of patients compared to 48% of infliximab-treated patients (RR 0.66; 95% CI, 0.51 to 0.87; moderate evidence).[1] GCS free-remission occurred in 37% of AZA patients compared to 44% of infliximab-treated patients (RR 0.68; 95% CI, 0.51 to 0.90; 1 trial; moderate evidence). Mucosal healing was more common in infliximab-treated patients compared to AZA (28% vs. 16%).[1] Adverse events were similar between groups. Similar results were found for the combination of AZA plus infliximab compared to infliximab alone. Combination therapy was more effective in clinical remission induction compared to infliximab monotherapy (ARR 12%; RR 1.26; 95% CI, 1.03 to 1.54).[1] GCS-free clinical remission was more common in patients treated with combination treatment compared to monotherapy (60% vs. 48%; RR 1.23; 95% CI, 1.02 to 1.47).[1] Combination therapy of infliximab plus AZA was more effective at mucosal healing compared to infliximab (ARR 14%; RR 1.50; 95% CI, 1.02 to 2.19; moderate strength of evidence).[1]

In conclusion, the use of AZA or 6-MP may have a GCS-sparing effect, potentially reducing the impact of GCS-related adverse events. Infliximab was found to be more effective than AZA in patients with Crohn's disease. Strong conclusions on placebo-controlled comparisons cannot be made due to inherent limitations related to the duration of the studies. Additional active treatment comparisons would help to delineate the most effective treatment option for remission induction in patients with Crohn's disease.

<u>Cochrane – Mycophenolic Acid versus Azathioprine as Primary Immunosuppression for Kidney Transplant Recipients</u>

The use of MMF was compared to AZA in patients requiring immunosuppression due to kidney transplant in a 2015 Cochrane review.[2] Twenty-three trials (n=3,301) were included. Thirteen of the studies did not use any antibody induction therapy. Maintenance immunotherapy was used in all studies, most commonly calcineurin inhibitors (cyclosporine or tacrolimus) combined with GCS, in addition to AZA or MMF. Most studies had an unclear risk of bias. Mycophenolic acid was more effective at preserving graft survival and prevention of acute rejection compared to AZA; however, cytomegalovirus (CMV) was more common with MMF therapy (**Table 1).**[2] Adverse events more common with MMF treatment were gastrointestinal and thrombocytopenia. Elevated liver enzymes were associated more with AZA use.

Limitations to the findings include the lack of reporting of panel reactive antibodies (PRA) and previous loss of a kidney graft, which are indicative of baseline immunological risk. Adverse events were only reported in a small number of studies. The risk of bias was unclear in a majority of studies.

Table 1. Primary Immunosuppression in Kidney Transplant Recipients Treated with Mycophenolic Acid or Azathioprine[2]

Outcome	Result*	Strength of Evidence	Conclusion
All-cause Death	AZA: 49/1000 MMF: 47/1000 RR 0.95 (95% CI, 0.7 to 1.29)	Moderate	No difference in death between treatments
Graft loss (censored for death)	AZA: 11/100 MMF: 9/100 RR 0.78 (95% CI, 0.61 to 0.98)	High	MMF associated with an absolute reduction in graft loss of 9% compared to 11.4% for AZA (ARR 2.4%/NNT 42)
Acute rejection, steroid resistant/antibody treated	AZA: 11/100 MMF: 5/100 RR 0.48 (95% CI, 0.36 to 0.65)	High	MMF associated with an ARR of 5.5%/NNT 18 compared to AZA
Infection, CMV tissue invasive	AZA: 4/100 MMF: 7/100 RR 1.7 (95% CI, 1.1 to 2.61)	High	Increased risk of infection with MMF vs. AZA
Acute rejection	AZA: 35/100 MMF: 23/100 RR 0.65 (95% CI, 0.57 to 0.73)	High	MMF associated with a reduced risk of acute rejection.
Key: * Illustrative comparative risk Abbreviations: AZA = azathioprine; CMV = cytomegalovirus; MMF = mycophenolate mofetil; NNT = number needed to treat; RR = relative risk			

After review, 50 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
High Quality Guidelines:

NICE – Crohn's Disease: Management
A 2019 NICE guidance evaluated the evidence for the surgical and pharmacological management of patients with Crohn's disease.[3] Drug therapy recommendations for inducing remission and maintenance will be discussed. Endoscopic relapse and clinical relapse are important outcomes in determining response to therapy. Conventional GCS are recommended for remission of disease. Azathioprine, 6-MP, or methotrexate are not recommended to be used as monotherapy to induce remission and should be combined with other therapies. Recommendations for the role of traditional immunosuppressants are presented in **Table 2**. Patients taking AZA should be monitored for neutropenia.

Table 2. NICE Recommendations for the Use of Immunosuppressants in Patients with Crohn's Disease[3]

Indication	Recommendation
Remission Induction Add-on Treatment Options	• Glucocorticoids (GCS) are recommended first-line • AZA or 6-MP added to conventional GCS or budesonide for remission induction* • Infliximab, adalimumab, ustekinumab and vedolizumab recommended for patients unresponsive to conventional therapy (immunosuppressants or GCS)
Maintaining Remission Options	• AZA or 6-MP as monotherapy to maintain remission when previously used with conventional GCS or budesonide to induce remission • AZA or 6-MP are recommended to those who have not previously used these treatments
Maintaining Remission in Crohn's Disease after Surgery	• AZA in combination with up to 3 months postoperative metronidazole in patients with ileocolonic Crohn's disease with complete macroscopic resection within the last 3 months • AZA monotherapy is appropriate for patients with metronidazole intolerance
Key: * Assess thiopurine methyltransferase (TPMT) activity prior to use. If TPMT is deficient do not use and use lower doses if TPMT activity is below normal. Abbreviations: AZA = azathioprine; GCS = glucocorticoids; 6-MP = mercaptopurine	

NICE – Immunosuppressive Therapy for Kidney Transplant in Adults

A 2017 review of immunosuppressants from NICE offered guidance for patients who are undergoing kidney transplantation.[6] Recommendations were for induction and maintenance therapies, which included the following: basiliximab, rabbit anti-human thymocyte immunoglobulin (rATG), tacrolimus (immediate-release and prolonged-release), mycophenolate mofetil, mycophenolate sodium, sirolimus, everolimus, and betacept.[6] Induction therapy consists of approximately 2 weeks of an intensive immunosuppressive regimen. Maintenance therapy is started right after transplant and continued for the duration of the patient's life.

Evidence for the recommendations was provided by an assessment group that performed a systematic review and critical appraisal. These current recommendations are related to therapy (induction and maintenance) used around the time of transplant (**Table 3**).[6] There was insufficient evidence to make strong conclusions on comparative efficacy between maintenance therapies. Initial treatment with r-ATG, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended.[6] Everolimus is associated with an increased risk of anemia and sirolimus may cause peripheral edema and bone marrow suppression contributing to intolerance. There was insufficient evidence to recommend options for preventing organ rejection in adults who are not able to tolerate therapies in Table 3 or standard triple therapy with CSA, AZA, and a GCS.

Table 3. NICE Recommendations for Kidney Transplant in Adults – Treatment Related to Immediate Transplant Phase.[6]

Initial Therapy	*Comments*
Basiliximab* (induction)	In conjunction with a calcineurin inhibitor. No statistical difference was identified between basiliximab and rabbit anti-human thymocyte immunoglobulin (rATG) with no evidence of a clinical difference between therapies.
Immediate release tacrolimus	As part of an immunosuppressive regimen
Mycophenolate mofetil	As part of an immunosuppressive regimen
Key:*Basiliximab is the most cost-effective treatment	

NICE- Immunosuppressive Therapy for Kidney Transplant in Children and Young People

An October 2017 guidance from NICE provided recommendations on immunotherapy for children and young people undergoing kidney transplant.[7] Drugs included in this review are: basiliximab, rATG, tacrolimus (immediate-release and prolonged-release), mycophenolate mofetil, mycophenolate sodium, sirolimus, and everolimus. Immunosuppressant recommendations for children and young people mirror those for adult kidney transplant recipients. These current recommendations are related to therapy (induction and maintenance) used around the time of transplant (**Table 4)**.[7] Initial treatment with rATG, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended. Overall, comparative evidence between immunosuppressants is limited in children and young people undergoing a kidney transplant.

Table 4. NICE Recommendations for Kidney Transplant in Children and Young People – Treatment Related to Immediate Transplant Phase.[7]

Initial Therapy	*Comments*
Basiliximab (induction)	In conjunction with a calcineurin inhibitor
Immediate-release tacrolimus	As part of an immunosuppressive regimen
Mycophenolate mofetil	As part of an immunosuppressive regimen

NICE – Ulcerative Colitis: Management

NICE updated the recommendations for the management of ulcerative colitis in 2019.[8] Most of the evidence related to studies of patients with mild to moderate ulcerative colitis. Immunosuppressants are usually reserved for more severe disease. Recommendations for the use of immunosuppressants in severe ulcerative colitis are presented in **Table 5**.

Table 5. NICE Recommendations for the use of Immunosuppressants in the Management of Ulcerative Colitis.[8]

Recommendation	*Comments*
Severe Ulcerative Colitis	
IV cyclosporine	For patients whom IV GCS are not appropriate
IV cyclosporine	In combination with IV GCS in patients who fail to respond within 72 hours of starting IV GCS or worsen during GCS treatment
Remission Maintenance	
AZA or 6-MP	After 2 or more inflammatory exacerbations in 12 months that require treatment with systemic GCS or if remission isn't maintained by aminosalicylates
Remission Maintenance After a Single Episode of Acute Ulcerative Colitis	
Azathioprine or mercaptopurine	Aminosalicylates can be considered if intolerant to other therapies
Abbreviations: AZA = azathioprine; GCS = glucocorticoids; IV = intravenous; 6-MP = mercaptopurine	

After review, 22 guidelines were excluded due to poor quality.[9–30]

New Formulations/Indications:

Everolimus (Afinitor®)

In 2018 everolimus received an approval for the use as adjunctive treatment of adult and pediatric patients aged 2 years and older with TSC-associated partial-onset seizures at a dose of 5 mg/m^2.[4] Evidence for this indication was provided by a phase 3 trial (EXIST-3) described below in **Table 7**.[31]

In 2016 everolimus was approved for use in adults with renal angiomyolipoma and TSC not requiring immediate surgery at a dose of 10 mg orally daily.[4] Evidence for the approval was based on one phase 3 trial (EXIST-2) described below in **Table 7**.[32]

Tacrolimus (Astagraf XL®)

The FDA approved tacrolimus for the use in pediatric patients in November of 2018.[33] Approval was based on pharmacokinetic studies demonstrating similar tacrolimus concentrations at 24 hours as immediate-release tacrolimus (Prograf) in pediatric de novo kidney transplant patients.

Tacrolimus (Envarsus XR®)

Envarsus XR was FDA approved in 2018 for the prophylaxis of organ rejection in de novo kidney transplant patients in combination with other immunosuppressants.[34] This formulation of tacrolimus was previously indicated for use in patients who had transitioned from immediate-release tacrolimus. The recommended dose is 0.14 mg/kg once daily.

New FDA Safety Alerts:

Table 6. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Everolimus[4, 5]	Afinitor®/Zortress	2015	Warnings	Can cause fetal harm. Patients should be advised of reproductive potential risk to a fetus and to use contraception if of reproductive potential.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
azathioprine	AZATHIOPRINE	TABLET	Y
azathioprine	IMURAN	TABLET	Y
cyclosporine	CYCLOSPORINE	CAPSULE	Y
cyclosporine	SANDIMMUNE	CAPSULE	Y
cyclosporine	SANDIMMUNE	SOLUTION	Y
cyclosporine, modified	CYCLOSPORINE MODIFIED	CAPSULE	Y
cyclosporine, modified	GENGRAF	CAPSULE	Y
cyclosporine, modified	NEORAL	CAPSULE	Y
cyclosporine, modified	CYCLOSPORINE MODIFIED	SOLUTION	Y
cyclosporine, modified	GENGRAF	SOLUTION	Y
cyclosporine, modified	NEORAL	SOLUTION	Y
everolimus	ZORTRESS	TABLET	Y
mycophenolate mofetil	CELLCEPT	CAPSULE	Y
mycophenolate mofetil	MYCOPHENOLATE MOFETIL	CAPSULE	Y
mycophenolate mofetil	CELLCEPT	SUSP RECON	Y
mycophenolate mofetil	MYCOPHENOLATE MOFETIL	SUSP RECON	Y
mycophenolate mofetil	CELLCEPT	TABLET	Y
mycophenolate mofetil	MYCOPHENOLATE MOFETIL	TABLET	Y
mycophenolate sodium	MYCOPHENOLIC ACID	TABLET DR	Y
mycophenolate sodium	MYFORTIC	TABLET DR	Y
sirolimus	RAPAMUNE	SOLUTION	Y
sirolimus	SIROLIMUS	SOLUTION	Y
sirolimus	RAPAMUNE	TABLET	Y
sirolimus	SIROLIMUS	TABLET	Y
tacrolimus	PROGRAF	CAPSULE	Y
tacrolimus	TACROLIMUS	CAPSULE	Y
azathioprine	AZASAN	TABLET	N
tacrolimus	ASTAGRAF XL	CAP ER 24H	N
tacrolimus	PROGRAF	GRAN PACK	N
tacrolimus	ENVARSUS XR	TAB ER 24H	N

Appendix 2: New Comparative Clinical Trials

A total of 549 citations were manually reviewed from the initial literature search. After further review, 547 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 7. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Bissler, et al[32] (EXIST-2) Phase 3, DB, MC, PC, RCT	Everolimus 10 mg daily Vs. Placebo daily Median exposure 36 weeks	Adult patients with renal angiomyolipoma 3 cm or larger and TSC diagnosis or sporadic lymphangioleio-myomatosis, not requiring immediate surgery4 (n=118)	Proportion of patients with confirmed angiomyolipoma response of at least a 50% reduction in total volume of target angiomyolipoma relative to baseline	<u>Response rate:</u> Everolimus: 42% Placebo: 0% MD 42% (95 CI, 24-58%) P < 0.0001
French, et al[31] (EXIST-3) Phase 3, DB, MC, PC, RCT	Everolimus 3-7 ng/mL (low exposure) Vs. Everolimus 9-15 ng/mL (high exposure) Vs. Placebo 18 week core phase (followed an 8 week baseline phase)	Patients with TSC and treatment-resistant seizures receiving 1-3 concomitant antiepileptic drugs (n=366)	Change from baseline in the frequency of seizures during the maintenance period defined as a response rate* and median percentage reduction in seizure frequency	<u>Response rate:</u> Everolimus low exposure: 28.2% Everolimus high exposure: 40% Placebo: 15.1% Everolimus low exposure vs. placebo P = 0.0077 Everolimus high exposure vs. placebo P < 0.001 <u>Reduced seizure frequency:</u> Everolimus low exposure: 29.3% Everolimus high exposure: 39.6% Placebo: 14.9% Everolimus low exposure vs. placebo P = 0.0028 Everolimus high exposure vs. placebo P < 0.0001

Key: * Response rate was defined as the proportion of patients achieving 50% or greater reduction in seizure frequency
Abbreviations: CR = complete response; DB = double-blind; DLBCL = diffuse large B-cell lymphoma; IPI = International Prognostic Index; MC = multi-center; PC = placebo controlled; RCT = randomized clinical trial; TSC = tuberous sclerosis complex.

Appendix 3: Abstracts of Comparative Clinical Trials

Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial.

Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, Belousova E, Sauter M, Nonomura N, Brakemeier S, de Vries PJ, Whittemore VH, Chen D, Sahmoud T, Shah G, Lincy J, Lebwohl D, Budde K.

BACKGROUND:
Angiomyolipomas are slow-growing tumours associated with constitutive activation of mammalian target of rapamycin (mTOR), and are common in patients with tuberous sclerosis complex and sporadic lymphangioleiomyomatosis. The insidious growth of these tumours predisposes patients to serious complications including retroperitoneal haemorrhage and impaired renal function. Everolimus, a rapamycin derivative, inhibits the mTOR pathway by acting on the mTOR complex 1. We compared the angiomyolipoma response rate on everolimus with placebo in patients with tuberous sclerosis or sporadic lymphanioleiomyomatosis-associated angiomyolipomata.
METHODS:
In this double-blind, placebo-controlled, phase 3 trial, patients aged 18 years or older with at least one angiomyolipoma 3 cm or larger in its longest diameter (defined by radiological assessment) and a definite diagnosis of tuberous sclerosis or sporadic lymphangioleiomyomatosis were randomly assigned, in a 2:1 fashion with the use of an interactive web response system, to receive oral everolimus 10 mg per day or placebo. The primary efficacy endpoint was the proportion of patients with confirmed angiomyolipoma response of at least a 50% reduction in total volume of target angiomyolipomas relative to baseline. This study is registered with ClinicalTrials.gov number NCT00790400.
RESULTS: 118 patients (median age 31·0 years; IQR 18·0–61·0) from 24 centres in 11 countries were randomly assigned to receive everolimus (n=79) or placebo (n=39). At the data cutoff, double-blind treatment was ongoing for 98 patients; two main reasons for discontination were disease progression (nine placebo patients) followed by adverse events (two everolimus patients; four placebo patients). The angiomyolipoma response rate was 42% (33 of 79 [95% CI 31–53%]) for everolimus and 0% (0 of 39 [0–9%]) for placebo (response rate difference 42% [24–58%]; one-sided Cochran-Mantel-Haenszel test p<0·0001). The most common adverse events in the everolimus and placebo groups were stomatitis (48% [38 of 79], 8% [3 of 39], respectively), nasopharyngitis (24% [19 of 79] and 31% [12 of 39]), and acne-like skin lesions (22% [17 of 79] and 5% [2 of 39]).
INTERPRETATION: Everolimus reduced angiomyolipoma volume with an acceptable safety profile, suggesting it could be a potential treatment for angiomyolipomas associated with tuberous sclerosis.

Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study.

French JA, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, Curatolo P, de Vries PJ, Dlugos DJ, Berkowitz N, Voi M, Peyrard S, Pelov D, Franz DN

BACKGROUND:
Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, has been used for various benign tumours associated with tuberous sclerosis complex. We assessed the efficacy and safety of two trough exposure concentrations of everolimus, 3-7 ng/mL (low exposure) and 9-15 ng/mL (high exposure), compared with placebo as adjunctive therapy for treatment-resistant focal-onset seizures in tuberous sclerosis complex.

METHODS:
In this phase 3, randomised, double-blind, placebo-controlled study, eligible patients aged 2-65 years with tuberous sclerosis complex and treatment-resistant seizures (≥16 in an 8-week baseline phase) receiving one to three concomitant antiepileptic drugs were recruited from 99 centres across 25 countries. Participants were randomly assigned (1:1:1), via permuted-block randomisation (block size of six) implemented by Interactive Response Technology software, to receive placebo, low-exposure everolimus, or high-exposure everolimus. Randomisation was stratified by age subgroup (<6 years, 6 to <12 years, 12 to <18 years, and ≥18 years). Patients, investigators, site personnel, and the sponsor's study team were masked to treatment allocation. The starting dose of everolimus depended on age, body-surface area, and concomitant use of cytochrome 3A4/P-glycoprotein inducers. Dose adjustments were done to attain target trough ranges during a 6-week titration period, and as needed during a 12-week maintenance period of core phase. Patients or their caregivers recorded events in a seizure diary throughout the study. The primary endpoint was change from baseline in the frequency of seizures during the maintenance period, defined as response rate (the proportion of patients achieving ≥50% reduction in seizure frequency) and median percentage reduction in seizure frequency, in all randomised patients. This study is registered with ClinicalTrials.gov, number NCT01713946.
FINDINGS:
Between July 3, 2013, and May 29, 2015, 366 patients were enrolled and randomly assigned to placebo (n=119), low-exposure everolimus, (n=117), or high-exposure everolimus (n=130). The response rate was 15·1% with placebo (95% CI 9·2-22·8; 18 patients) compared with 28·2% for low-exposure everolimus (95% CI 20·3-37·3; 33 patients; p=0·0077) and 40·0% for high-exposure everolimus (95% CI 31·5-49·0; 52 patients; p<0·0001). The median percentage reduction in seizure frequency was 14·9% (95% CI 0·1-21·7) with placebo versus 29·3% with low-exposure everolimus (95% CI 18·8-41·9; p=0·0028) and 39·6% with high-exposure everolimus (95% CI 35·0-48·7; p<0·0001). Grade 3 or 4 adverse events occurred in 13 (11%) patients in the placebo group, 21 (18%) in the low-exposure group, and 31 (24%) in the high-exposure group. Serious adverse events were reported in three (3%) patients who received placebo, 16 (14%) who received low-exposure everolimus, and 18 (14%) who received high-exposure everolimus. Adverse events led to treatment discontinuation in two (2%) patients in the placebo group versus six (5%) in the low-exposure group and four (3%) in the high-exposure group.
INTERPRETATION:
Adjunctive everolimus treatment significantly reduced seizure frequency with a tolerable safety profile compared with placebo in patients with tuberous sclerosis complex and treatment-resistant seizures.

Appendix 4: Medline Search Strategy

Database(s): Ovid MEDLINE(R) 1946 to October Week 1 2019
Search Strategy:

#	Searches	Results
1	azathioprine.mp. or Azathioprine/	21289
2	cyclosporine.mp. or Cyclosporine/	43181
3	everolimus.mp. or Everolimus/	5880
4	mycophenolate mofetil.mp. or Mycophenolic Acid/	11137
5	sirolimus.mp. or Sirolimus/	19233
6	tacrolimus.mp. or Tacrolimus/	22267
7	1 or 2 or 3 or 4 or 5 or 6	96850
8	limit 7 to (english language and humans and yr="2015 -Current")	11564
9	limit 8 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	549

Appendix 5: Key Inclusion Criteria

Population	Patients with an indication for immunosuppressants
Intervention	Immunosuppressant
Comparator	Active treatment or placebo
Outcomes	Mortality, graft loss, infection, clinical remission, induction, and withdrawals due to adverse events
Timing	Any duration
Setting	Inpatient or outpatient