Review of the Available Evidence on Tacrolimus in Adults and Children for the Prevention and Treatment of Transplant Rejection, and Proposal for Inclusion

FOR THE WHO MODEL LIST OF ESSENTIAL MEDICINES (EML)

Tina Poklepović Peričić[1,2], Svjetlana Došenović[3], Ana Utrobičić[1,2], Livia Puljak[1,4]

[1] Cochrane Croatia | University of Split School of Medicine | Split, Croatia

[2] Department of Research in Biomedicine and Health | University of Split School of Medicine | Split, Croatia

[3] University Hospital of Split | Split, Croatia

[4] Center for Evidence Based Medicine | Catholic University | Zagreb, Croatia

Person to contact:

Assist. Prof. Tina Poklepović Peričić, DMD, PhD | University of Split School of Medicine | Šoltanska 2 | 21000 Split, Croatia

Tel. +38521557923

Mobile: +385992565607

E-mail: tpoklepo@mefst.hr; tinapoklepovic@gmail.com

Prof. Livia Puljak, MD, PhD | Catholic University | Ilica 242, Zagreb, Croatia

Tel: + 38513706633

Mobile: +395912557807

E-mail: livia.puljak@unicath.hr; livia.puljak@gmail.com

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General Items

1. Summary statement of the proposal for inclusion

Tacrolimus has been extensively studied, and there is a substantial body of evidence on the efficacy and safety of tacrolimus in post-transplant immunosuppression, with numerous randomized controlled trials (RCTs) and systematic reviews (SRs), consistently showing a favourable benefit-risk profile following the use of tacrolimus.

Compared to other treatments tacrolimus has been shown to be superior for the most important outcomes such as graft loss and acute rejection, and has been used as a first-line treatment in children and adults having solid organ transplantation.

Combination therapy comprising tacrolimus, mycophenolate, steroids, and an induction agent (either basiliximab or anti-thymocyte globulin) is considered the most appropriate for improving graft survival and preventing acute rejection in solid organ transplants.

Immediate-release tacrolimus as part of an immunosuppressive regimen is recommended as an initial treatment option to prevent organ rejection.

Prolonged-release tacrolimus is recommended as an option only for restricted use for the prophylaxis of transplant rejection, and may be used as an option for maintenance immunosuppression as second-line agent for patients who suffer intolerable side effects related to peak dose toxicity. However, is not recommended for the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients. For children, immediate-release tacrolimus should be started on the day of transplantation for both, living and deceased donor transplants, because early after transplantation the rejection risk is the highest and maximum immunosuppression is required. Also, in children and young people having a solid organ transplant, prolonged-release tacrolimus is not recommended as a therapeutic approach for preventing organ rejection.

For patients receiving cyclosporine-based immunosuppression, a switch to tacrolimus is recommended for optimizing maintenance therapy.

Tacrolimus is effective in obtaining graft survival in patients with kidney transplants. In patients receiving heart transplants, tacrolimus is recommended over cyclosporine as the preferred CNI, because tacrolimus provides superior protection against rejection and has a more favorable side effect profile than cyclosporine. In adult liver transplantation patients tacrolimus is used as a

treatment option with or without corticosteroids. Tacrolimus is recommended over cyclosporine in lung transplants, as well. For optimizing maintainance in after lung transplantation, a switch from cyclosporine to tacrolimus-based immunosuppression is recommended. Evidence from RCTs are also pointing out the superiority of tacrolimus in patients receiving simultaneous kidney-pancreas transplants.

Tacrolimus was found to be the ideal immunosuppression in pregnancy, with the maintenance of therapeutic levels throughout pregnancy, and good pregnancy outcomes.

Considering the balance of benefits and harms from the available evidence, it may be concluded that tacrolimus is an effective, safe and cost-effective treatment option for induction and maintenance of immunosuppression to most transplant patients in addition to or as an alternative to the immunosuppressive medications already listed in the EML.

2. Relevant WHO technical department and focal point (if applicable)

The current application was done in agreement with the WHO Essential Medicines and Health Products Department.

3. Name of organization(s) consulted and/or supporting the application

Cochrane Croatia, University of Split School of Medicine, Croatia

4. International Nonproprietary Name (INN, generic name) and Anatomical Therapeutic Chemical (ATC) code of the medicine

The International Nonproprietary Name (INN) of the medicine is: tacrolimus (calcineurin inhibitor).
The anatomical Therapeutic Chemical (ATC) code of the medicine is: L04AD02
(accessed via: https://www.whocc.no/atc_ddd_index/)

5. Dose, formulation(s) and strength(s) proposed for inclusion

Tacrolimus	Immediate release	0,5 mg, 0,75 mg, 1 mg, 2 mg, 5 mg capsules
		0,2 mg and 1mg granules
		5mg/ml solution

The list of tacrolimus formulations along with doses and administration routes used for prevention and treatment of transplant rejection is presented in Annex 1 of this application.

Tacrolimus is available as immediate and prolonged-release drug formulations.

Immediate-release tacrolimus has consistently shown its superiority against prolonged-release tacrolimus in adults in terms of clinical efficacy and cost-effectiveness. Due to insufficient evidence on the safety and efficacy of prolonged-release tacrolimus in children under 18 years of age, recommendations regarding prolonged-release tacrolimus in children are not applicable.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class

The current application is for tacrolimus to be listed on the Model List of Essential Medicines as an individual medicine for prevention and treatment of graft rejection following transplantation.

7. Treatment details, public health relevance and evidence appraisal and synthesis

7.1 Treatment details (requirements for diagnosis, treatment and monitoring)

Calcineurin inhibitors (CNIs) cyclosporine and tacrolimus are considered the cornerstone of immunosuppressive therapy in allograft recipients. The introduction of this class of agents in the 1980s dramatically improved patient and graft survival rates, and substantially reduced comorbidity following transplantation [1, 2]. Cyclosporine was introduced in 1980 as a novel immunosuppressive medicine, resulting in considerably improved outcomes in patients undergoing liver transplantation [1]. In 1994, two pivotal trials of tacrolimus were published in liver transplant recipients; the results showed a significant reduction in the incidence of acute rejection, but no difference in mortality or graft loss compared to cyclosporine at 1 year [3, 4].

Tacrolimus is a macrolide derived from the fungus *Streptomyces tsukubaensis*, and was developed as an alternative to cyclosporin. Tacrolimus has been used for preventing and controlling graft rejection in liver transplants since 1989. In 1994, tacrolimus was first approved for prevention and treatment of liver transplantation rejection, and in 1997, it gained approval for kidney transplantation. The use of tacrolimus subsequently expanded rapidly into transplantation management of other organs as well [5, 6].

Nowadays, tacrolimus is used in solid organ transplantation as the treatment of organ rejection in kidney, liver, and heart allogeneic transplants, with an off-label indication for the prevention of rejection in lung transplant patients [7].

Tacrolimus inhibits T-cell proliferation by binding to FK506 binding protein (FKBP). Inhibition of calcineurin by tacrolimus indirectly prevents transcription of cytokines genes that encode for interleukin-2, interleukin-3, interleukin-4, granulocyte-macrophage-colony-stimulating factor, tumor necrosis factor-alpha and gamma interferon in the early phase of T-cell activation [8].

Initially, tacrolimus was administered as a twice-daily “immediate-release” formulation (Prograf, Astellas Pharma Inc., Tokyo, Japan), but in recent times a once-daily prolonged-release formulation has been developed (Advagraf, Astellas Pharma Inc., Tokyo, Japan).

Rejection, whether acute or chronic, remains a major cause of dysfunction and graft loss. Chronic rejection is a slow progressive process and is responsible for 25% to 35% of graft losses one year after transplantation. The major risk factor for the development of chronic rejection is acute rejection. Acute rejection occurs in 30-50% of all transplants, usually during the first three months, but can be successfully treated in more than 90% of cases [9].

Immunosuppression aims to maintain graft and patient survival without exposing the patient to the risks of excessive immunosuppression or nephrotoxicity related to the use of immunosuppressants [2]. Immunosuppressive agents, therefore, play a key role in the prevention of rejection [10].

Usually, a combination of drugs is used for immunosuppression, including a CNI (cyclosporine A or tacrolimus) and a corticosteroid (methylprednisolone), or a combination of CNI, antimetabolite (mycophenolate mofetil, mycophenolic acid, or azathioprine), and a corticosteroid [11]. The main purpose of these combinations is to decrease the adverse effects of the individual drugs by reducing the doses, and to suppress immunity by multiple

mechanisms [12]. However, immunosuppressive drugs may be used alone, with treatment usually including either CNIs or antimetabolites [13].

Other available treatment options include mTOR (mammalian target of rapamycin) inhibitors (sirolimus, everolimus) and antibody-based therapies (thymoglobulin, antithymocyte globulin, alemtuzumab, basiliximab, daclizumab) [11, 12].

Tacrolimus has been used increasingly for acute rejection, as clinical experience and case studies suggest that it is better tolerated by the patients and is more effective [14-16].

Children represent a specific group of organ transplant candidates. They differ from their adult counterparts in some important aspects, including the aetiology of organ failure, the complexity of the surgical procedure, the pharmacokinetic properties of immunosuppressants, the immune response following organ transplantation, the success of the transplant procedure, the amount and the degree of comorbidities and the susceptibility to post-transplant complications, infections in particular [17].

7.2 Pharmacodynamics of Tacrolimus

The magnitude of the pharmacodynamic variability of tacrolimus remains unclear, with some available data on tacrolimus concentrations and its effect on organ rejection and potential adverse effects. The main adverse effects associated with tacrolimus include nephrotoxicity, neurotoxicity, diabetogenesis, gastrointestinal disturbances, hypertension, infections and malignant complications [18] and are more frequently observed or more severe at higher concentrations [19, 20]. Tacrolimus is rarely associated with the ciclosporin-specific adverse effects like hirsutism, gingivitis and gum hyperplasia, but can cause alopecia and pruritus in some patients [18]. Adverse events tend to occur the most frequently in the first few months after transplantation and decline thereafter, possibly in line with reductions in tacrolimus concentrations [20].

7.3 Pharmacokinetics

Tacrolimus shows considerable inter- and intra-individual variability. When administered orally, tacrolimus is rapidly absorbed in most subjects, with peak plasma/ blood concentrations being obtained in 0.5–1 hour [21]. In others, however, drug uptake occurs slowly over a prolonged time, with an essentially flat absorption profile [21]. The composition of food may

highly influence its absorption, whereas high fat, as well as high carbohydrate meals, may substantially decrease the maximal concentration [22]. This phenomenon may be due to the highly lipophilic character of tacrolimus [23].

The bioavailability of tacrolimus has been found to be approximately 15%, though it may vary among healthy persons [24]. During the first days after transplantation, the bioavailability may be even more variable.

In blood, tacrolimus is mainly found within erythrocytes (85–95%), which makes blood drug concentrations significantly higher (average 15 times, range 4–114 times) than the corresponding plasma values [21, 25]. In plasma, approximately 60% of tacrolimus is bound to the proteins albumin and a1-acid glycoprotein (AGP), 30% to high-density lipoprotein (HDL), 8% to low-density lipoprotein (LDL), and 1% to very-low-density lipoprotein (VLDL). Only 0.3–2% of plasma tacrolimus is unbound [26]. The mean disposition half-life of tacrolimus is about 12 h [27], so the steady-state concentrations are expected within two to three days. The therapeutic levels of whole blood tacrolimus trough concentrations range from 5–20 mg/L. To prevent toxicity, the usual range is 5–15mg/L [28, 29]. In everyday practice, whole blood tacrolimus trough concentrations 12 h after administration are generally used for therapeutic drug monitoring, even though it has been demonstrated that 6 h post-administration concentrations better correlate with the 12 h area under the concentration-time curve (AUC) in stable transplantation patients [30-32].

Due to the high distribution of tacrolimus into the erythrocytes, its apparent volume of distribution based on whole blood concentrations is much lower (1.0–1.5 L/kg) than that based on plasma concentrations (about 30 L/kg) [33]. Because of this, many authors prefer whole blood tacrolimus concentrations instead of tacrolimus plasma concentrations to monitor patients. Tacrolimus is mainly metabolized in the liver, but also in the gut and kidney [34]. Tacrolimus is mainly excreted via the bile, while the renal clearance rate accounts for less than 1% of the overall body clearance [35]. Approximately 80–95% of the total tacrolimus dose is excreted via feces and more than 99% is excreted as metabolite [35].

7.4 Drug Interactions

CYP3A/P-glycoprotein inhibitors and inducers primarily affect the oral bioavailability of tacrolimus rather than its clearance, which indicates a key role of intestinal P-glycoprotein and

CYP3A. Drugs that interact with P-glycoprotein may change the distribution of tacrolimus in tissue, and by that modify its toxicity and immunosuppressive activity [36].

7.5 Administration of Tacrolimus, Doses, Population groups, Generics

Tacrolimus for post-transplant immunosuppression can be administered by oral or intravenous (IV) route.
Oral tacrolimus is available as immediate-release (IR) and prolonged- or extended-release (ER: XR and XL) formulations. The various formulations have different pharmacokinetic parameters and are not interchangeable. Doses should be titrated to target trough concentrations.

Immediate-release oral tacrolimus is available as 0.5 mg, 0.75 mg, 1 mg, 2 mg, 5 mg capsules, 0.2 mg and 1 mg granules for oral suspension, and as 5 mg/ml solution for parenteral use.

Prophylaxis of transplant rejection using immediate release tacrolimus is delivered orally in two divided doses (e.g. morning and evening), depends on the type of organ transplanted, and should start approximately 12 hours from the end of surgery. If a patient is unable to take the drug orally, intravenous tacrolimus therapy should be administered as a continuous 24-hour infusion. Patients should be carefully monitored and doses should be adjusted during the post-transplant period which may lead to dose reduction in adults and children, and may even include withdrawal of adjacent immunosuppressive therapy. In general, it is considered that **paediatric patients require doses 1½ - 2 times higher than adults** to achieve similar blood levels.

Tacrolimus granules are IR tacrolimus formulation intended for children and adults with kidney, heart or liver transplants to prevent rejection, and are taken twice daily in the morning and in the evening. The dose depends on the type of transplant the patient has received. In kidney transplant patients, the starting daily dose for adults is 0.2 to 0.3 mg per kilogram, whilst for children the suggested dose is 0.3 mg/kg. In liver transplant patients, the starting daily dose is 0.1 to 0.2 mg/kg for adults and 0.3 mg/kg for children. The starting daily dose for heart transplant patients is 0.075 mg/kg for adults and 0.3 mg/kg for children. For treating kidney and liver transplant rejection, the same doses may be used. Suggested dose for treating heart transplant rejection is 0.15 mg/kg/day for adults and 0.2 to 0.3 mg/kg for children.

Prolonged-release tacrolimus is available in 0.5 mg, 1 mg, 3 mg, 5 mg capsules and 0.5 mg, 0.75 mg, 1 mg, 2 mg to 5 mg tablets; it is given once a day, in the morning, at least one hour

before or two to three hours after food. Doses for each patient are calculated based on patient's weight, and depend on the type of transplant received. For prolonged-release tacrolimus it is important to monitor blood levels of tacrolimus to check that they stay within certain limits. Treatment is adjusted according to the tacrolimus blood levels and the patient's response. In patients with liver dysfunction doses may be lowered.

Prevention of Post-Organ Transplant Rejection:

Starting doses of immediate-release tacrolimus used for **prophylaxis of transplant rejection** according to the transplanted organ are listed below. Treatment is administered either orally in two divided doses (e.g. morning and evening) for IR and in one oral dose for ER, or intravenously.

Liver Transplantation:

Liver transplantation in adults:

- IR: 0.10 - 0.20 mg/kg/day twice a day orally or
- IR: 0.01 - 0.05 mg/kg/day as a continuous 24-hour infusion [37]
- ER: 0.10 to 0.20 mg/kg in combination with corticosteroid. The XL formulation is not approved for liver transplant in the US due to increased mortality in female liver transplants receiving the XL formulation. Initial dose is 0.03 to 0.05 mg/kg/day as a continuous infusion [37].

Liver transplantation in children:

- IR: 0.30 mg/kg/day twice a day orally or
- IR: 0.05 mg/kg/day as a continuous 24-hour infusion

Kidney Transplantation (in combination with an antimetabolite agent):

Kidney transplantation in adults:

- IR: 0.20 - 0.30 mg/kg/day twice daily orally in combination with azathioprine or 0.1 mg/kg/day in combination with mycophenolate mofetil or
- IR: 0.05 - 0.10 mg/kg/day as a continuous 24-hour infusion.

IV tacrolimus use is not common due to increased nephrotoxic adverse effects [38, 39].

Tacrolimus can be administered with or without food. However, since the presence of food affects the bioavailability of tacrolimus, if taken with food, it should be taken consistently the same way each time. IR doses should be 12 hours apart. Dose rounding should be to a whole number that is feasible with the available strengths. For example, IR tacrolimus comes in 0.5 mg, 1 mg, and 5 mg strengths [40].

When converting from IR to ER formulations, the following factors are utilized [37, 41]:

- IR to XL: 1 to 1
- IR to XR: 1 to 0.8

Sublingual to oral conversion rates have varied from 1 to 1 to 1 to 3, but 1 to 2 has recently been the most commonly suggested in studies. There has been no optimally established dosing [42, 43].

- ER: Initially 0.17 mg/kg/day to 2 mg/kg/day based on basiliximab induction; usual dose: 0.20 to 0.30 mg/kg a day taken in the morning.

Kidney transplantation in children:

- IR: 0.30 mg/kg/day twice a day orally or
- IR: 0.075 – 0.100 mg/kg/day as a continuous 24-hour infusion

Heart Transplantation (in combination with an antimetabolite):

Heart transplantation in adults:

- IR: 0.075 mg/kg/day twice a day orally starting 5 days after the transplantation or
- IR: 0.01 to 0.02 mg/kg/day as a continuous 24-hour infusion
- ER: Initial oral dose of 0.15 mg/kg/day once daily in the morning.

Starting doses for preventing rejection in heart, lung, pancreas or intestine transplants for ER are 0.10 to 0.30 mg/kg. In patients with lung transplants, prolonged-release tacrolimus starts at an initial oral dose of 0.10 - 0.15 mg/kg/day, whereas in patients receiving pancreas tacrolimus treatment starts at 0.2 mg/kg/day, and at 0.3 mg/kg/day for treating intestinal transplant rejection.

Alternatively, an initial oral dose of 2 to 4 mg tacrolimus daily with mycophenolate mofetil and corticosteroids or in combination with sirolimus and corticosteroids may be used for patients with preserved organ function.

Heart transplantation in children:

- 0.03 - 0.05 mg/kg/day as a continuous 24-hour infusion followed by
- 0.30 mg/kg/day orally 8 to 12 hours after discontinuing with intravenous therapy;
- In case the treatment started orally: 0.10 - 0.30 mg/kg/day twice daily per os + antibody induction [37-39, 44].

Treatment of Post-Organ Transplant Rejection

Tacrolimus rejection therapy in adults and children with kidney and liver transplants requires increased doses, additional corticosteroid therapy, and the introduction of short courses of mono- or polyclonal antibodies. In case of adverse events or toxicity, tacrolimus dose should be reduced. In adult patients having heart transplant 0.15 mg/kg/day dose of tacrolimus is used twice daily, and in children suggested dose of tacrolimus for the treatment of rejection is 0.20 - 0.30 mg/kg/day. Recommended doses for treatment of graft rejection in lung, pancreas, and intestinal transplants are based on limited quality evidence, with the initial oral doses as follows: in lung-transplants 0.10 - 0.15 mg/kg/day, after pancreas transplantation 0.2 mg/kg/day, and in intestinal transplantation initial dose is 0.3 mg/kg/day.

When used during pregnancy, the dose of tacrolimus needs to be increased and carefully monitored to provide safe and stable tacrolimus trough levels during pregnancy. Although most of the pregnancies with tacrolimus have been successful, there is an increased risk of maternal and fetal complications, including allograft loss, low birth weight, spontaneous abortus, and preeclampsia. There is some evidence, though, of the increased risk of long-term graft loss associated with pregnancy. Evidence is mostly applicable to women having kidney or liver transplants. Clinical data show that tacrolimus is excreted in breast milk, but because no strong evidence on the effects of tacrolimus have been available, women taking tacrolimus should avoid breastfeeding [44].

Contraindications for treatment with tacrolimus include hypersensitivity to tacrolimus, other macrolides, or any of the excipients. Low-medium dose tacrolimus (trough target 4-8 ng/mL)

is recommended for patients who are also taking steroids and are not at high risk of developing post-transplant diabetes mellitus [44].

Evidence on bioequivalence of generic and brand-name tacrolimus is limited and is not consistenst across various study designs.

Data from an observational studiy involving kidney transplant patients who were switched from IR tacrolimus to a generic tacrolimus, suggested switching from brand name to generic durg was feasible and appeared to be safe, but required careful monitoring of patients' trough concentrations of tacrolimus and plasma creatinine levels and overall status [45, 46]. The conversion was found to bring savings, despite costs for extra monitoring [46]. Consistent results were found in another non-RCT with liver-transplantation patients who switched to generic tacrolimus and were followed for 6 months, finding that the use of the generics is effective and seemed to be safe and cost-efficient in stable liver transplant patients [47].

Findings of a systematic review mostly based on observational data and studies with some concerns regarding the risk of bias concluded that there was no significant difference in terms of biopsy-proven acute rejection rates (BPAR) and even found some evidence suggesting lower BPAR risk following generic tacrolimus [48].

However, unlike evidence from observational studies, an RCT involving stable elderly kidney transplant patients, found that generic and original IR tacrolimus were not bioequivalent. Patients on generic tacrolimus experienced significantly higher levels of systemic drug exposure, which may increase the likelihood of nephrotoxicity and other adverse effects, along with other negative effects on long-term patient [49].

8. Information supporting the public health relevance

It is important to provide optimal maintenance immunosuppression so that the transplants and the person can survive for the longest time possible. This is particularly important given the shortage of donor organs [2]. According to the 2019 Eurotransplant statistics, 668 hearts have been transplanted, 1375 lungs, 1571 livers, 176 pancreases, and 3191 kidney transplants were carried out, with tens of thousands on an active waiting list [44].

Transplantation is the optimal therapy for end-stage renal failure as it improves the patient's duration and quality of life, encourages occupational rehabilitation and is more cost-effective

compared with the alternative of dialysis [2, 50]. In 1992, the cost of transplantation was calculated to be £11,600 for the transplant procedure, with each subsequent year of a successful transplant costing £4000 per annum [51]. In contrast, the annual cost for dialysis was calculated to be £21,000 in the National Institute for Health and Clinical Excellence (NICE) appraisal of home versus hospital haemodialysis (£21,000 and £22,000 for haemodialysis in a satellite unit and hospital, respectively) [52].

The prevalence of a liver disease is increasing. The British Liver Trust has reported that since 1970, deaths due to liver disease have increased by 400% [53]. The UK's Office for National Statistics reported that in 2018 in England, cirrhosis and other liver diseases were among the top 5 leading causes of death for persons aged 20 to 34 years and were the leading cause of death for persons aged 35 to 49 years accounting for more than 10% of deaths in that particular age group. Deaths from cirrhosis and other liver diseases were also in the top 5 leading causes for people ages between 50 and 64 years [54]. In 2018, there were 42,838 deaths recorded in the USA due to cirrhosis and chronic liver disease [55]. Chronic liver failure is the most common indication for liver transplantation [56]. Other important indications are acute liver failure and hepatocellular carcinoma [56]. The median survival after liver transplantation is more than 10 years [57, 58], and there may also be an improvement in the quality of life of people with chronic liver disease after liver transplantation [59].

Since the early 1980s, lung transplantation has shown increasing success to become the treatment for many people with end-stage lung diseases. Worldwide, more than 30,000 lung transplantations have been reported to the International Society for Heart and Lung Transplantation [60]. Currently, more than 2700 lung transplantations are reported annually worldwide, with one-year survival of over 80%, and five-year survival of 60% [60].

However, achieving long-term survival after lung transplantation remains challenging, mainly due to the occurrence of bronchiolitis obliterans syndrome. Bronchiolitis obliterans syndrome and late graft failure are responsible for more than 40% of deaths beyond the first year of transplantation [60]. Maintenance immunosuppressive therapy in lung transplantation often involves three types of drugs directed against the T-cell activation and proliferation: antiproliferative agents (mycophenolate mofetil or azathioprine), steroids (prednisolone), and CNIs [61]. The International Society for Heart and Lung Transplantation has reported that at both, one and five years after lung transplantation, tacrolimus is currently the most frequently used CNI [60]. The therapeutic success of heart transplantation has been largely attributable to the development of effective and balanced immunosuppressive treatment regimens [62, 63]. In

particular, CNIs were considered essential in reducing acute rejection and improving early survival [63].

9. Review of benefits: summary of evidence of comparative effectiveness

Identification of clinical evidence

The identification of clinical evidence on efficacy and safety of tacrolimus as immunosuppressive therapy in transplant recipients, both in adults and children, was searched through the following publication types: systematic reviews (SR), randomized controlled trials (RCT), clinical practice guidelines (CPG) and health technology assessment reports (HTA). Only full study reports were included, with the exclusion of preliminary results, interim analysis results and results reported in conference abstracts only. Pooled analyses of multiple RCTs that are not systematic reviews were also excluded as well as study protocols.

Types of participants

To be considered eligible for this application, studies had to include individuals, both adults and children, following solid organ transplantation. Studies where topical tacrolimus was used following keratoplasty were excluded.

Intervention

As for the intervention, studies had to include tacrolimus administered alone or in combination, in any dose. This application is focused on the therapeutic value of tacrolimus following transplantation. Thus, not all combinations were eligible, as tacrolimus is often used in various combinations as background immunosuppression, and this application focused only on the most commonly used combinations, i.e. tacrolimus, corticosteroids, mycophenolate mofetil, azathioprine, or sirolimus.

Reports were excluded if they:

- solely evaluated strategies for corticoid withdrawal or corticoid tapering regimens,
- investigated switch between tacrolimus and other immunosuppressants,

- included different antibody induction regimens with tacrolimus being used as background immunosuppression,
- included any calcineurin inhibitor in a study arm (and not only tacrolimus),
- compared different formulations of tacrolimus,
- compared different dosing regimens of tacrolimus.

Comparator

Any type of comparator was eligible for inclusion in this application.

Outcomes

Primary outcomes

1. Episodes of rejection (hyperacute rejection, acute rejection, chronic rejection)
2. Mortality
3. Quality of life (QoL) - all instruments, of any validity

Secondary outcomes

1. Opportunistic infections (including cytomegalovirus (CMV) and non-CMV infections)
2. Adverse events (e.g. nephrotoxicity, cardiotoxicity, post-transplant development of diabetes mellitus)
3. Individual preference
4. Hospitalization
5. Cost-effectiveness

Sources of information

Relevant literature was searched in the appropriate sources depending on the specific types of literature. Records retrieved via searching were exported to EndNote software and duplicates were removed.

Search methods

Search for systematic reviews

To be included, systematic reviews (SRs) had to comply with the PRISMA 2009 criteria [4], or at least:

• clearly state its objectives with pre-defined eligibility criteria for studies;

• describe an explicit, reproducible methodology,

• describe the sources (electronic databases or other sources) where the eligible studies have been systematically searched, including the date last searched

• assess the validity of the findings of the included studies (risk of bias assessment)

• present a synthesis of the characteristics and findings of the included studies.

• present qualitative or quantitative synthesis of the results.

In assessing the comparative effectiveness of tacrolimus vs. any other comparator, we first looked at the availability of direct, head-to-head comparisons. If direct evidence was lacking we searched for evidence from indirect comparisons, as described in the section Intervention. Systematic reviews were searched by consulting the following databases from January 1, 2000, to December 31, 2019:

- Cochrane Database of Systematic Reviews (CDSR)

- Cochrane Library: Health Technology Assessment

- Database of Abstracts of Reviews of Effects (DARE)

- BMJ Clinical Evidence

- HTA.UK - www.hta.ac.uk

- AHRQ - www.ahrq.gov/

- Canadian Agency for Drugs and Technologies in Health (CADTH)

- National Institute for Health and Clinical Excellence (NICE)

- Haute Autorité de Santé - http://www.has-sante.fr/portail/index.jsp

The strategy adopted was specific to each source. In synthesis, if a "search" function was available the database was checked with the term "tacrolimus"; if a "search" engine was not available the documents were searched through the "browse" function.

- MEDLINE;

Search for RCTs

RCTs were searched from January 1, 2000 to December 31, 2019 and appraised if they had not been included in the selected SRs. To be included, RCTs had to be randomized, double-blind, controlled with any type of comparator, using tacrolimus (as specified in the section Intervention) for at least one of the outcomes listed above.

We searched the following sources:

- Cochrane Central Register of Controlled Trials (CENTRAL)

- MEDLINE;

Search for guidelines:

To be included, guidelines had to present a series of recommendations produced through a systematic search of the literature by a multidisciplinary panel and adopting a grading system of the recommendations. Guidelines containing recommendations on the use of tacrolimus for immunosuppression transplant recipients were searched by consulting the following sources (November 2019):

- European Association for the Study of the Liver
- European Society for Organ Transplantation
- World Health organization (WHO)
- The international society for heart and lung transplantation
- National Institute for Health and Clinical Excellence (NICE)
- Scottish Intercollegiate Guidelines Network (SIGN)
- TRIP Database
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- National Institute for Health and Clinical Excellence (NICE)

Guidelines were screened if they were produced or updated in the last 10 years. The strategy adopted was specific to each source. In synthesis, if a “search” function was available the database was checked with the term “tacrolimus”; if a “search” engine was not available the documents were searched through the “browse” function. Only guidelines originally developed by the authors were considered; guidelines adapted from other existing guidelines were not considered for inclusion in this document.

Search for HTA reports

The Health Technology Assessment (HTA) reports were searched for through the HTA database. The database however is not being updated from 2016, but is nevertheless considered for this search because it covers reports from 2015. and the begging of 2016.

The following strategy was used for searching HTA reports:

Database: EBM Reviews - Health Technology Assessment <4th Quarter 2016>
Search Strategy:
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1 exp Transplantation/ (320)
2 Transplant Recipients/ (9)
3 exp Transplants/ (6)
4 (transplant$ or graft$).tw. (564)
5 or/1-4 (564)
6 exp Immunosuppression/ (19)
7 immunosuppress$.tw. (99)
8 ((prevent$ or diminution or suppress$ or reduction or decline or decrease) adj3 immune response).tw. (2)
9 or/6-8 (110)
10 Graft Rejection/ (15)
11 ((graft$ or transplant$) adj3 reject$).tw. (28)
12 10 or 11 (28)
13 5 and 9 (43)
14 12 or 13 (58)
15 Tacrolimus/ (9)
16 (tacrolimus or calcineurin inhibitor$).tw. (19)
17 Prograf.tw. (0)
18 Advagraf.tw. (0)
19 Astagraf XL.tw. (0)
20 (LCP-Tacro or LCPT).tw. (0)
21 (Envarsus or Envarsus XR).tw. (0)
22 Tacni.tw. (0)
23 Tacrocel.tw. (0)
24 Direnil.tw. (0)

25 Modigraf.tw. (0)
26 Tacforius.tw. (0)
27 Fujimycin.tw. (0)
28 Protopic.tw. (0)
29 FK-506.tw. (1)
30 FK506.tw. (0)
31 or/15-30 (19)
32 14 and 31 (12)
33 limit 32 to yr="2000 -Current" (12)

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The search strategy developed for MEDLINE was appropriately revised for each database to take account of differences in controlled vocabulary and syntax rules. The strategy adopted was specific to each source. In synthesis, if a "search" function was available the database was checked with the term "tacrolimus"; if a "search" engine was not available the documents were searched through the "browse" function. We used a combination of controlled vocabulary and free text terms for the subject search. The detailed search strategy used for every database is provided in Annex 2.

Overall, the search yielded 12169 records, consisting of titles with or without abstracts. Records retrieved via searching were exported to EndNote software and duplicates were removed. Two authors independently screened the titles and abstracts of study reports for eligibility. In cases when the relevance of a report was unclear, the full text was assessed.

All disagreements were resolved via discussion.

Details on the number of systematic reviews, RCTs, guidelines and HTA reports obtained in full-text format and screened, with reasons for exclusion are provided in Annex 3.

FINDINGS FROM RELEVANT SOURCES

Recommendations from guidelines

Summary

Tacrolimus is recommended for induction and maintenance of immunosuppression by multiple major guidelines, including the:

- 2017 guidelines of the National Institute for Health and Care Excellence (NICE) for a **kidney** transplant in **adults** [64], as well as in **children and young adults** [65],
- 2020 Clinical Practice Guidelines - Standardisation of immunosuppressive and anti-infective drug regimens in UK **Paediatric Renal** transplantation: The Harmonisation Programme [66]
- European Association of Urology (EAU) Guidelines on **Renal** Transplantation updated in 2018 [67]
- 2010 KDIGO clinical practice guideline for the care of **kidney** transplant recipients, by the International Society of Nephrology [68]
- 2017 Renal association clinical practice guideline in post-operative care in the kidney transplant recipient [69]
- 2020 guidelines of the Canadian Cardiovascular Society/Canadian Cardiac Transplant Network for **heart** transplantation [70]
- 2015 Antibody-Mediated Rejection in **Cardiac** Transplantation: Emerging Knowledge in Diagnosis and Management - A Scientific Statement From the American Heart Association [71]
- 2012 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, Monitoring of Nonsteroidal Immunosuppressive Drugs in Patients With Lung Disease and **Lung Transplant** Recipients [72]
- 2020 Adult **liver** transplantation: UK clinical guideline - part 2: surgery and post-operation [73]
- 2016 EASL Clinical Practice Guidelines: **Liver** transplantation [74]
- Long-Term Management of the Successful Adult **Liver** Transplant: 2012 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation.

More detailed recommendations from the guidelines

2017 NICE guidance for kindey transplant in adults

Based on the **NICE** Guidance "Immunosuppressive therapy for kidney transplant in adults" published on 11 October 2017, **immediate-release tacrolimus**, when used as part of an immunosuppressive regimen, is **recommended as an initial option to prevent organ**

rejection in adults having a kidney transplant [64]. Furthermore, analysis of **maintenance** therapies indicates that the incidence of acute rejection with CNIs (tacrolimus and ciclosporin) is significantly lower compared to belatacept, everolimus and sirolimus, where **tacrolimus** was showed to reduce the incidence of acute rejection compared with ciclosporin [64].

Specific recommendations of the NICE Guidance for adults include:

- To start with the least expensive product
- Prolonged-release tacrolimus does not have an advantage over immediate-release tacrolimus in clinical efficacy and cost-effectiveness studies.

2017 NICE guidance for a kidney transplant in children and young people

Based on the **NICE** Guidance "Immunosuppressive therapy for kidney transplant in children and young people" published on 11 October 2017, regarding initial immunosuppressive therapy, including **induction and maintenance** therapy (that is, to be started around the time of kidney transplant), **immediate-release tacrolimus was a cost-effective, cheaper and clinically effective option for preventing organ rejection in children and young people having a kidney transplant and is recommended as an initial option to prevent organ rejection in children and young people** [65].

Specific recommendations of the NICE Guidance for children and young people include:

- the initial treatment may be started with an alternative dosage form, for example, capsules may be replaced with tacrolimus granules for oral suspension,
- prolonged-release tacrolimus administered orally as one capsule a day was not considered to be cost-effective, based on the available evidence,
- rabbit anti-human thymocyte, immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended as a therapeutic approach for preventing organ rejection in children and young people having an organ transplant
- mycophenolate mofetil used alongside tacrolimus is a **cost-effective use of resources** for preventing organ rejection in children and young people having a kidney transplant. Basiliximab and rabbit anti-human thymocyte immunoglobulin (r-ATG) are recommended as induction therapies. Immediate-release tacrolimus, prolonged-release tacrolimus, mycophenolate mofetil are maintenance therapies.

- mycophenolate **sodium**, everolimus, sirolimus and belatacept were **not** cost-effective options for preventing organ rejection in children and young people having a kidney transplant.

2020 Clinical Practice Guidelines - Standardisation of immunosuppressive and anti-infective drug regimens in UK Paediatric Renal transplantation: The Harmonisation Programme

These guidelines [66] specify that in children under 18 years undergoing **kidney** transplantation, **tacrolimus** should be considered. According to the consensus-based recommendation with 85% agreement, initial dosing of **tacrolimus** should be prescribed at 0.15 mg/kg twice daily with a maximum initial dose of 5 mg twice daily. For children and young people receiving either 'steroid maintenance' therapy comprising **tacrolimus**, azathioprine and prednisolone (PAT) with IL-2 receptor antagonist induction with basiliximab (PAT-B), or TWIST regimens, with early steroid withdrawal regimens comprising IL-2 receptor antagonist induction, **tacrolimus**, mycophenolate mofetil (MMF), and a short course of prednisolone (the 'TWIST' regimen), it was recommended by the guideline that **tacrolimus** should be started on the day of transplant (day 0) for living and deceased donor transplants.

The committee noted the existing variation in practice across the UK, with some centres commencing tacrolimus up to 48 hours before living donor transplant. In the absence of evidence of improved outcomes in children and young people receiving tacrolimus before the day of the transplant, the committee agreed to recommend that time of commencement of tacrolimus for children and young people receiving living donor transplants should be the same as that for children and young people receiving DD transplants.

European Association of Urology (EAU) Guidelines on Renal Transplantation updated in 2018

The European Association of Urology (EAU) Guidelines on Renal Transplantation updated in 2018 [67] strongly recommend initial rejection prophylaxis to be performed with combination therapy comprising a CNI, **preferably tacrolimus**, mycophenolate, steroids, and an induction agent (either basiliximab or anti-thymocyte globulin).

KDIGO clinical practice guideline for the care of kidney transplant recipients

KDIGO clinical practice guideline for the care of kidney transplant recipients, published in 2010 by the International Society of Nephrology [68] suggest **tacrolimus to be the first-line CNI used**, and to be started before or at the time of transplantation, rather than delayed until the onset of graft function.

2017 Renal association clinical practice guideline in post-operative care in the kidney transplant recipient

The Post-Operative Care in the Kidney Transplant Recipient - Renal Association; Guideline 3.4 – KTR: Maintenance immunosuppression; Renal Association Clinical Practice Guideline – Post-Operative Care, published in 2017 [69], suggests that **low-medium dose tacrolimus (trough target 4-8 ng/mL) is recommended** as the CNI of choice in patients also taking steroids who are low and medium immunological risk and are not at high risk of developing post-transplant diabetes mellitus (2C). For maintenance immunosuppression, the guidelines suggest that slow-release tacrolimus may be used as an option as second-line agents for patients who suffer intolerable side effects related to peak dose toxicity (2C). When planning immunosuppressive treatment, it is essential to consider the risks to the recipient. The risks of immunosuppressive therapy are largely predictable and should be balanced against the risk of harm to the individual patient from under-immunosuppression and resulting rejection, and the benefits of a well-functioning transplant.

2020 Canadian position statement on heart transplantation

In 2020, the Cardiovascular Society/Canadian Cardiac Transplant Network Position Statement on Heart Transplantation: Patient Eligibility, Selection, and Post-Transplantation Care [70] was published, indicating that they **recommend a CNI** and mycophenolic acid-based immunosuppression regimen after HTx for most patients (Strong Recommendation, Moderate-Quality Evidence). Specifically, the Position Statement **recommended tacrolimus over cyclosporin as the preferred CNI** (Strong Recommendation, Low-Quality Evidence), as tacrolimus provides superior protection against rejection and has a more favorable side effect profile than cyclosporin.

Antibody-Mediated Rejection in Cardiac Transplantation: Emerging Knowledge in Diagnosis and Management - A Scientific Statement From the American Heart Association

The 2015 publication "Antibody-Mediated Rejection in Cardiac Transplantation: Emerging Knowledge in Diagnosis and Management - A Scientific Statement From the American Heart Association " [71] was endorsed by the International Society for Heart and Lung Transplantation. The document recommends optimizing **maintenance** therapy by switching from cyclosporine-based immunosuppression to **tacrolimus** or by increasing the dose of MMF may be considered.

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, Monitoring of Nonsteroidal Immunosuppressive Drugs in Patients with Lung Disease and Lung Transplant Recipients

2012 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [72] regarding **lung transplant** recipients make recommendations for the monitoring of CNIs in patients with lung disease and lung transplant recipients. The Guidelines report that **tacrolimus is approved by the FDA for the prophylaxis of organ rejection** in patients receiving allogeneic liver, kidney, or heart transplants and for treatment of severe atopic dermatitis. The Guidelines highlight that in addition to FDA-approved indications, tacrolimus has been used for **antirejection prophylaxis in pancreatic, intestinal, and lung transplantation**, as well as to treat graft-vs-host disease, rheumatologic disorders (lupus erythematosus, rheumatoid arthritis, scleroderma, polymyositis), inflammatory bowel disease, various skin conditions other than atopic dermatitis, and uveitis. The Guideline presents evidence from randomized clinical trials regarding the use of tacrolimus in lung transplant patients, and guidance for monitoring drug concentrations in patients undergoing CNI therapy.

Adult liver transplantation: UK clinical guideline - part 2: surgery and post-operation

In 2020 guideline titled Adult **liver** transplantation: UK clinical guideline - part 2: surgery and post-operation [73], the recommendation is that maximum immunosuppression is required early post-transplant, when rejection risk is greatest. Frequently used agents are shown in online supplementary appendix 2. The most common regimens include a CNI (**usually tacrolimus**) with or without corticosteroids.

EASL Clinical Practice Guidelines: Liver transplantation

The 2016 publication reporting clinical practice guidelines of the European Association for the Study of the Liver (EASL) regarding Liver transplantation [74] report that CNIs are the principal choice for immunosuppression after liver transplantation both in Europe and in the US, whereas **tacrolimus is the drug of choice in almost 90% of liver transplanted patients**, resulting in a significant increase in its use since 1998.

Long-Term Management of the Successful Adult Liver Transplant: 2012 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation

The 2012 American guideline titled Long-Term Management of the Successful Adult Liver Transplant: 2012 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation [75] indicates that CNIs are immunosuppressors of choice, both **tacrolimus** and cyclosporine. The guideline also recommends tacrolimus in pregnancy, indicating that [quote]: "*the ideal immunosuppression for pregnancy is tacrolimus monotherapy, which should be maintained at therapeutic levels throughout pregnancy; cyclosporine, azathioprine and prednisone may also be used if they are necessary (grade 1, level B)*."

Health technology assessment (HTA)

Immunosuppressive therapy for kidney transplantation in adults: a systematic review and economic model. Health Technol Assess 2016;20(62). [76]

Jones-Hughes et al. included 89 RCTs in their clinical effectiveness review. They developed a statistical model to compare the cost-effectiveness of 16 different combinations of medications, indicating that only **one combination (basiliximab followed by immediate-release tacrolimus and mycophenolate mofetil) would be cost-effective**.

For graft loss outcomes reported by maintenance studies, tacrolimus is associated with lower odds of reduced graft function (GRF) for the following regimens:

Tacrolimus (TAC) + mycophenolate mofetil (MMF) versus cyclosporin (CSA) + MMF (at 3 years, eGFR WMD 4.60 ml/minute/1.73 m 2, 95% CI 1.35 ml/ minute/1.73 m 2 to 7.85 ml/minute/1.73 m 2) TAC + MMF versus TAC-PR + MMF (at 0.5 years, eGFR WMD 1.90 ml/minute/1.73 m 2 , 95% CI

1.70 to 2.10 ml/minute/1.73 m 2) TAC + SRL versus CSA + SRL (at 0.5 years, eGFR MD 6.35 ml/minute/1.73 m 2, $p < 0.0001$; 1 year MD 5.25 ml/minute/1.73 m 2 , $p = 0.0004$).

According to this study, **prolonged**-release tacrolimus is **not** predicted to be cost-effective [76].

All Wales Medicines Strategy Group Final Appraisal Recommendation – Advice no. 0811, Tacrolimus (Advagraf®) June 2011 v1.3

All Wales Medicines Strategy Group issued the advice concerning the use of prolonged-release tacrolimus, Advagraf for the prophylaxis of transplant rejection in adult kidney or liver allograft recipients and the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients [77]. They recommend as follows:

- Tacrolimus (Advagraf ®) **recommended** as an option for restricted use for the **prophylaxis of transplant rejection in adult kidney or liver** allograft recipients;
- Tacrolimus (Advagraf ®) is **not** recommended for use for the treatment of allograft rejection **resistant to treatment** with other immunosuppressive medicinal products in adult patients;
- Tacrolimus (Advagraf ®) should be prescribed by brand name to reduce the risk of medication errors;

- AWMSG recommended that tacrolimus (Advagraf ®) may be suitable for shared care for the above indication [77].

The front page of the HTA report indicates that the advice was **superseded** by the NICE guidance TA481 (Immunosuppressive therapy for kidney transplant in adults, Technology appraisal guidance [TA481]), which is **detailed in the section on Guidelines** [64].

All Wales Medicines Strategy Group Final Appraisal Recommendation – Advice no. 2315, Tacrolimus (Envarsus®) July 2015

Recommendation of AWMSG Tacrolimus (Envarsus®) is the following: **recommended** as an option for use within NHS Wales for the prophylaxis of transplant rejection in adult kidney or liver allograft recipients and the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients [78].

The web page of the HTA report indicates that the advice was **partially superseded** by the NICE guidance TA481 (Immunosuppressive therapy for kidney transplant in adults, Technology appraisal guidance [TA481]), which is **detailed in the section on Guidelines** [64].

Immunosuppressive therapy for kidney transplantation in children and adolescents: systematic review and economic evaluation

The report from 2016 [79], published in the Health Technology Assessment, NIHR health technology assessment programme monograph, aimed to systematically review and update the evidence for the clinical effectiveness and cost-effectiveness of basiliximab and rabbit antihuman thymocyte immunoglobulin as induction therapy and **immediate-release tacrolimus, prolonged-release tacrolimus**; belatacept (BEL), mycophenolate mofetil, mycophenolate sodium, sirolimus and everolimus as maintenance therapy in children and adolescents undergoing renal transplantation. The report concluded that "TAC is likely to be cost-effective (vs. CSA, in combination with AZA) at £20,000-30,000 per QALY." [79].

Calcineurin Inhibitors for Renal Transplant: Agency for Healthcare Research and Quality (AHRQ Comparative Effectiveness Reviews)

The AHRQ Comparative Effectiveness Review, published in 2016 [80], indicated that **tacrolimus is widely used** in the current practice. Among the conclusions, the report states that there is high-strength evidence suggesting that immunosuppression with low-dose CsA or **tacrolimus**, in combination with mycophenolic acid formulations or mTOR inhibitors, results in a lower risk of acute rejection and graft loss and improved renal function.

Evidence from systematic reviews

Multiple systematic reviews, published from 2005 onwards, reported that tacrolimus is superior or equal to comparators for the most important outcomes such as graft loss and acute rejection, including systematic reviews that have included:

- kidney transplant patients - adults [81-84],
- kidney transplant patients - children [85],
- kidney transplant patients of any age [86, 87],
- liver transplant patients – adults [11, 88, 89],
- liver transplant patients – adults and children [90, 91],
- lung transplant patients – adults [92, 93],
- heart transplant patients – adults and children [94, 95].

SRs that did not focus on efficacy, concluded that:

- compared to cyclosporine, tacrolimus treatment was associated with a lower incidence of hyperlipidemia and hypertension, but a higher rate of diabetes [96],
- tacrolimus was associated with an increased risk for diabetes and lower risk of dyslipidemia, compared to cyclosporine [97],
- reported incidence of new-onset diabetes mellitus (NODM) after solid organ transplantation was significantly higher among patients receiving tacrolimus than cyclosporine [98].

More detailed description of included systematic reviews

Kidney transplant

Kidney transplant; adults, tacrolimus versus cyclosporine

Comparison of Tacrolimus and Cyclosporine for Immunosuppression after Renal Transplantation: An Updated Systematic Review and MetaAnalysis [81]

Azarfar et al. published their SR in 2018. The SR concluded that **tacrolimus is significantly superior to cyclosporine** regarding graft loss, acute rejection, and hypercholesterolemia, but cyclosporine seems to be significantly superior to tacrolimus regarding diabetes. However, the authors suggested that further large randomized trials are needed [81].

The SR included 21 RCTs.

Sixteen trials reported on mortality, and between TAC and CyA and found no significant difference (RR 1.072; 95% CI 0.792–1.452, P = 0.651).

Eighteen trials reported on graft loss. There was a significant difference, and higher graft loss was seen in the CyA group compared with TAC (RR 0.089; 95% CI 0.057–0.122, P <0.001).

Eighteen trials reported on acute rejection. There was a lower frequency of acute rejection with TAC therapy (RR 0.638; 95% CI 0.5710.713, P <0.001).

Eighteen trials reported on diabetes. An insignificant trend toward more diabetes was seen in the TAC group compared with the CyA group (RR 1.891; 95% CI 1.522–2.350, P <0.001).

The frequency and type of infections were similar in the two treatment groups throughout the study (RR 1.053; 95% CI 0.924–1.94, P = 0.11).

The incidence of hypertension was reported in 10 studies and there was no significant difference was found between the TAC and CyA groups (RR 0.958; 95% CI, 0.849–1.081, P = 0.489).

Regarding hypercholesterolemia, pooled results failed to show statistically significant differences between the TAC and CyA groups in the incidence of hypercholesterolemia (RR 0.634; 95% CI 0.539–0.746, P <0.001) [81].

Kidney transplant; adults; Sirolimus + Tacrolimus vs Mycophenolate Mofetil + Tacrolimus

Comparison of Sirolimus Combined With Tacrolimus and Mycophenolate Mofetil Combined With Tacrolimus in Kidney Transplantation Recipients: A Meta-Analysis [82]

Gao et al. published this SR in 2018 to compare sirolimus (SRL) combined with tacrolimus (TAC) and mycophenolate mofetil (MMF) combined with TAC in kidney transplantation recipients. They concluded that SRL combined with TAC and MMF combined with TAC were equally safe and effective for the kidney transplantation recipients. However, the MMF group exhibited a marginally significant advantage of the lower incidence of hyperlipidemia and lymphocele [82].

The SR included 10 studies with a total of 2357 patients (n = 1256 receiving SRL vs n = 1101 receiving MMF).

SRL combined with TAC might lead to higher rates of diabetes, hyperlipidemia, and lymphocele compared to MMF combined with TAC, while no significant differences were found in terms of the rates of delayed graft function, acute rejection, graft survival, infectious complications, anaemia, or seroma (particularly delayed graft function, AR rate, and graft survival) [82].

Kidney transplant; adults; belatacept vs tacrolimus; tacrolimus vs. ciclosporin

Indirect treatment comparison of belatacept versus tacrolimus from a systematic review of immunosuppressive therapies for kidney transplant patients [83]

Muduma et al. published an SR in 2016 that compared the clinical effectiveness of tacrolimus and belatacept for renal transplant recipients; a meta-analysis was done of tacrolimus versus ciclosporin and belatacept versus ciclosporin and indirect analysis of belatacept versus tacrolimus. The SR authors concluded that **tacrolimus is significantly superior to belatacept** in terms of acute rejection outcomes but **comparable** for graft and patient survival. The authors recommended further clinical trials that will compare tacrolimus against belatacept directly [83].

The SR included 21 studies.

The acute rejection rate was significantly lower with **tacrolimus** (Prograf* and Advagraf*) compared with belatacept (0.22 [0.13, 0.39] to 0.44 [0.20, 0.99]) [83].

Kidney transplant; adults; tacrolimus vs cyclosporine (MetS and CV risk factors)

Effects of tacrolimus and cyclosporine treatment on metabolic syndrome and cardiovascular risk factors after renal transplantation: a meta-analysis [96]

Wenrui et al. published a MA in 2014, in which they compared the effects of tacrolimus and cyclosporine on metabolic syndrome (MetS) and cardiovascular risk factors after renal transplantation. The authors concluded that compared to tacrolimus, **cyclosporine treatment was associated with a higher incidence of hyperlipidemia and hypertension, but a lower rate of diabetes**. They recommended that future large-scale studies are needed to further confirm these findings [96].

The SR included 5 RCTs with a total of 923 patients. The SR excluded studies on children.

MetS incidence: no significant difference between the tacrolimus group and the cyclosporine group; RR: 1.06, 95% *CI*: 0.73–1.55, *P*=0.76.

Hyperlipidemia: Cyclosporine treatment was associated with a higher incidence of hyperlipidemia (*RR*: 0.50, 95% *CI*: 0.39–0.64, *P* <0.01).

Hypertension: Cyclosporine treatment was associated with a higher incidence of hypertension, but there was no significant difference compared to tacrolimus (*RR*: 0.91, 95% *CI*: 0.83–1.00, *P*=0.06).

Diabetes after renal transplantation: tacrolimus treatment was associated with a higher incidence of diabetes after renal transplantation (*RR*: 1.79, 95% *CI*: 0.98–3.27, q *P*=0.06) compared to cyclosporine treatment [96].

Kidney transplant; adult; belatacept vs cyclosporine vs tacrolimus

A network meta-analysis of the efficacy of belatacept, cyclosporine and tacrolimus for immunosuppression therapy in adult renal transplant recipients [84]

Goring et al. published their network meta-analysis in 2014. to estimate the efficacy of belatacept relative to tacrolimus and cyclosporine among adults receiving a single kidney transplant. They concluded that **the most favorable effects were evident in the newer therapies, belatacept and tacrolimus** [84].

SR included 28 RCTs comparing tacrolimus with cyclosporine, and three comparing belatacept with cyclosporine.

Belatacept was associated with significant improvement in GFR versus cyclosporine. Compared with tacrolimus, this difference was clinically meaningful yet statistically non-significant. The probability of being the best treatment was highest for belatacept for graft survival (68%), patient survival (97%) and renal function (89%), and highest for tacrolimus for acute rejection (99%). Variability in the donor, recipient, and trial characteristics was present in the included RCTs; however, minimal statistical heterogeneity was detected in the analysis of acute rejection, graft or patient survival, and none of the characteristics were found to be significantly associated with the relative effect. Although the direction of the effect of immunosuppressants on GFR was consistent across RCTs. GFR among tacrolimus-treated subjects was also found to be significantly higher than among those treated with cyclosporine (6.03 mL/min/1.73 m2; 95% CrI: 1.60 to 11.00).

Belatacept had significantly increased odds of acute rejection over tacrolimus (OR 2.50; 95% CrI 1.21 to 4.81). Tacrolimus was the immunosuppressive agent with the highest probability of being best for avoiding episodes of acute rejection [84].

Kidney transplant; patients over age 16; immunosuppressive drugs for maintenance

Safety of Immunosuppressive Drugs Used as Maintenance Therapy in Kidney Transplantation: A Systematic Review and Meta-Analysis [97].

Cardoso Almeida et al. published this SR in 2013; it included RCTs and cohort studies comparing the **safety** of treatment regimens that included the immunosuppressants azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil or enteric mycophenolate, sirolimus, or everolimus in any dose and with at least 6-month follow-up. The authors concluded that the **choice of treatment** must be **made by the clinical staff based on specific patient characteristics** [97].

The SR included 48 articles (11,432 participants) reporting 42 studies (38 RCTs and four cohorts). The eligibility criteria specified that renal disease patients over age 16 were included.

Tacrolimus was associated with an increased risk for diabetes and a lower risk of dyslipidemia, compared to cyclosporine. Mycophenolate mofetil (MMF) was associated with an increased risk for total infections, abdominal pain, diarrhea and vomiting, compared with azathioprine. Sirolimus was associated with a higher risk of anemia, diabetes, dyslipidemia, lymphoceles and withdrawal compared to tacrolimus or cyclosporine, with no significant differences for infections, UTI, leukopenia, hypertension, or malignancies. Cyclosporine was associated with an increased risk of CMV infection. The combination of CNI with antimetabolites was associated with more adverse events than CNI alone. TOR-I was related to more adverse events than MMF [97].

Kidney transplant; children, tacrolimus versus cyclosporine

A Comparison Between Tacrolimus and Cyclosporine As Immunosuppression after Renal Transplantation in Children, A Meta-Analysis and Systematic Review [85]

Ravanshad et al. published a systematic review in 2020, aimed to compare the benefits and disadvantages of tacrolimus versus cyclosporine as the primary immunosuppression after **kidney** transplantation in **children**. The SR authors concluded that **tacrolimus seems insignificantly superior to cyclosporine respecting graft loss and acute rejection**. However, cyclosporine was shown to be insignificantly superior regarding the mortality rate. However, the SR authors recommended additional studies with a larger sample size are highly recommended [85].

Five studies were enrolled in the systematic review (all of them were clinical trials or retrospective studies).

For **mortality rate, no difference** was found between Tacrolimus and Cyclosporine (RR = 1.06, 95% CI: 0.59 - 1.90; P > .05).

For graft loss, no significant difference was found in graft loss between Tacrolimus and Cyclosporin (RR = 0.67, 95% CI: 0.40 -1.11)

Regarding acute rejection, an insignificant trend towards more acute rejection seen for Tacrolimus compared with Cyclosporine (RR = 0.79, 95% CI: 0.59 – 1.05, P > .05

This SR was of poor methodological quality; the method for quality assessment was not reported, there was no grading of the evidence, no reported prospective protocol publication/registration [85].

Kidney transplant; population age not reported, tacrolimus vs sirolimus

Sirolimus Versus Tacrolimus as Primary Immunosuppressant After Renal Transplantation: A Meta-Analysis and Economics Evaluation [86]

Liu et al. published in 2016 a meta-analysis of RCTs and cost evaluation model that showed **renal transplant recipients maintained on tacrolimus have better outcomes than patients maintained on sirolimus**, and that **tacrolimus may be more cost-effective** than sirolimus for the primary prevention of AR in renal transplant [86].

The SR included 8 RCTs with 1189 participants. The SR did not use any age limitations but did not report on the age (adults vs children) of participants in the included trials.

Regarding **mortality**, 7 trials reported on mortality, the sirolimus group had a 2.43% mortality (14/575), whereas the tacrolimus group had a 2.65% mortality (14/529). Pooled results did not show statistically significant differences between recipients treated with sirolimus and tacrolimus (RR 5 0.94; 95% CI, 0.46–1.91; P = 5 0.86).

Regarding **graft loss**, data from 8 trials including 1189 patients showed that there was no statistically significant difference between the 2 groups (RR 5 1.23; 95% CI, 0.76– 1.97; P = 5 0.40).

Incidences of **acute rejection** (AR) were reported in 8 studies. Significantly fewer tacrolimus-treated patients had AR (RR 5 2.08; 95% CI, 1.47–2.95; P < 0.0001).

Data concerning **patient withdrawal** were available in 4 trials including 1189 patients. Sirolimus-treated patients were significantly more likely than tacrolimus-treated patients to have withdrawn (RR 5 1.93; 95% CI, 1.32–2.83; P < 0.0007).

Data regarding the **incidence of infection** was reported in 4 studies (654 patients), a significant decrease in the risk of infection was observed with sirolimus (RR 5 0.43; 95% CI, 0.26–0.72; P < 0.001) [86].

Kidney transplant; adults and children; tacrolimus vs cyclosporin

Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients [87]

Webster et al. published a **Cochrane** review in 2005, which aimed to compare the effects of tacrolimus with cyclosporine as primary therapy for kidney transplant recipients. The authors concluded that **tacrolimus was superior to cyclosporin in improving graft survival and preventing acute rejection after kidney transplantation**, but increases post-transplant diabetes, neurological and gastrointestinal side effects [87].

The SR included 30 RCTs with 4102 patients, both adults and children.

At six months graft loss was significantly reduced in tacrolimus-treated recipients (RR 0.56, 95% CI 0.36 to 0.86), and this effect was persistent up to three years.

At one year, tacrolimus patients suffered less acute rejection (RR 0.69, 95% CI 0.60 to 0.79), and less steroid-resistant rejection (RR 0.49, 95% CI 0.37 to 0.64), but more insulin-requiring diabetes mellitus (RR 1.86, 1.11 to 3.09), tremor, headache, diarrhoea, dyspepsia and vomiting.

Cyclosporin-treated recipients experienced significantly more constipation and cosmetic side-effects. There was no difference in infection or malignancy.

Compared with cyclosporin, treating recipients of kidney transplants with tacrolimus resulted in a substantial improvement in graft survival, with a 44% reduction in graft loss (censored for death) within the first six months after transplantation; an effect revealed only by meta-analysis, and not evident when considering each study in isolation. Treating with tacrolimus led to 31% fewer patients experiencing acute rejection, and 51% fewer experiencing severe rejection episodes that required therapy more intensive than steroids, within the first year post-transplantation [87].

Liver transplant

Liver transplant; adults; maintenance immunosuppression

Maintenance immunosuppression for adults undergoing liver transplantation: a network meta-analysis [88]

Rodríguez-Perálvarez et al. published this **Cochrane** systematic review in 2017 [88]. The authors **found no reliable evidence that any of the other interventions are better than tacrolimus** in this review. Findings apply only to maintenance immunosuppression. This is in line with the previous Cochrane SR of Haddad et al. from 2006., which concluded that tacrolimus was better than cyclosporine A in terms of patient survival for liver transplanted patients [90].

The SR included 23 trials (3693 participants) in quantitative synthesis assessing benefits and harms of different maintenance immunosuppressive regimens in adults undergoing liver transplantation.

The mortality (maximal follow-up) and graft loss (maximal follow-up) were higher for tacrolimus plus sirolimus (HR 2.76, 95% CrI 1.30 to 6.69) compared with tacrolimus (HR 2.34, 95% CrI 1.28 to 4.61) in a single trial including 222 participants based on direct comparisons-low-certainty evidence; however, there was no evidence of difference based on network meta-analysis results (very low-certainty evidence).

It appears that adding sirolimus to the standard immunosuppressive regimen worsens the outcomes. Most trials did not report serious adverse events, despite this being an important outcome for patients and healthcare funders.

Based on very low-quality evidence from network meta-analysis and low-quality evidence from direct comparison, cyclosporine A causes more retransplantation compared with tacrolimus (HR 3.08, 95% CrI 1.13 to 9.90) [88].

Liver transplant; adults, tacrolimus versus cyclosporine

Systematic Review and MetaAnalysis of Tacrolimus versus Ciclosporin as Primary Immunosuppression After Liver Transplant [89]

Muduma et al. published this SR in 2016 and concluded that RCTs published since 2000 showed **tacrolimus to be superior to ciclosporin** in terms of patient mortality and hypertension, while ciclosporin was superior in terms of NODAT. No significant differences

were identified in terms of graft loss or AR. These findings provide further evidence supporting the use of tacrolimus as the cornerstone of immunosuppressive therapy in liver transplant recipients [89].

The SR included 11 RCTs.

Regarding survival (RR 1.26; P = 0.04; 95% CI 1.01, 1.58) and hypertension (RR 1.26; P = 0.005; 95% CI 1.07, 1.47), tacrolimus was significantly more effective than ciclosporin.. Conversely, patients on ciclosporin had a lower risk of developing new onset diabetes post transplantation (NODAT) than those on tacrolimus, with a risk ratio of 0.60 (P<0.0001; 95% CI 0.47, 0.77).

The finding that patient mortality was significantly reduced in patients using tacrolimus relative to ciclosporin was consistent with previous meta-analyses. For instance, in 2006, Haddad et al. [90] reported a RR of mortality of 0.85 (95% CI 0.73, 0.99) with tacrolimus relative to ciclosporin. Similarly, Haddad et al. [90] reported a significantly higher risk of NODAT with tacrolimus relative to ciclosporin with a risk ratio of 1.27, compared to the RR of 0.59 with ciclosporin relative to tacrolimus in the present study. However, the Haddad et al. [90] meta-analysis also reported an 18% reduction in the risk of acute rejection with tacrolimus versus ciclosporin, an endpoint around which we identified no significant difference.

Liver transplant; adults; immunosuppression monotherapy

Efficacy of immunosuppression monotherapy after liver transplantation: A meta-analysis [11]

Lan et al. published this SR and MA in 2014, in which they explored the efficacy of immunosuppression monotherapy after liver transplantation. They concluded that **tacrolimus and cyclosporine monotherapy may be as effective as immunosuppression combination therapy**. Mycophenolate mofetil monotherapy was not considerable. Tacrolimus monotherapy does not increase the recurrence of HCV [11].

The SR included 14 RCTs with 1814 patients (≥ 18 years old).

MA showed that the tacrolimus and cyclosporine monotherapy may be as effective as immunosuppression by steroid-based combination therapy for liver transplantation and is associated with fewer complications. Mycophenolate mofetil monotherapy is not recommended

post-transplantation because of a high rate of acute rejection events. Tacrolimus monotherapy did not increase HCV recurrence in HCV-infected liver transplant recipients.

TAC and CSA effectively reduce immunosuppression-related complications. However, mycophenolate mofetil monotherapy results failed to show an association between immunosuppression monotherapy and the graft survival rate, the patients' long-term survival rate [11].

Liver transplant; adults and children, tacrolimus versus cyclosporine

Cyclosporin versus tacrolimus for liver transplanted patients [90]

Haddad et al. published this **Cochrane** SR in 2006 and concluded that **tacrolimus was superior to cyclosporin** in improving survival (patient and graft) and preventing acute rejection after liver transplantation, but it increases the risk of post-transplant diabetes.

The SR included 16 RCTs (3813 participants). Most of the randomised trials restricted enrolment to adults, but one included children (U. S. Study 1994) and one was restricted to children (Kelly 2004).

The number of deaths was 254 in the tacrolimus group (1899 patients) and 302 in the cyclosporin group (1914 patients).

At one year, mortality (RR 0.85, 95% CI 0.73 to 0.99) and graft loss (RR 0.73, 95% CI 0.61 to 0.86) were significantly reduced in tacrolimus-treated recipients.

Tacrolimus reduced the number of recipients with acute rejection (RR 0.81, 95% CI 0.75 to 0.88), and steroid-resistant rejection (RR 0.54, 95% CI 0.47 to 0.74) in the first year. Differences were not seen with respect to lymphoproliferative disorder or de-novo dialysis rates, but more de-novo insulin-requiring diabetes mellitus (RR 1.38, 95% CI 1.01 to 1.86) occurred in the tacrolimus group. More patients were withdrawn from cyclosporin therapy than from tacrolimus (RR 0.57, 95% CI 0.49 to 0.66) [90].

Liver transplant; adults and children; tacrolimus vs cyclosporin

Cyclosporin versus Tacrolimus as Primary Immunosuppressant After Liver Transplantation: A Meta-Analysis [91]

McAlister et al. published an SR in 2006, intending to evaluate the benefits and harms of immunosuppression with cyclosporin versus tacrolimus for liver transplanted patients. The authors concluded that compared to cyclosporin, **tacrolimus significantly reduced the risks after liver transplantation of death, graft loss, acute rejection and steroid-resistant rejection**. Tacrolimus increased the risk of new-onset diabetes. More patients discontinued cyclosporin than tacrolimus. Tacrolimus's superiority to cyclosporin after liver transplantation has to be considered in the context of the excellent overall results using either drug [91].

The SR included 16 RCTs with 3813 participants. Most of the RCTs restricted enrolment to adults but one also included children and one was restricted to children.

Mortality and graft loss at 1 year were significantly reduced in tacrolimus treated recipients (Death: RR 0.85, 95% CI 0.73–0.99; graft loss: RR 0.73, 95% CI 0.61–0.86).

Acute rejection: tacrolimus reduced the number of recipients with acute rejection (RR 0.81, 95% CI 0.75–0.88) and steroid-resistant rejection (RR 0.54, 95% CI 0.47–0.74) in the first year.

Lymphoproliferative disorder or dialysis rates were not different, but more de novo diabetes (RR 1.38, 95% CI 1.01–1.86) occurred with tacrolimus.

More patients stopped cyclosporin than tacrolimus (RR 0.57, 95% CI 0.49–0.66) [91]

Lung transplant

Lung transplant; adults; tacrolimus vs cyclosporin

Tacrolimus versus cyclosporin as primary immunosuppression for lung transplant recipients [92]

Penninga et al. in 2013 published a **Cochrane** SR on tacrolimus vs cyclosporin as primary immunosuppression for lung transplant recipients. The SR concluded **tacrolimus may be superior to cyclosporin** regarding bronchiolitis obliterans syndrome, lymphocytic bronchitis, treatment withdrawal, and arterial hypertension, but may be inferior regarding the development of diabetes. No difference in mortality and acute rejection was observed between the group treated with tacrolimus and cyclosporin. There were few studies comparing tacrolimus and cyclosporin after lung transplantation, and the numbers of patients and events in the included

studies were limited. Furthermore, the included studies were deemed to be at high risk of bias. The authors urged that more RCTs are needed on this topic [92].

The SR included only 3 RCTs that enrolled a total of 413 **adult** patients that compared tacrolimus with microemulsion or oral solution cyclosporin.

Tacrolimus appeared to be significantly superior to cyclosporin regarding the incidence of bronchiolitis obliterans syndrome (RR 0.46, 95% CI 0.29 to 0.74), lymphocytic bronchitis score (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). Finding for arterial hypertension was not confirmed when analysed using a random-effects model (RR 0.54, 95% CI 0.17 to 1.73). Furthermore, the trial sequential analysis found that none of the meta-analyses reached the required information sizes and cumulative Z-curves did not cross-trial sequential monitoring boundaries.

Diabetes mellitus occurred more frequently among patients receiving tacrolimus compared with the cyclosporin group when the fixed-effect model was applied (RR 4.24, 95% CI 1.58 to 11.40), but no difference was found when the random-effects model was used for analysis (RR 4.43, 95% CI 0.75 to 26.05). The trial sequential analysis found that the required information threshold was not reached and the cumulative Z-curve did not cross the trial sequential monitoring boundary. No significant difference between treatment groups was observed regarding mortality (RR 1.06, 95% CI 0.75 to 1.49), incidence of acute rejection (RR 0.89, 95% CI 0.77 to 1.03), numbers of infections/100 patient-days (MD -0.15, 95% CI -0.30 to 0.00), cancer (RR 0.21, 95% CI 0.04 to 1.16), kidney dysfunction (RR 1.41, 95% CI 0.93 to 2.14), kidney failure (RR 1.57, 95% CI 0.28 to 8.94), neurotoxicity (RR 7.06, 95% CI 0.37 to 135.19), and hyperlipidaemia (RR 0.60, 95% CI 0.30 to 1.20). The trial sequential analysis showed the required information thresholds were not reached for any of these outcome measures [92].

Lung transplant; adults; tacrolimus vs cyclosporine

Tacrolimus Versus Cyclosporine for Adult Lung Transplant Recipients: A Meta-Analysis [93]

Fan et al. published an SR in 2009, which aimed to compare the benefits and harms of tacrolimus and cyclosporine as the primary immunosuppressant for lung transplant recipients.

The authors concluded that **using tacrolimus** as a primary immunosuppressant for lung transplant recipients **resulted in comparable survival and reduction in acute rejection episodes when compared with cyclosporine** [93].

The SR included three RCTs with 297 adult patients.

Three RCTs including 297 patients were assessed in this analysis.

Mortality: there was no difference in 1-year mortality between patients receiving tacrolimus or cyclosporine (odds ratio [OR], 0.94; 95% CI, 0.42–2.10; P = .88).

Acute rejection: **tacrolimus-treated patients experienced fewer incidences of acute rejection** (MD 0.14; 95% CI, 0.28 to 0.01; P =0 .04).

Pooled analysis showed a trend toward a lower risk of bronchiolitis obliterans syndrome (BOS) among tacrolimus-treated patients, although it did not reach significances (OR, 0.53; 95% CI, 0.25–1.12; P < 0.10).

Tacrolimus was associated with fewer withdrawals (OR, 0.12; 95% CI, 0.03–0.48; P =0.003).

The rate of new-onset diabetes was higher among the tacrolimus group (OR, 3.69; 95% CI, 1.17–11.62; P =0.03).

The incidence of hypertension and renal dysfunction were comparable between tacrolimus and cyclosporine (OR, 0.24; 95% CI, 0.03–1.70; P = 0.15; and OR, 1.67; 95% CI, 0.70–3.96; P = 0.25, respectively). There was a trend toward lower risk of malignancy in tacrolimus-treated patients, although it did not reach significance either (OR, 0.19; 95% CI, 0.03–1.13; P =0.07). The incidence of infection was comparable between tacrolimus and cyclosporine (MD 0.29, 95% CI, 0.68 to 0.11; P = 0.16) [93].

Heart transplant

Heart transplant; adults and children, tacrolimus vs cyclosporine

Tacrolimus versus cyclosporine as primary immunosuppression after heart transplantation: systematic review with meta-analyses and trial sequential analyses of randomised trials [94]

Penninga et al. published an SR with MA and trial sequential analyses of RCTs in 2010, which aimed to compare the benefits and harms of tacrolimus versus cyclosporine as primary immunosuppression after heart transplantation. The authors concluded that **tacrolimus seems to be superior to cyclosporine** in heart transplant patients with regard to hypertension, hyperlipidaemia, gingival hyperplasia and hirsutism. Also, **tacrolimus seems to be superior** to microemulsion cyclosporine in heart transplant patients concerning multiple outcomes, including **death**. The authors recommended that more trials with a low risk of bias are needed to determine if the results can be confirmed [94].

The SR included 11 RCTs; the MA included 10 RCTs with 952 patients. In 8 trials included in MA the population consisted of adult patients, in 1 trial the population consisted of a combination of adult and paediatric patients, and in 1 trial only paediatric patients were included.

Mortality: no significant difference was found between tacrolimus and cyclosporine (relative risk [RR] 0.78; 95% CI 0.54–1.13, p=0.19).

Grade 3A or higher rejection: five trials provided results of no significant difference between tacrolimus and cyclosporine (both formulas combined) (RR 0.86; 95% CI 0.62–1.20, p=0.38).

Basocellular skin cancer: three trials found no significant difference between tacrolimus and microemulsion cyclosporine for (RR 1.20; 95% CI 0.29–4.93, p= 0.80).

Hypertension: eight trials found significantly less hypertension in patients treated with tacrolimus compared with cyclosporine (RR 0.80; 95% CI 0.69–0.93, p=0.003)

Treatment for hyperlipidaemia: significantly fewer patients treated with tacrolimus received treatment for hyperlipidaemia compared with cyclosporine (RR 0.57; 95% CI 0.44–0.74, p< 0.0001) – four trials.

A proportion of patients with infection: no significant difference between tacrolimus and cyclosporine (RR 1.01; 95% CI 0.84–1.21, p=0.91).

Diabetes: based on data from eight trials, a non-significant trend towards more diabetes was seen in tacrolimus compared with cyclosporine (RR 1.35; 95% CI 0.93–1.94, p=0.11).

Renal failure requiring haemodialysis: no significant difference between tacrolimus and cyclosporine was seen concerning (RR 1.45; 95% CI 0.50–4.26, p=0.49).

Five trials reported on chronic allograft vasculopathy, and no significant difference (RR 1.22; 95% CI 0.72–2.05, p= 0.46)

Hirsutism was reported in 2 trials and was significantly less frequently seen in patients treated with tacrolimus than in those treated with microemulsion cyclosporine (RR 0.17; 95% CI 0.04–0.62, p=0.008).

Neurotoxicity was reported in 5 trials and was analysed as the number of patients who experienced at least one neurotoxic reaction or stroke. No significant difference was observed (RR 1.31; 95% CI 0.58–3.00, p=0.50) [94].

Heart transplant; adults and children; tacrolimus versus cyclosporine microemulsion

Tacrolimus Versus Cyclosporine Microemulsion for Heart Transplant Recipients: A Meta-analysis [95]

Fan et al. published an SR in 2009 which compared the beneficial and harmful effects of tacrolimus and microemulsion cyclosporine for heart transplant recipients. The authors concluded that the use of tacrolimus as a primary immunosuppressant for heart transplant recipients resulted in comparable survival and a significant reduction in acute rejection compared with cyclosporine microemulsion [95].

The SR included 7 RCTs with 885 patients. In 5 trials the recipients were all adults, whereas the other 2 studies included children.

Mortality: there was no difference in mortality at 1 year between recipients treated with tacrolimus and cyclosporine microemulsion (RR, 0.70; 95% CI, 0.45–1.08; p = 0.11).

Acute rejection risk was lower in tacrolimus-treated recipients at 6 months (RR, 0.61; 95% CI, 0.49–0.75; p = 0.00001) and 1 year (RR, 0.69; 95% CI, 0.48–0.98; p = 0.04).

Tacrolimus-treated patients had less acute rejection risk at 6 months and 1 year.

More patients stopped taking cyclosporine microemulsion than tacrolimus (RR, 0.57; 95% CI, 0.40–0.83; p =0.003).

The rate of new-onset diabetes mellitus requiring insulin treatment was higher with tacrolimus (RR, 1.65; 95% CI, 1.18–2.29; p =0.003).

More cases of post-transplantation hypertension were reported with cyclosporine microemulsion (RR, 0.88; 95% CI, 0.81–0.96; p = 0.004).

The groups had comparable incidences of malignancy (RR, 0.64; 95% CI, 0.31–1.32; p = 0.23) and renal failure needing dialysis (RR, 1.68; 95% CI, 0.81–3.52; p = 0.17).

A sensitivity analysis was conducted by using both random- and fixed-effects models and practically the same outcomes were found, except the result of the risk of new-onset diabetes mellitus, which showed no difference between tacrolimus and cyclosporine microemulsion when under the random-effect model (RR, 1.49; 95% CI, 0.78–2.84; p =0.22) [95].

Diabetes mellitus onset; adults; tacrolimus vs cyclosporine

New Onset Diabetes Mellitus in Patients Receiving Calcineurin Inhibitors: A Systematic Review and Meta-Analysis [98]

Heisel et al. published an SR in 2004, which aimed to evaluates the reported incidence of new-onset diabetes mellitus (NODM) after solid organ transplantation in patients receiving CNI treatment. The authors concluded that the reported incidence of NODM during the past decade was **significantly higher among patients receiving tacrolimus than cyclosporine** [98].

The SR included 56 publications that were published between 1992 and 2002. Eligible studies were prospective and retrospective studies that reported the incidence of NODM in adult recipients treated with either TAC or CSA following **solid organ transplantation** (excluding pancreatic transplantation).

New-onset diabetes mellitus was reported in 13.4% of patients after solid organ transplantation, with a higher incidence in patients receiving tacrolimus than cyclosporine (16.6% vs. 9.8%). This trend was observed across renal, liver, heart and lung transplant groups. Meta-analysis of 16 studies included patients receiving either tacrolimus (n = 1636) or cyclosporine (n = 1407). The incidence of insulin-dependent diabetes mellitus was significantly higher among tacrolimus-treated patients (10.4% vs. 4.5%, p < 0.00001) [98].

Full list of the RCTS included in the described systematic reviews is available in the Annex 4. of this application.

Evidence from RCTs not included in presented systematic reviews

Simultaneous pancreas and kidney (SPK) transplantation

In the four RCTs that compared the efficacy of tacrolimus and cyclosporine after simultaneous pancreas and kidney transplantation, the authors of **three RCTs concluded that regimens using tacrolimus were superior to the analyzed comparators** [99-101], while one concluded that there is no convincing evidence that Prograf should be preferred to Neoral [102].

Details of the RCT results:

Ciancio et al, 2015 [99] reported results for the advantage of rapamycin over mycophenolate mofetil when used with tacrolimus for simultaneous pancreas-kidney transplants, from a randomized, single-center trial at 10 years. The authors concluded that in this 10-year SPKT study, **rapamycin in combination with tacrolimus was better tolerated and more effective than MMF.** Overall, the patient and allograft survival were equivalent.

In the trial, 170 SPK transplant recipients were randomized to Rapamycin (n = 84) or MMF (n = 86). All patients received dual induction therapy with thymoglobulin and daclizumab, and low-dose maintenance therapy with tacrolimus and corticosteroids.

Rates of freedom from first biopsy-proven acute kidney or pancreas rejection were superior for rapamycin at year 1 (kidney: 100% vs. 88%; P = 0.001; pancreas: 99% vs. 92%; P = 0.04) and at year 10 (kidney: 88% vs. 71%, P = 0.01; pancreas: 99% vs. 89%, P = 0.01), compared to MMF. The higher rates of rejection were associated with withholding MMF (vs. Rapamycin, P = 0.009). Creatinine levels, proteinuria, c-peptide, viral infections, lymphoproliferative disorders and post-transplant diabetes incidence were comparable between groups. There were no significant differences in patient or allograft survival [99].

Boggi et al, 2005 [102] was an open-label RCT in which 47 simultaneous pancreas and kidney recipients were randomized to tacrolimus (Prograf) (n=25) or cyclosporine (Neoral) (n=22) in the setting of mycophenolate mofetil and steroid-based immunosuppression. The authors concluded that in MMF-based immunosuppression **there is no convincing evidence that Prograf should be preferred to Neoral** in SPKTx.

There was no pancreas rejection episode. One acute kidney rejection was observed in the Neoral group (4.5%) compared with 7 (28.0%), including one steroid-resistant episode, in the Prograf

group (P=0.03). The cumulative incidence of adverse events was 31.8% (n=7) in the Neoral group compared with 92.0% (n=23) in the Prograf group (P<0.0001). One patient died in each study group. There was no difference in patient, pancreas, and kidney survivals at 1- and 3-years post-transplant; namely all 95.4% for the Neoral group compared with 95.8%, 91.8%, and 95.8%, respectively, for the Prograf group (P>0.05) [102].

Bechstein et al, 2004 [100] reported 1-year results of an open-label, multicenter study, which compared tacrolimus with the cyclosporine microemulsion (ME) in primary simultaneous pancreas-kidney transplantation. The authors concluded that their findings **support the use of tacrolimus therapy for uremic patients with type 1 diabetes who are undergoing SPK transplantation**.

One hundred three patients were randomly assigned to tacrolimus and 102 to cyclosporine-ME after simultaneous pancreas and kidney transplant. All patients received concomitant rabbit anti–T-cell globulin induction therapy, mycophenolate mofetil (MMF), and short-term corticosteroids. The primary outcomes were the incidence of biopsy-proven acute rejection of either the pancreas or kidney at 1 year, and the incidence of treatment failure for any reason.

The 1-year incidence of biopsy-proven kidney or pancreas acute rejection was lower with tacrolimus (27.2%) than with cyclosporine-ME (38.2%; P=0.09). Pancreas graft survival at 1 year was higher with tacrolimus than with cyclosporine-ME (91.3% vs 74.5%; P<0.0005). Renal graft survival was similar between the groups. There were no significant differences in renal or pancreatic graft function. The number of patients switching treatment was significantly lower in the tacrolimus group than in the cyclosporine-ME group (P<0.0001, 95% CI 17.3–37.7). There was no difference in the incidence of urinary tract infection, CMV infection, and peritonitis between the two treatment groups [100].

Woeste et al, 2002 [101] reported 5-year results of a randomized study that compared tacrolimus/mycophenolate mofetil vs cyclosporine A/Azathioprine after simultaneous pancreas and kidney transplantation. The conclusion was that **the combination of TAC/MMF with induction therapy is beneficial to recipients of SPK**; it results in excellent patient and graft survival with a low risk of acute rejection.

The trial randomized 30 adult SPK transplant recipients into two groups of 15 patients each: group 1 received CSA, AZA, prednisone, and a single shot of ATG; group 2 received TAC,

MMF, prednisone, and a 10-day couple of ATG. Mean follow-up time was 65.6 months (range 60.5 - 72.4 months).

Acute rejection within the first 6 months after SPK occurred in 8/15 group 1 patients (53%) and 3/15 (20%) group 2 patients (P=0.128). After the first 6 months three acute rejections were observed in group 1, and two in group 2 (P=0.067). In group 1, 8/11 rejection episodes were steroid-resistant with the need for antibody-therapy. All but one rejection in group 2 was steroid-sensitive (P=0 .154). There was no difference in patient, kidney, and pancreas graft survival after 1 and 5 years (100%, 87%, 73% and 100%, 87%, 73% in group 1 and 100%, 100%, 80% and 87%, 73%, 80% in group 2; P=NS). The mean serum creatinine levels of patients with functioning kidney grafts were similar (P=0.77). There was no difference in CMV infections (P=0.680) within the first 6 months [101].

Lung transplantation

One additional RCTs compared the efficacy of tacrolimus and cyclosporine in lung transplant patients. **Treede 2001** [103] was a 2-center, prospective trial which included 50 primary lung transplant recipients randomized to receive either cyclosporine A (n=24) or tacrolimus (n=26) in combination with mycophenolate mofetil and steroids. The six-month and 1-year survival was similar. Freedom from acute rejection at 6 months and 1 year after lung transplantation were not significantly different (57.7% and 50% TAC vs 45.8% and 33.3% CSA, p =n.s). The number of treated rejection episodes per 100 patient days was significantly lower in the TAC group (0.225 vs 0.426, P<0.05). The incidence of infections was similar between the groups, only a trend toward more fungal infections in the TAC group was observed (n = 7 vs n = 1, p =n.s.). Tacrolimus seems to be more potent than cyclosporine in the prevention and treatment of acute rejection.

Heart transplantation

We found three additional RCTs about tacrolimus-based immunosuppression in heart transplant recipients that were not covered in SRs.

The first one, **Baran 2011** [104], presented results from The Tacrolimus in Combination, Tacrolimus Alone Compared (**TICTAC**) Trial after a median 3-year follow up. This open-label trial enrolled 150 adult heart transplant patients in 2004-2008 at 2 centers. All participants received tacrolimus, mycophenolate mofetil and steroids. Participants were randomized in a 1:1 fashion within 14 days following the transplant to either discontinue

mycophenolate mofetil (MONO group) or to continue the drug long-term (COMBO group). Steroids were successfully discontinued over 8-9 weeks. The primary endpoint of the trial was the mean cumulative International Society for Heart and Lung Transplantation (ISHLT) biopsy score over the first 6 months after transplantation. There was no difference in the composite biopsy score at 6 and 12 months: 6-month MONO, 0.70±0.44 (95% CI 0.60 -0.80) versus COMBO, 0.65±0.40 (95% CI, 0.55 -0.74; P=0.44). No significant differences were noted in allograft vasculopathy. Three-year survival was also similar (92.4% MONO versus 97% COMBO; P=0.58, log-rank). The results of this study support the efficacy of either TAC monotherapy or TAC/MMF, along with a brief course of corticosteroids after transplantation.

Kaczmarek 2013 [105] was a single-centre randomized trial conducted between 2003 and 2005. The 78 adults, de novo, heart transplant recipients were randomized 2:2:1 to receive steroids and tacrolimus plus mycophenolate mofetil (TAC/MMF; n= 34), TAC and sirolimus (TAC/SRL; n = 29), or SRL and MMF (SRL/MMF) plus anti-thymocyte globulin (ATG; n =15). After 6 months, steroids were withdrawn. The 5-year **survival** was **similar** between the groups: 85.3% for TAC/MMF, 93.1% for TAC/SRL, and 86.7% for SRL/MMF. Patients in the SRL/MMF group had a trend toward fewer freedom from acute rejection episodes: TAC/MMF, 82.4%; TAC/SRL, 85.2%; SRL/MMF, 73.3% (p = 0.33). Mean creatinine levels at 5 years showed preserved renal function in the SRL/MMF vs the TAC/MMF group (p = 0.045). The trend in freedom from cardiac allograft vasculopathy was also observed in the SRL/MMF group (93.3%) compared with TAC/MMF (73.5%) and TAC/SRL (80.8%) groups, P=NS. Freedom from cytomegalovirus infection was TAC/MMF, 72.2%; TAC/SRL, 89.7%; and SRL/MMF, 86.7%. More frequent discontinuations of study medication occurred in SRL-based group (TAC/SRL vs TAC/MMF, p = 0.034; SRL/MMF vs TAC/MMF, p = 0.003).

Sanchez-Lazaro 2011 study [106] randomized 106 adult heart transplant patients, in a single centre between 2006-2009, to tacrolimus of cyclosporine (53 per group), using induction with daclizumab and maintenance immunosuppression with mycophenolate mofetil (MMF) and steroids. There **was no difference in patient survival** (CSA: 88.68%, TAC: 81.13%, P= 0.492) after a median follow-up of 445 ± 324 days in the CSA group, and 516 ± 347 days in the TAC group. There was a trend for a longer time to first rejection with CSA (93 ± 110 vs. 55 ± 81 days; P = 0.122), and for more rejection-free patients with TAC (39 vs. 28%; P = 0.233). Patients in CSA group contracted more viral infections (0.41 ± 0.58 vs. 0.11 ± 0.31; P

= 0.003) and developed hypertension more often (64 vs. 43%; p = 0.032), while gastrointestinal complications were more frequent in TAC group (16 vs. 6%; p = 0.042). The two groups showed no difference in renal function, dyslipidemia, and the development of diabetes or neurological complications.

Liver transplantation

Asrani 2014 [107] studied the use of sirolimus with reduced-dose tacrolimus, compared to standard-dose tacrolimus, after liver transplantation. This international multicenter, open-label, randomized trial (2000-2003) included 222 adult primary liver transplant recipients and was terminated after 21 months due to an imbalance in adverse events. The 24-month cumulative incidence of graft loss (26.4% vs. 12.5%, p=0.009) and patient death (20% vs. 8%, p=0.010) was higher in sirolimus group. Sirolimus group also exhibited a higher rate of hepatic artery thrombosis/portal vein thrombosis (8% vs. 3%, p=0.065), and a higher incidence of sepsis (20.4% vs. 7.2%, p=0.006). Early use of sirolimus, using a loading dose followed by maintenance doses and reduced-dose tacrolimus, in de novo liver transplant recipients was associated with higher rates of graft loss, death and sepsis when compared to standard dose tacrolimus alone.

Becker 2008 [108] randomized 602 liver transplant recipients to tacrolimus (TAC) immunosuppression with a single-steroid bolus and two doses of daclizumab (DAC) or mycophenolate mofetil (MMF). The incidence of biopsy-proven acute rejection was comparable between groups (19.7% TAC/DAC vs 16.2% TAC/MMF). Three-month patient and graft survival were similar. Significantly higher incidences of causally related adverse events (AEs) and significantly more dose modifications, interruptions, or discontinuations due to an AE were reported with TAC/MMF. Study withdrawal due to leucopenia was significantly higher with TAC/MMF (0.0% vs. 1.7%. $P \leq 0.05$). Leucopenia and bacterial infection were significantly more frequent in TAC/MMF group. Renal function was similar, and increases in serum lipids were negligible in both groups. Incidences of de novo diabetes mellitus were low in both groups.

Boillot 2001 [109] studied 345 adult liver transplant patients randomized from October 1995 to December 1997 in 12 centres in France to tacrolimus-based immunosuppressive therapy either as a dual regimen (with corticosteroids, n=172) or as a triple regimen (with corticosteroids and azathioprine, n=173) (3-month cohort). A further analysis was performed on the first 195 patients randomised, who were followed up for 12 months (12-month cohort). Patient survival, graft survival, acute rejections and corticosteroid-resistant rejections were similar in both cohorts. There were no significant differences in the safety profiles of the treatment groups in the 12-month cohort.

The study by **Lerut 2008** [110], was a double-blind, placebo-controlled, single-center study. Adult primary liver transplant patients were randomized 1:1 to TAC-low dose and short-term steroids (TAC-ST; n =78) or into TAC-placebo (TAC-PL; n=78) group. The 3- and 12-month patient and graft survival rates **were not different** between the study groups. There was no difference in the incidence of rejection by 3 and 12 months (P=0.20 and 0.54). Corticosteroid-resistant rejection at 3 and 12 months was recorded in 12.8% (10 pts) of TAC-PL patients and 3.8% (3 pts) of TAC-ST patients (P=0.04). The higher incidence of early corticosteroid-resistant rejection in the TAC-PL group was related to the significantly higher number of patients transplanted while being on artificial organ support.

An open-label, randomized study by **Otero et al, 2009** [111] compared the efficacy of corticosteroids and tacrolimus (standard therapy, n =79) with daclizumab induction therapy in combination with mycophenolate mofetil and tacrolimus (modified therapy group, n =78) in primary liver transplant recipients. There was no significant difference between groups in patient or graft survival. The incidence of biopsy-proven acute rejection (BPAR) at 24 weeks was **significantly reduced** in the modified compared to standard therapy group (11.5% versus 26.6%, respectively, P=0.017), and was not different according to hepatitis C status. The time to rejection was significantly shorter in the standard therapy group (P=0.044).

Another open-label, multicenter, randomized trial was performed by **Garcia Gonzalez** et al. [112] to compare TAC and corticosteroids (dual therapy [D]) and TAC, corticosteroids, and azathioprine (triple therapy [T]) in liver transplantation. A total of 180 adult patients were randomized (dual, n= 92; triple, n= 88). The rate of biopsy-proven acute rejection was higher in dual compared to in triple regimen group (40.7% vs. 24.4%; P = 0.021). A higher incidence of positive HCV status in the dual group (55.6% vs. 40.7%; P = 0.049) may explain this difference, because more patients from HCV positive subpopulation experienced acute rejection when treated with dual therapy (48% vs. 20%; P = 0.008). Such differences were not observed for HCV-negative patients. There was a trend towards lower 24-month graft survival in the triple group, 69.8% vs. 75.8% (P = 0.283). A similar trend was observed in patient survival at 24-months (72.9% vs. 76.9%, P = 0.573), favoring the dual group. Safety profiles, except for hematological abnormalities, which were more frequent in the triple group, were comparable.

A Randomized Trial Comparing Cyclosporine A and Tacrolimus on Fibrosis After Liver Transplantation for Hepatitis C (**REFINE**) [113] was a prospective, open-label study of 356 patients receiving primary liver transplant for HCV cirrhosis at 55 liver transplant centers in 18 countries in North America, South America, Europe and Asia between January 2006 and September 2010. Patients were 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 the availability of liver biopsies, comprised 165 patients (88 CsA, 77 tacrolimus). There was no difference in fibrosis stage 2 at 12 months (primary outcome), which occurred in 63/88 CsA- treated patients (71.6%) and 52/77 tacrolimus-treated patients (67.5%); nor at 24 months follow up. Among steroid-free patients, fibrosis score 2 was significantly less frequent with CsA vs tacrolimus at 12-month follow up (7/37 [18.9%] vs. 16/ 38 [42.1%]; p = 0.029). Biopsy-proven acute rejection, graft loss and death were comparable. No marked safety advantage was observed for either agent.

Klintmalm 2011 [114] study was a multicenter trial that randomized HCV-positive liver transplant recipients to steroid-free immunosuppression (IS) or 2 standard immunosuppression regimens. Patients were randomized in a 1:1:2 ratio to 1 of 3 arms: arm 1 (n = 77) received tacrolimus and corticosteroids; arm 2 (n = 72) received TAC, corticosteroids, and mycophenolate mofetil (MMF); and arm 3 (n =146) received daclizumab (DAC) induction, TAC, and MMF (a steroid-free regimen).At 2 years, there were no differences in acute cellular rejection, HCV recurrence, patient survival, or graft survival rates. The side effects of immunosuppressive regimens were not different, although there was a trend toward less diabetes in the steroid-free group. Liver biopsy samples showed no significant differences in the proportions of patients in arms 1, 2, and 3 with advanced HCV recurrence at 1 year (48.2%, 50.4%, and 43.0%, respectively) and 2-year follow up (69.5%, 75.9%, and 68.1%, respectively).

Takada 2013 [115] conducted a prospective, randomized, multicenter trial on 75 hepatitis C virus (HCV)–positive adult liver transplantation recipients. They were randomized to receive TAC plus corticosteroids (ST; n =35) or TAC plus mycophenolate mofetil (MMF; n = 40). The event-free survival rates at 1, 3, and 5 years were similar between the groups (38.2%, 11.8%, and 5.9% in the ST group; and 25.0%, 17.5%, and 14.6% in the MMF group; P = 0.45). The overall 5- year patient survival rates were also similar; 82.7% in the ST group and 81.0% in the MMF group (P =0.28). Hepatocellular carcinoma recurrence occurred in 1

patient from the ST group and 2 patients from the MMF group. There was no difference in HCV recurrence rates with a fibrosis stage ≥ F1 at 1 year and 3 years after transplantation (P =0.57).

An RCT by **Martin** et al, **2004** [116] randomized in open-label fashion 79 adult HCV-positive liver transplant patients to receive tacrolimus or cyclosporine-based immunosuppression. All patients also received corticosteroids (prednisone tapered to 5 mg/day at day 90), and azathioprine, which was withdrawn gradually after 60 days. Patients in both groups experienced similar cumulative probabilities of histological hepatitis C recurrence (tacrolimus 0.38, 95% CI: 0.21 –.056), cyclosporine 0.54, 95% CI 0.37 –0.72); P=.19) and graft failure / death (tacrolimus 0.25, cyclosporine 0.28; P=0.789) at 12 months. No significant differences were observed between the two treatment arms in histologically-diagnosed HCV recurrence/survival rates, although the cyclosporine group had significantly larger increases in median serum HCV RNA levels at 1, 6, and 12-month follow-up.

An open-label, randomized study by **Neumann** et al, **2012** [117] compared HCV recurrence in HCV-positive liver allograft recipients using steroid-free immunosuppression, with inconclusive results due to the lower completion rates in the steroid-free group. The steroid-free group (TAC/daclizumab (TAC/DAC, n = 67)) received daclizumab induction, and the steroid group (TAC/steroid (TAC/STR, n = 68)) received a steroid bolus (≤ 500mg) followed by 15–20 mg/day with discontinuation after month 3.Participants in both groups had similar median HCV viral levels at 12 months: 5.46 (0.95–6.54) IU/mL in the TAC/DAC, and 5.91 (0.95–6.89) IU/mL in TAC/STR group. The rate of patients free of HCV recurrence at 12 months was 19.1% in the TAC/DAC versus 13.8% in the TAC/STR group. There was no difference in freedom from biopsy-proven rejection between TAC/DAC and TAC/STR group (78.4 versus 66.1%). The overall estimated patient survival was significantly lower in the TAC/DAC than in the TAC/STR group (83.1 versus 95.5%; 95% CI, −0.227 to −0.019%). Graft survival was not significantly different (80.1 versus 91.1%, P = NS). Completion rates (45% versus 82%) indicated poorer tolerability of TAC/DAC combination compared to TAC/STR regimen.

Only one additional RCT was conducted in **pediatric** liver transplant population. **Spada 2006** [118] was a single-center, randomized study comparing immunosuppression with tacrolimus (TAC) and steroids versus TAC and basiliximab (BAS). Seventy-two patients were recruited

(36 in each arm). Overall 1-year patient and graft survival rates were not different: 91.4% and 85.5% in the steroid group, and 88.6% and 80% in the BAS group. There was a significant difference in patients free from rejection (87.7% in the BAS group vs 67.7% in the steroid group; P = 0.036). The use of BAS was associated with a 63.6% reduction in the incidence of acute rejection episodes. The overall incidence of infection was higher in the steroid group compared to the BAS group (72.3% vs 50%; P= 0.035).

Kidney transplantation

ATLAS (Antibody, TacroLimus And Steroid withdrawal) study [119] was a 6-month, phase III, multicenter, open-label study conducted to compare steroid-free maintenance immunosuppression with a tacrolimus-based triple regimen as a control group. The 451 adults were randomized (1:1:1) to receive tacrolimus (Tac) monotherapy plus basiliximab (Bas) administration, Tac/mycophenolate mofetil (MMF) or Tac/MMF/corticosteroids triple therapy as a control. The incidences of biopsy-proven acute rejection were 8.2% (triple therapy), 30.5% (Tac/MMF), and 26.1% (Bas/Tac), $p<0.001$ (multiple test for comparison with triple therapy); Bas/Tac vs. Tac/MMF, p=ns. There were no significant differences between the groups in the incidences of corticosteroid-resistant acute rejection, graft and patient survival, and serum creatinine concentration at 6 months. The overall safety profiles were similar.

Cyclosporine (Group I) and tacrolimus (Group II) were compared in **Abou-Jaoude 2003** RCT which included 52 adult kidney transplant recipients [120]. The timing and the rate of acute rejection were similar in both groups, except for more steroid-resistant rejections in Group II ($P = 0.04$). The 6 months actuarial patient and graft survival were identical in both groups (100 and 100%). The infection rate was similar, except for more viral infections in Group II. CMV infections were related to the presence of more CMV-negative recipients receiving kidneys from CMV-positive donors in Group II. The metabolic profile was comparable between the two groups except for HDL, which was higher in group II ($P = 0.021$). Mean serum creatinine levels upon discharge, at 1, 3 and 6 months were: 1.62 ± 0.32, 1.4 ± 0.17, 1.39 ± 0.14 and 1.4 ± 0.14 in Group I and 2.15 ± 0.5, 1.48 ± 0.23, 1.41 ± 0.21 and 1.23 ± 0.11 in Group II, respectively (at 6-months $P = 0.03$).

Two large, open-label, multicenter RCTs, **Pascual 2002** [121] and **Chang 2001** [122], compared tacrolimus-based dual (tacrolimus /corticosteroids) and triple therapy (tacrolimus /corticosteroids/ azathioprine) after adult renal transplantation. Patient and graft survival were similar at 3 and 12-month follow- up. There was no difference in the incidence of treated acute rejection or incidence of corticosteroid-resistant rejection between the two arms. Incidences of leukopenia were significantly lower in the dual-therapy group than in the triple-therapy group. Tacrolimus was shown to be efficacious and safe with both dual and triple low-dose regimens.

A single-center, open-label, RCT by **Vacher-Coponat 2012** [123], compared CsA/azathioprine (Aza) and Tac/MMF in 289 adult kidney transplant recipients treated with antithymocyte globulins and prednisone. The results indicated that BPAR 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. There was a difference in eGFR at 1 year, which was lower in the CsA/Aza group compared to Tac/MMF group (P=0.007). There was no significant difference in the incidence of diabetes after transplantation.

An RCT by **Miller 2000** [124] randomized adult renal transplant patients to tacrolimus in combination with either azathioprine (AZA, n=59), MMF 1 g/day (n=59), or MMF 2 g/day group (n=58). The incidence of biopsy-proven acute rejection at 1 year was 32.2%, 32.2%, and 8.6% in the AZA, MMF 1 g/day, and MMF 2 g/day groups, respectively (P<0.01). The patient and graft survival estimates at 12 months follow-up were similar for all three groups. The incidence of de novo diabetes mellitus was lowest in the MMF 2 g/day group (4.7%). The incidence of malignancies and opportunistic infections was low and similar across treatment groups.

Kumar 2005 RCT [125] compared the safety and efficacy of steroid avoidance in tacrolimus (TAC)/ mycophenolate mofetil (MMF) and TAC/sirolimus (SRL) combinations in 150 adult kidney transplant recipients. Acute rejection was observed in 12% of TAC/MMF and 8% of TAC/SRL patients. Two-year patient and graft survival were equivalent. Subclinical acute rejection (P=0.04) and moderate/severe chronic allograft nephropathy (P=0.06) were lower in the TAC/SRL compared to the TAC/MMF group, while graft function was equivalent. The incidence of new-onset diabetes mellitus was not different between the groups (4%).

Patients in **Gallon 2006** [126] RCT were prospectively randomized to two maintenance immunosuppressive regimens with Tac/MMF (n = 45) or Tac/SRL (n = 37). There was one kidney loss in the Tac/MMF vs. 6 kidney losses in the Tac/SRL group (log-rank test p = 0.04). GFR was consistently and statistically higher in the Tac/MMF than in the Tac/SRL group. The slope of GFR decline per month was flatter in the Tac/MMF than in the Tac/SRL group. This study showed significantly lower renal graft survival and graft function in Tac/SRL than in Tac/MMF group.

An RCT by **Asher 2014** [127] was performed on 19 pairs of kidneys from each donor randomized to tacrolimus or sirolimus-based regimen. Renal graft function was similar in both groups at 3-monthly intervals up to 1-year post-transplant, despite a higher incidence of biopsy-proven acute rejection in the sirolimus arm. Graft and patient survival at 1 year were 100% in the tacrolimus group, with one death with functioning graft in the sirolimus group (95% survival). Ten of the 19 patients in the sirolimus arm were switched to tacrolimus due to acute rejection or intolerable side effects.

Huh 2017 [128] randomly assigned 158 renal transplant patients to low-dose sirolimus (SRL) or MMF in combination with extended-release TAC (ER-TAC) and corticosteroids. The efficacy failure rate at 12 months follow-up, a composite of biopsy-proven acute rejection (BPAR), graft loss, death or loss to follow-up, was 6.6% in the low-dose SRL group and 13.3% in the MMF group in the intention-to-treat population. There was no difference in the incidence of BPAR at 12 months (5.3% in the low-dose SRL group and 13.3% in the MMF group; P= 0.09). There was no difference in the mean eGFR rate at 12 months (P=0.76). Adverse events and serious adverse events incidence were similar in both groups.

A single-center, open-label, RCT by **de Graav** et al., **2017** [129] randomized 40 kidney transplant recipients to belatacept or tacrolimus combined with basiliximab, mycophenolate mofetil, and prednisolone. The 1-year incidence of biopsy-proven acute rejection was higher in the belatacept-treated than a tacrolimus-treated group: 55% vs 10% (P = 0.006). Belatacept-based immunosuppressive regimen resulted in higher and more severe acute rejection compared with tacrolimus-based immunosuppression.

Rostaing 2005 [130] analyzed 538 adult renal patients randomized to immunosuppression with tacrolimus, mycophenolate mofetil, in combination with daclizumab induction therapy (Dac/Tac/MMF) or control (Tac/MMF/corticosteroids) regimen. The results showed that corticosteroid-free immunosuppression with Dac/Tac/MMF regimen was as effective at preventing acute rejection after renal transplantation as a standard triple regimen of Tac/MMF/corticosteroids. The overall safety profile was similar, however, a significantly lower incidence of new-onset insulin-dependent diabetes mellitus (5.4% vs. 0.4%, P=0.003) was found in the Dac/Tac/MMF group.

Ciancio 2016 [131] conducted a single-center, open-label, randomized pilot trial comparing two maintenance immunosuppression regimens in 30 adults, primary kidney transplant recipients: tacrolimus/ everolimus vs standard regimen of TAC plus enteric-coated mycophenolate mofetil. During the first 12 months, there were no significant differences in any of the primary (the incidence of biopsy-proven acute rejection) or secondary outcomes (biopsy-proven chronic allograft injury, serum creatinine levels and estimated glomerular filtration rate, new-onset diabetes mellitus, infections, graft loss, and death) between the two groups. Most of the study participants (80%) were a minority (African American and Hispanic).

Jarzembowski 2003 [132] performed an RCT comparing tacrolimus (TAC) and cyclosporine (CSA) immunosuppression in the African–American population. The study randomized (1:1) 35 primary cadaveric renal transplant recipients. There was no difference in patient and graft survival rates between the groups at 1, 3 and 5 years. Twelve patients in the CSA group were converted to tacrolimus. Significantly lower creatinine and cholesterol levels were observed at 1 year follow up, but the difference was not significant at 3 and 5 years.

Kojima 2018 [133] randomized 43 elderly (over 60 years old) kidney transplant recipients to tacrolimus-sirolimus and tacrolimus-mycophenolate regimen. The incidence of Cytomegalovirus infection was higher in the mycophenolate group (60.9%) compared to the sirolimus group (16.7%; P=.004). The rates of biopsy-proven acute rejection, patient survival, graft survival, and estimated glomerular filtration rate at 12-month follow up were similar. The use of tacrolimus combined with sirolimus in elderly kidney transplant recipients was safe.

10. Review of harms and toxicity: summary of evidence of safety

Tacrolimus was found to be effective in improving graft survival and preventing acute rejection after solid organ transplantation, but besides the beneficial effects, treatment of tacrolimus carries certain risks. Most often reported side-effects include the new onset of diabetes mellitus (NODM) following transplantation, neurological and various gastrointestinal complications including nausea, vomiting and diarrhea, changes in renal function, cardiotoxicity, as well as tremor, headache, hyperkalaemia (raised potassium blood levels), and dyspepsia. However, compared to cyclosporine, most tacrolimus-related side effects are either less likely to occur or have milder intensity.

The incidence of NODM after solid organ transplantation during the past decades has been reported as significantly higher among patients receiving tacrolimus [98]. Still, many reports imply no difference between tacrolimus and cyclosporine in the incidence of diabetes [82], and that despite diabetes occurring more often in patients who are treated with tacrolimus, more people continue their tacrolimus treatment than those treated with cyclosporine [82]. Regarding the impact of drug combinations, a systematic review including 10 studies with a total of 2357 patients found that sirolimus combined with tacrolimus may lead to higher rates of diabetes, hyperlipidemia, and lymphocele compared to a combination consisting of tacrolimus and MMF [82].

This is in line with the results of a three-arm, multicenter RCT that showed a trend toward less diabetes in the steroid-free group containing daclizumab (DAC) induction, tacrolimus, and MMF [114]. When treatment based on cyclosporine plus azathioprine was compared to tacrolimus with MMF group, no significant difference in the incidence of diabetes after transplantation was observed [123]. Tacrolimus in combination with 2 g/day MMF showed the lowest incidence of *de novo* diabetes mellitus compared to tacrolimus and azathioprine or 1 mg/day MMF [124].

Similar results were found in an RCT on 538 adult renal patients that found a significantly lower incidence of insulin-dependent diabetes if treatment was based on the combination of dacilizimab, tacrolimus and MMF (5.4% vs. 0.4%, P=0.003) [130].

Furthermore, despite the risk of post-transplantation diabetes, the use of tacrolimus for uremic patients with type 1 diabetes who are undergoing primary simultaneous pancreas-kidney transplantation is supported [100].

Gastrointestinal complications were more likely among patients treated with tacrolimus, but compared to Cyclosporine A, tacrolimus was less likely to lead to viral infections and hypertension [106].

Chronic kidney disease is a potential complication of non-renal transplantation, and there are some evidence that it might be higher in children than in adults, with the mean prevalence ranging from 20% to 40% and severe kidney disease ranging from 1,7% up to 46% [134].

Available evidence shows that there is no difference between tacrolimus and cyclosporine in kidney dysfunction (RR 1.41, 95% CI 0.93 to 2.14), or kidney failure (RR 1.57, 95% CI 0.28 to 8.94. There is also evidence of no difference in renal failure requiring hemodialysis between tacrolimus and cyclosporine (RR 1.45; 95% CI 0.50–4.26, p=0.49). However, a study that monitored mean creatinine levels at 5 years showed preserved renal function in the sirolimus and MMF versus the tacrolimus and MMF treatment approach [92].

There is consistent evidence of no difference in neurotoxicity between tacrolimus and cyclosporine, as well as no difference in the rates of stroke [92].

No difference was observed in the frequency and type of infections between tacrolimus and cyclosporine [92]. However, when sirolimus is combined with tacrolimus, that was shown to lead to higher rates of infectious complications [82].

In general, there was no difference in the malignancy rates in patients treated with tacrolimus compared to cyclosporine, with one study showing a trend toward lower risk of malignancy in patients treated with tacrolimus [87]. The incidence of malignancies and opportunistic infections was low and was found similar to those of cyclosporine [93].

Compared to cyclosporine, tacrolimus was shown to be associated with a lower incidence of hyperlipidemia and hypertension [94, 96].

The frequency and type of infections were similar in people treated with tacrolimus as in those treated with cyclosporine. Tacrolimus showed lower rates of hyperlipidemia and hypertension than cyclosporine [94], with evidence of no significant difference in the incidence of hypertension between tacrolimus and cyclosporine [96].

11. Summary of available data on comparative cost and cost-effectiveness of the medicine

Immediate-release tacrolimus is considered a cost-effective, cheaper and clinically effective option for preventing organ rejection in children and young people, as well as in adults having a kidney transplant [64, 65]. Based on an HTA report that compared as much as 16 tacrolimus combinations, basiliximab induction followed by maintenance with immediate-release tacrolimus and mycophenolate mofetil is the only cost-effective combination at £20,000-30,000 per QALY (quality-adjusted life years) [79]. Based on this it is believed that this combination is to be used in regular treatment. Mycophenolate mofetil used alongside tacrolimus is a cost-effective use of resources for preventing organ rejection in children and young people having a kidney transplant [65]. Twice daily tacrolimus with mycophenolate mofetil and corticosteroids is more cost-effective compared to belatacept in terms of acute rejection outcomes in adult kidney transplant patients [64, 83].

Prolonged-release tacrolimus administered orally as one capsule a day is not considered to be cost-effective [65, 76].

Compared to CSA with azathioprine, TAC is likely to be cost-effective at £20,000-30,000 per QALY (quality-adjusted life years) for maintenance therapy in children and adolescents undergoing renal transplantation [79]. A study that compared costs of tacrolimus versus cyclosporine treatment measured resource-use quantities, cost of drugs, concomitant medications, hospitalization, dialysis and rejection episodes from 50 centres in Western European countries and found that per-patient savings by tacrolimus ranged from 1776 to 524 euros. Most of the savings were due to shorter initial hospitalization stay, as well as rehospitalizations, lower cost of immunosuppressive drugs for graft rejection and lower incidence of dialysis [135].

Compared to sirolimus, tacrolimus is a more-cost effective treatment for preventing adverse events after renal transplantation, as it reduces the incidence of graft rejection and provides a big reduction in the cost of treatment with steroids and antibody treatment [136].

12. Summary of regulatory status and market availability of tacrolimus

Tacrolimus was first approved in the US by the US Food and Drug Administration (FDA) in 1994 in the oral capsule [137] and injectable form [138] or prophylaxis of organ rejection in patients receiving allogeneic liver transplants. The indications were subsequently extended to

include kidney, heart, small bowel, pancreas, lung, trachea, skin, cornea, bone marrow, and limb transplants.

In the **European Union**, tacrolimus was approved for medical use in 2002, for the treatment of moderate to severe atopic dermatitis [139]. In 2007, tacrolimus was approved in European Union for the following therapeutic indications: Prophylaxis of transplant rejection in adult kidney or liver allograft recipients, and treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in **adult** patients [140]. In 2009, in European Union, tacrolimus was approved for the following therapeutic indications: prophylaxis of transplant rejection in adult and paediatric, kidney, liver or heart allograft recipients; treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in **adult** and **paediatric** patients [141].

13. Availability of pharmacopoeial standards

Tacrolimus monohydrate is included in the European Pharmacopoeia [142].

Tacrolimus is included in the US Pharmacopoeia [143].

The British Pharmacopoeia [144] found no reports concerning tacrolimus, including Advagraf and Prograf.

Tacrolimus is not included in the International Pharmacopoeia.

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122. Chang RW, Snowden S, Palmer A, Kwan JT, Nicholson M, Kashi SH, Fernando ON, Perner F, Neild GH: **European randomised trial of dual versus triple tacrolimus-based regimens for control of acute rejection in renal allograft recipients**. *Transpl Int* 2001, **14**(6):384-390.
123. Vacher-Coponat H, Moal V, Indreies M, Purgus R, Loundou A, Burtey S, Brunet P, Moussi-Frances J, Daniel L, Dussol B *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.

124. Miller J, Mendez R, Pirsch JD, Jensik SC, Group ftFMD-RKTS: **SAFETY AND EFFICACY OF TACROLIMUS IN COMBINATION WITH MYCOPHENOLATE MOFETIL (MMF) IN CADAVERIC RENAL TRANSPLANT RECIPIENTS1**. *Transplantation* 2000, **69**(5):875-880.
125. Anil Kumar MS, Heifets M, Fyfe B, Saaed MI, Moritz MJ, Parikh MH, Kumar A: **Comparison of steroid avoidance in tacrolimus/mycophenolate mofetil and tacrolimus/sirolimus combination in kidney transplantation monitored by surveillance biopsy**. *Transplantation* 2005, **80**(6):807-814.
126. Gallon L, Perico N, Dimitrov BD, Winoto J, Remuzzi G, Leventhal J, Gaspari F, Kaufman D: **Long-term renal allograft function on a tacrolimus-based, pred-free maintenance immunosuppression comparing sirolimus vs. MMF**. *Am J Transplant* 2006, **6**(7):1617-1623.
127. Asher J, Vasdev N, Wyrley-Birch H, Wilson C, Soomro N, Rix D, Jaques B, Manas D, Torpey N, Talbot D: **A Prospective Randomised Paired Trial of Sirolimus versus Tacrolimus as Primary Immunosuppression following Non-Heart Beating Donor Kidney Transplantation**. *Current urology* 2014, **7**(4):174-180.
128. Huh KH, Lee JG, Ha J, Oh CK, Ju MK, Kim CD, Cho HR, Jung CW, Lim BJ, Kim YS *et al*: **De novo low-dose sirolimus versus mycophenolate mofetil in combination with extended-release tacrolimus in kidney transplant recipients: a multicentre, open-label, randomized, controlled, non-inferiority trial**. *Nephrology, dialysis, transplantation* 2017, **32**(8):1415-1424.
129. de Graav GN, Baan CC, Clahsen-van Groningen MC, Kraaijeveld R, Dieterich M, Verschoor W, von der Thusen JH, Roelen DL, Cadogan M, van de Wetering J *et al*: **A Randomized Controlled Clinical Trial Comparing Belatacept With Tacrolimus After De Novo Kidney Transplantation**. *Transplantation* 2017, **101**(10):2571-2581.
130. Rostaing L, Cantarovich D, Mourad G, Budde K, Rigotti P, Mariat C, Margreiter R, Capdevilla L, Lang P, Vialtel P *et al*: **Corticosteroid-free immunosuppression with tacrolimus, mycophenolate mofetil, and daclizumab induction in renal transplantation**. *Transplantation* 2005, **79**(7):807-814.
131. Ciancio G, Tryphonopoulos P, Gaynor JJ, Guerra G, Sageshima J, Roth D, Chen L, Kupin W, Mattiazzi A, Tueros L *et al*: **Pilot Randomized Trial of Tacrolimus/Everolimus vs Tacrolimus/Enteric-Coated Mycophenolate Sodium in Adult, Primary Kidney Transplant Recipients at a Single Center**. *Transplantation Proceedings* 2016, **48**(6):2006-2010.
132. Jarzembowski T, Panaro F, Raofi V, Dong G, Testa G, Sankary H, Benedetti E: **Long-term results of a prospective randomized trial comparing tacrolimus versus cyclosporine in African-American recipients of primary cadaver renal transplant**. *Transpl Int* 2005, **18**(4):419-422.
133. Kojima CA, Nga HS, Takase HM, Bravin AM, Martinez Garcia MFF, Garcia PD, Contti MM, de Andrade LGM: **Sirolimus Associated with Tacrolimus at Low Doses in Elderly Kidney Transplant Patients: A Prospective Randomized Controlled Trial**. *Experimental and clinical transplantation : official journal of the Middle East Society for Organ Transplantation* 2018, **16**(3):301-306.
134. Gijsen VM, Hesselink DA, Croes K, Koren G, de Wildt SN: **Prevalence of renal dysfunction in tacrolimus-treated pediatric transplant recipients: a systematic review**. *Pediatric transplantation* 2013, **17**(3):205-215.

135. Lazzaro C, McKechnie T, McKenna M: **Tacrolimus versus cyclosporin in renal transplantation in Italy: cost-minimisation and cost-effectiveness analyses**. *Journal of nephrology* 2002, **15**(5):580-588.
136. Liu JY, Song M, Guo M, Huang F, Ma BJ, Zhu L, Xu G, Li J, You RX: **Sirolimus Versus Tacrolimus as Primary Immunosuppressant After Renal Transplantation: A Meta-Analysis and Economics Evaluation**. *Am J Ther* 2016, **23**(6):E1720-E1728.
137. **US Food and Drug Administration. FDA-approved drugs. Prograf. Oral capsule. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=050708. Date accessed: October 30, 2020**.
138. **US Food and Drug Administration. FDA-approved drugs. Prograf. Injectable. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=050709. Date accessed: October 30, 2020**.
139. **European Medicines Agency. European Public Assessment Report. Protopic. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/protopic. Date accessed: October 30, 2020**.
140. **European Medicines Agency. European Public Assessment Report. Advagraf. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/advagraf. Date accessed: October 30, 2020**.
141. **European Medicines Agency. European Public Assessment Report. Modigraf. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/modigraf. Date accessed: October 30, 2020**.
142. European Pharmacopoeia: **European Pharmacopoeia. Available at: https://www.edqm.eu/en/european-pharmacopoeia-ph-eur-10th-edition**. 2020.
143. US Pharmacopoeia: **US Pharmacopoeia. Tacrolimus. Available at: https://www.usp.org/search?search_api_fulltext=tacrolimus**. 2020.
144. British Pharmacopoeia: **British Pharmacopoeia. Available at: https://www.pharmacopoeia.com/bp**. 2020.

ANNEX 1. International availability and proprietary names of tacrolimus drugs with available doses used for pevention and treatment of rejection

Name of the drug	Manufacturer	Formulation	Dose
Advagraf	Astellas Pharma S.p.A.	Prolonged release capsules	0,5 mg 1 mg 3 mg 5 mg
Prograf	Astellas Pharma S.p.A.	Immediate release capsules	0,5 mg 1 mg 5 mg
		Solution (**parenteral use**)	5 mg/ml
		Granules for oral suspension	0,2 mg; 1 mg
Adoport	Sandoz S.p.	Immediate release capsules	0,5 mg 0,75 mg 1 mg 2 mg 5 mg
Modigraf	Astellas Pharma B.V.	Granules for oral suspension	0.2 mg 1 mg
Conferoport	Sandoz S.p.A.	Prolonged release capsules	0,5 mg 1 mg 3 mg 5 mg
Envarsus	Chiesi Farmaceutici S.p.A	Prolonged release tablets	0,75 mg 1 mg 4 mg
Tacforius	Teva B.V.:	Prolonged release capsules	0,5 mg 1 mg 3 mg 5 mg
Tacrocel	Lek Pharmaceuticals d.d., Slovenia; Lek S.A., Poland	Prolonged release capsules	O,5 mg 1 mg 5 mg
Tacni	Teva Italia S.r.l.	Prolonged release capsules	0,5 mg 5 mg

https://www.halmed.hr; https://www.codifa.it; https://www.ema.europa.eu; https://www.medicines.org.uk

ANNEX 2. Search strategies used for specific databases

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to July 23, 2020>

Search Strategy:

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1 exp Transplantation/ (502503)
2 Transplant Recipients/ (3216)
3 exp Transplants/ (21655)
4 (transplant$ or graft$).tw. (666454)
5 or/1-4 (835973)
6 exp Immunosuppression/ (58854)
7 immunosuppress$.tw. (140952)
8 ((prevent$ or diminution or suppress$ or reduction or decline or decrease) adj3 immune response).tw. (3216)
9 or/6-8 (186026)
10 Graft Rejection/ (58830)
11 ((graft$ or transplant$) adj3 reject$).tw. (23964)
12 10 or 11 (69665)
13 5 and 9 (75405)
14 12 or 13 (124391)
15 Tacrolimus/ (15555)
16 (tacrolimus or calcineurin inhibitor$).tw. (20247)
17 Prograf.tw. (261)
18 Advagraf.tw. (96)
19 Astagraf XL.tw. (6)
20 (LCP-Tacro or LCPT).tw. (36)
21 (Envarsus or Envarsus XR).tw. (15)
22 Tacni.tw. (4)
23 Tacrocel.tw. (0)
24 Direnil.tw. (1)
25 Modigraf.tw. (3)
26 Tacforius.tw. (0)
27 Fujimycin.tw. (7)
28 Protopic.tw. (114)
29 FK-506.tw. (1970)
30 FK506.tw. (5927)
31 or/15-30 (28767)
32 14 and 31 (12933)
33 exp animals/ not humans.sh. (4648880)
34 32 not 33 (11483)
35 limit 34 to yr="2000 -Current" (10381)

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Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 23, 2020>

Search Strategy:

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1 Transplantation.kw. (209)
2 Transplant Recipients.kw. (1)
3 Transplants.kw. (3)
4 (transplant$ or graft$).tw. (1391)
5 or/1-4 (1391)
6 Immunosuppression.kw. (22)
7 immunosuppress$.tw. (702)
8 ((prevent$ or diminution or suppress$ or reduction or decline or decrease) adj3 immune response).tw. (20)
9 or/6-8 (710)
10 Graft Rejection.kw. (31)
11 ((graft$ or transplant$) adj3 reject$).tw. (106)
12 10 or 11 (106)
13 5 and 9 (283)
14 12 or 13 (313)
15 Tacrolimus.kw. (20)
16 (tacrolimus or calcineurin inhibitor$).tw. (120)
17 Prograf.tw. (2)
18 Advagraf.tw. (1)
19 Astagraf XL.tw. (0)
20 (LCP-Tacro or LCPT).tw. (0)
21 (Envarsus or Envarsus XR).tw. (1)
22 Tacni.tw. (0)
23 Tacrocel.tw. (0)
24 Direnil.tw. (0)
25 Modigraf.tw. (1)
26 Tacforius.tw. (0)
27 Fujimycin.tw. (1)
28 Protopic.tw. (4)
29 FK-506.tw. (7)
30 FK506.tw. (18)
31 or/15-30 (129)
32 14 and 31 (97)
33 limit 32 to yr="2000 -Current" (73)

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Database: EBM Reviews - Cochrane Central Register of Controlled Trials <July 2020>

Search Strategy:

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1 exp Transplantation/ (11343)
2 Transplant Recipients/ (95)
3 exp Transplants/ (386)
4 (transplant$ or graft$).tw. (47817)
5 or/1-4 (50065)
6 exp Immunosuppression/ (1979)
7 immunosuppress$.tw. (9595)
8 ((prevent$ or diminution or suppress$ or reduction or decline or decrease) adj3 immune response).tw. (200)
9 or/6-8 (11300)
10 Graft Rejection/ (2186)
11 ((graft$ or transplant$) adj3 reject$).tw. (2407)
12 10 or 11 (3943)
13 5 and 9 (5401)
14 12 or 13 (7552)
15 Tacrolimus/ (1832)
16 (tacrolimus or calcineurin inhibitor$).tw. (5159)
17 Prograf.tw. (286)
18 Advagraf.tw. (116)
19 Astagraf XL.tw. (8)
20 (LCP-Tacro or LCPT).tw. (43)
21 (Envarsus or Envarsus XR).tw. (58)
22 Tacni.tw. (3)
23 Tacrocel.tw. (0)
24 Direnil.tw. (0)
25 Modigraf.tw. (2)
26 Tacforius.tw. (0)
27 Fujimycin.tw. (2)
28 Protopic.tw. (59)
29 FK-506.tw. (153)
30 FK506.tw. (288)
31 or/15-30 (5686)
32 14 and 31 (2899)
33 limit 32 to yr="2000 -Current" (2596)

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Database: EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>

Search Strategy:

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1 Transplantation.kw. (747)
2 Transplant Recipients.kw. (0)
3 Transplants.kw. (9)
4 (transplant$ or graft$).tw. (1579)
5 or/1-4 (1579)
6 Immunosuppression.kw. (21)
7 immunosuppress$.tw. (346)
8 ((prevent$ or diminution or suppress$ or reduction or decline or decrease) adj3 immune response).tw. (0)
9 or/6-8 (346)
10 Graft Rejection.kw. (83)
11 ((graft$ or transplant$) adj3 reject$).tw. (100)
12 10 or 11 (100)
13 5 and 9 (130)
14 12 or 13 (181)
15 Tacrolimus.kw. (47)
16 (tacrolimus or calcineurin inhibitor$).tw. (78)
17 Prograf.tw. (2)
18 Advagraf.tw. (0)
19 Astagraf XL.tw. (0)
20 (LCP-Tacro or LCPT).tw. (0)
21 (Envarsus or Envarsus XR).tw. (0)
22 Tacni.tw. (0)
23 Tacrocel.tw. (0)
24 Direnil.tw. (0)
25 Modigraf.tw. (0)
26 Tacforius.tw. (0)
27 Fujimycin.tw. (0)
28 Protopic.tw. (0)
29 FK-506.tw. (0)
30 FK506.tw. (3)
31 or/15-30 (78)
32 14 and 31 (43)
33 limit 32 to yr="2000 -Current" [Limit not valid; records were retained] (43)

ANNEX 3. List of studies evaluated in full text (reasons for exclusion)

148 Guidelines		31 full texts screened	19 excluded: not intervention/ population of interest	12 included
12 HTAs found		9 full texts screened	4 excluded: not intervention/ population of interest	5 included
114 Systematic reviews		47 full texts screened	28 excluded: Not intervention/ population of interest	19 included
837 RCTs	401 ineligible; 372 RCTs already included in SRs	64 full texts screened	29 excluded: 2 – ineligible intervention; 6 – ineligible drug combinations; 1 - Tacrolimus conversion to/from; 1 – antibody induction; 1 – duplicate; 3 – not RCTs; 9 – full texts not available; 3 – conference abstract; 1 – protocol; 1 – RCT follow-up; 1 – not eligible.	35 included

ANNEX 4 List of studies included in systematic reviews

Kidney transplant

Kidney transplant; adults, tacrolimus versus cyclosporine

Azarfar et al, 2018, Comparison of Tacrolimus and Cyclosporine for Immunosuppression after Renal Transplantation: An Updated Systematic Review and MetaAnalysis [81]

The SR included the following 21 RCTs:

Shapiro R, Jordan M, Scantlebury V, et al. FK 506 in clinical kidney transplantation. Transplant Proc **1991**;23:3065-7.

Mayer AD, Dmitrewski J, Squifflet JP, et al. Multicenter randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of renal allograft rejection: A report of the European Tacrolimus Multicenter RenalStudy Group. Transplantation **1997**;64:436-43.

Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. FK506 kidney transplant study group. Transplantation **1997**; 63:977-83.

Morris-Stiff G, Ostrowski K, Balaji V, et al. Prospective randomised study comparing tacrolimus (Prograf) and cyclosporin (Neoral) as primary immunosuppression in cadaveric renal transplants at a single institution: Interim

report of the first 80 cases. Transpl Int 1998;11 Suppl 1:S334-6.

Radermacher J, Meiners M, Bramlage C, et al. Pronounced renal vasoconstriction and systemic hypertension in renal transplant patients treated with cyclosporin A versus FK 506. Transpl Int 1998;11:3-10.

Raofi V, Holman DM, Coady N, et al. A prospective randomized trial comparing the efficacy of tacrolimus versus cyclosporine in black recipients of primary cadaveric renal transplants. Am J Surg **1999**;177:299-302.

Yang HC, Holman MJ, Langhoff E, et al. Tacrolimus/"low-dose" mycophenolate mofetil versus microemulsion cyclosporine/"low- dose" mycophenolate mofetil after kidney transplantation –1-year follow-up of a prospective, randomized clinical trial. Transplant Proc

1999;31:1121-4.

Wang XH, Tang XD, Xu D. Tacrolimus vs. cyA neoral in combination with MMF and steroids after cadaveric renal transplantation. Transplant Proc **2000**;32:1702-3.

White SA, Jain S, Williams ST, et al. Randomized trial comparing neoral and tacrolimus immunousuppression for recipients of renal transplants procured from different donor groups. Transplant Proc **2000**;32:600.

Ahsan N, Johnson C, Gonwa T, et al. Randomized trial of tacrolimus plus mycophenolate mofetil or azathioprine versus cyclo-sporine oral solution (modified) plus mycophenolate mofetil after cadaveric kidney transplantation: Results at 2 years. Transplantation 2001;72:245-50.

Campos HH, Abbud Filho M; Brazilian Tacrolimus Study Group. One-year follow-up of a Brazilian randomized multicenter study comparing tacrolimus versus cyclosporine in kidney transplantation. Transplant Proc **2002**;34:1656-8.

Charpentier B; European Tacrolimus vs. Microemulsified Cyclosporin Study Group. A three arm study comparing immediate tacrolimus therapy with ATG induction therapy followed by either tacrolimus or cyclosporine in adult renal transplant recipients. Transplant Proc **2002**;34:1625-6.

Margreiter R; European Tacrolimus vs. Ciclosporin Microemulsion Renal Transplantation Study Group. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: A randomised multicentre study. Lancet **2002**;359:741-6.

Trompeter R, Filler G, Webb NJ, et al. Randomized trial of tacrolimus versus cyclosporin microemulsion in renal transplantation. Pediatr Nephrol **2002**;17:141-9.

Jarzembowski T, Panaro F, Raofi V, et al. Long-term results of a prospective randomized trial comparing tacrolimus versus cyclosporine in African-American recipients of primary cadaver renal transplant. Transpl Int **2005**;18:419-22.

Cheung CY, Wong KM, Chan HW, et al. Paired kidney analysis of tacrolimus and cyclosporine microemulsion-based therapy in Chinese cadaveric renal transplant recipients. Transpl Int **2006**;19:657-66.

Krämer BK, Del Castillo D, Margreiter R, et al. Efficacy and safety of tacrolimus compared

with ciclosporin A in renal transplantation: Three-year observational results. Nephrol Dial Transplant **2008**;23:2386-92.

Cheung CY, Chan HW, Liu YL, Chau KF, Li CS. Long-term graft function with tacrolimus and cyclosporine in renal transplantation: Paired kidney analysis. Nephrology (Carlton) **2009**;14:758-63.

Lee YJ, Kim B, Lee JE, al. Randomized trial of cyclosporine and tacrolimus therapy with steroid withdrawal in living-donor renaltransplantation: 5-year follow-up. Transpl Int **2010**;23:147-54.

Liu LS, Li J, Chen XT, et al. Comparison of tacrolimus and cyclosporin A in CYP3A5 expressing Chinese *de novo* kidney transplant recipients: A 2-year prospective study. Int J Clin Pract Suppl **2015**;183:43-52.

Krämer BK, Montagnino G, Krüger B, et al. Efficacy and safety of tacrolimus compared with ciclosporin – A in renal transplantation: 7-year observational results. Transpl Int 2016; 29:307-14.

Kidney transplant; adults; Sirolimus + Tacrolimus vs Mycophenolate Mofetil + Tacrolimus

Gao et al, 2018, Comparison of Sirolimus Combined With Tacrolimus and Mycophenolate Mofetil Combined With Tacrolimus in Kidney Transplantation Recipients: A Meta-Analysis [82]

The SR included the following 10 studies:

Augustine JJ, Chang PC, Knauss TC, Aeder MI, Bodziak KA, Schulak JA, et al. Improved renal function after conversion from tacrolimus/sirolimus to tacrolimus/mycophenolate mofetil in kidney transplant recipients. Transplantation **2006**;81: 1004e9.

Ciancio G, Burke GW, Gaynor JJ, Ruiz P, Roth D, Kupin W, et al. A randomized long-term trial of tacrolimus/sirolimus versus tacrolimus/mycophenolate versus cyclosporine/sirolimus in renal transplantation: three-year analysis. Transplantation **2006**;81:845e52.

Valente JF, Hricik D, Weigel K, Seaman D, Knauss T, Siegel CT, et al. Comparison of sirolimus vs. mycophenolate mofetil on surgical complications and wound healing in adult kidney transplantation. Am J Transplant **2003**;3:1128e34.

Flechner SM, Goldfarb D, Modlin C, Feng J, Krishnamurthi V, Mastroianni B, et al. Kidney transplantation without calcineurin inhibitor drugs: a prospective, randomized trial of sirolimus versus cyclosporine. Transplantation **2002**;74:1070e6.

Gallon L, Perico N, Dimitrov BD, Winoto J, Remuzzi G, Leventhal J, et al. Long-term renal allograft function on a tacrolimus-based, pred-free maintenance immunosuppression

comparing sirolimus vs. MMF. Am J Transplant **2006**;6:1617e23.

Gonwa T, Mendez R, Yang HC, Weinstein S, Jensik S, Steinberg S, et al. Randomized trial of tacrolimus in combination with sirolimus or mycophenolate mofetil in kidney transplantation:results at 6 months. Transplantation **2003**;75:1213e20.

Gralla J, Wiseman AC. Tacrolimus/sirolimus versus tacrolimus/mycophenolate in kidney transplantation: improved 3-year graft and patient survival in recent era. Transplantation **2009**;87: 1712e9.

Rummo OO, Carmellini M, Rostaing L, Oberbauer R, Christiaans MH, Mousson C, et al. ADHERE: randomized controlled trial comparing renal function in de novo kidney transplant

recipients receiving prolonged-release tacrolimus plus mycophenolate mofetil or sirolimus. Transpl Int **2017**;30:83e95.

Sampaio EL, Pinheiro-Machado PG, Garcia R, Felipe CR, Park SI, Casarini DE, et al. Mycophenolate mofetil vs. sirolimus in kidney transplant recipients receiving tacrolimus-based immunosuppressive regimen. Clin Transplant **2008**;22:141e9.

Srivastava A, Muruganandham K, Vinodh PB, Singh P, Dubey D, Kapoor R, et al. Post-renal transplant surgical complications with newer immunosuppressive drugs: mycophenolate mofetil vs. m-TOR inhibitors. Int Urol Nephrol **2010**;42:279e84.

Kidney transplant; adults; belatacept vs tacrolimus; tacrolimus vs. ciclosporin

Muduma et al, 2016, Indirect treatment comparison of belatacept versus tacrolimus from a systematic review of immunosuppressive therapies for kidney transplant patients [83]

The SR included the following 21 studies:

Abou-Jaoude MM, Naim R, Shaheen J, et al. Tacrolimus (FK506) versus cyclosporin microemulsion (Neoral) as maintenance immunosuppression therapy in kidney transplant recipients. Transplant Proc **2005**;37:3025-8.

Vincenti F, Friman S, Scheuermann E, et al. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. Am J Transplant **2007**;7:1506-14

Vincenti F, Charpentier B, Vanrenterghem Y, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT Study). Am J Transplant 2010;10:535-46.

Durrbach A, Pestana JM, Pearson T, et al. A phase III study of belatacept versus ciclosporin in kidney transplants from extended criteria donors (BENEFIT-EXT study). Am J Transplant 2010;10:547-57.

Abou-Jaoude MM, Irani-Hakime N, Ghantous I, et al. Cyclosporine microemulsion (Neoral) versus tacrolimus (FK506) as maintenance therapy in kidney transplant patients. Transplant Proc 2003;35:2748-9.

Busque S, Shoker A, Landsberg D, et al. Canadian multicentre trial of tacrolimus/azathioprine/steroids versus tacrolimus/mycophenolate mofetil/steroids versus neoral/mycophenolate mofetil/steroids in renal transplantation. Transplant Proc **2001**;33:1266-7.

Hardinger KL, Bohl DL, Schnitzler MA, et al. A randomized, prospective, pharmacoeconomic trial of tacrolimus versus ciclosporin in combination with thymoglobulin in renal transplant recipients. Transplantation **2005**;80:41-6.

Johnson C, Ahsan N, Gonwa T, et al. Randomized trial of tacrolimus (Prograf) in combination with azathioprine or mycophenolate mofetil versus cyclosporine (Neoral) with mycophenolate mofetil after cadaveric kidney transplantation. Transplantation

2000;69:834-41.

Margreiter R, European Tacrolimus vs Ciclosporin Microemulsion Renal Transplantation Study Group. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre study. Lancet **2002**;359:741-6.

Martin Garcia D, Martin Gago J, Mendiluce A, et al. Tacrolimus–basiliximab versus ciclosporin–basiliximab in renal transplantation 'de novo': acute rejection and complications.

Transplant Proc **2003**;35:1694-6.

Morris-Stiff G, Ostrowski K, Balaji V, et al. Prospective randomised study comparing tacrolimus (Prograf) and cyclosporin (Neoral) as primary immunosuppression in cadaveric renal transplants at a single institution: interim report of the first 80 cases. Transpl Int

1998;11(Suppl 1):S334-6.

Murphy GJ, Waller JR, Sandford RS, et al. Randomized clinical trial of the effect of microemulsion cyclosporin and tacrolimus on renal allograft fibrosis. Br J Surg **2003**;90:680-6.

Raofi V, Holman DM, Coady N, et al. A prospective randomized trial comparing the efficacy of tacrolimus versus cyclosporine in black recipients of primary cadaveric renal transplants. Am J Surg **1999**;177:299-302.

Silva HT, Yang HC, Abouljoud M, et al. One-year results with extended-release tacrolimus/MMF, tacrolimus/MMF and ciclosporin/MMF in de novo kidney transplant recipients. Am J Transplant 2007;7:595-608.

Toz H, Sen S, Sezi M, et al. Comparison of tacrolimus and cyclosporin in renal transplantation by the protocol biopsies. Transplant Proc **2004**;36:134-6.

Wang XH, Tang XD, Xu D. Tacrolimus vs CyA Neoral in combination with MMF and steroids after cadaveric renal transplantation. Transplant Proc **2000**;32:1702-3.

White SA, Jain S, Williams ST, et al. Randomized trial comparing Neoral and tacrolimus immunosuppression for recipients of renal transplants procured from different donor groups. Transplant Proc **2000**;32:600.

Williams ST, Knight AL, White SA, et al. Preliminary analysis of a randomized trial comparing microemulsion cyclosporine and tacrolimus for recipients of renal transplants from non-heart-beating donors. Transplant Proc **2000**;32:196.

Yang HC, Holman MJ, Langhoff E, et al. Tacrolimus/'low-dose' mycophenolate mofetil versus microemulsion cyclosporine/'lowdose' mycophenolate mofetil after kidney transplantation – 1-year follow-up of a prospective, randomized clinical trial. Transplant

Proc **1999**;31:1121-4.

Campos HH, Abbud Filho M. One-year follow-up of a Brazilian randomized multicenter study comparing tacrolimus versus ciclosporin in kidney transplantation. Transplant Proc **2002**;34:1656-8.

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Kidney transplant; adults; tacrolimus vs cyclosporine (MetS and CV risk factors)

Wenrui et al, 2014, Effects of tacrolimus and cyclosporine treatment on metabolic syndrome and cardiovascular risk factors after renal transplantation: a meta-analysis [96]

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Kidney transplant; adult; belatacept vs cyclosporine vs tacrolimus

Goring et al. 2014, A network meta-analysis of the efficacy of belatacept, cyclosporine and tacrolimus for immunosuppression therapy in adult renal transplant recipients [84]

SR included 31 RCTS of which 28 RCTs comparing tacrolimus with cyclosporine, and 3 comparing belatacept with cyclosporine:

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and patient survival in quadruple therapy with tacrolimus versus cyclosporin

in combination with prednisone, mycophenolate mofetil, and ATGAM

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Transplantation Society; 25–30 August **2002**, Miami, USA.

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El Haggan W, Barthe N, Vendrely B, et al. One year evolution of bone mineral density in kidney transplant recipients receiving tacrolimus versus cyclosporine. Transplant Proc **2002**;34:1817-18.

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Kidney transplant; patients over age 16; immunosuppressive drugs for maintenance

Cardoso Almeida et al, 2013, Safety of Immunosuppressive Drugs Used as Maintenance Therapy in Kidney Transplantation: A Systematic Review and Meta-Analysis [97].

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Kidney transplant; children, tacrolimus versus cyclosporine

Ravanshad et al, 2020, A Comparison Between Tacrolimus and Cyclosporine As Immunosuppression after Renal Transplantation in Children, A Meta-Analysis and Systematic Review [85]

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Kidney transplant; population age not reported, tacrolimus vs sirolimus

Liu et al, 2016, Sirolimus Versus Tacrolimus as Primary Immunosuppressant After Renal Transplantation: A Meta-Analysis and Economics Evaluation [86]

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Liver transplant; adults, tacrolimus versus cyclosporine

Muduma et al, 2016, Systematic Review and MetaAnalysis of Tacrolimus versus Ciclosporin as Primary Immunosuppression After Liver Transplant [89]

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Liver transplant; adults; immunosuppression monotherapy

Lan et al, 2014, Efficacy of immunosuppression monotherapy after liver transplantation: A meta-analysis [11]

The SR included the following 14 RCTs with 1814 patients (≥ 18 years old):

Samonakis DN, Mela M, Quaglia A, Triantos CK, Thalheimer U, Leandro G, Pesci A, Raimondo ML, Dhillon AP, Rolles K, et al. Rejection rates in a randomised trial of tacrolimus monotherapy versus triple therapy in liver transplant recipients with hepatitis C virus cirrhosis. Transpl Infect Dis. **2006**;8:3–12.

Margarit C, Bilbao I, Castells L, Lopez I, Pou L, Allende E, Escartin A. A prospective randomized trial comparing tacrolimus and steroids with tacrolimus monotherapy in liver transplantation: the impact on recurrence of hepatitis C. Transpl Int. **2005**;18:1336–1345.

Manousou P, Samonakis D, Cholongitas E, Patch D, O'Beirne J, Dhillon AP, Rolles K, McCormick A, Hayes P, Burroughs AK. Outcome of recurrent hepatitis C virus after liver transplantation in a randomized trial of tacrolimus monotherapy versus triple therapy. Liver Transpl. **2009**;15:1783–1791.

Benítez CE, Puig-Pey I, López M, Martínez-Llordella M, Lozano JJ, Bohne F, Londoño MC, García-Valdecasas JC, Bruguera M, Navasa M, et al. ATG-Fresenius treatment and low-dose tacrolimus: results of a randomized controlled trial in liver transplantation. Am J Transplant. **2010**;10:2296–2304.

Boillot O, Mayer DA, Boudjema K, Salizzoni M, Gridelli B, Filipponi F, Trunecka P, Krawczyk M, Clavien PA, Ducerf C, et al. Corticosteroid-free immunosuppression with tacrolimus following induction with daclizumab: a large randomized clinical study. Liver Transpl. **2005**;11:61–67.

Weiler N, Thrun I, Hoppe-Lotichius M, Zimmermann T, Kraemer I, Otto G. Early steroid-free immunosuppression with FK506 after liver transplantation: long-term results of a prospectively randomized double-blinded trial. Transplantation. **2010**;90:1562–1566.

Chau TN, Quaglia A, Rolles K, Burroughs AK, Dhillon AP. Histological patterns of rejection using oral microemulsified cyclosporine and tacrolimus (FK506) as monotherapy induction after orthotopic liver transplantation. Liver. **2001**;21:329–334.

Moench C, Barreiros AP, Schuchmann M, Bittinger F, Thiesen J, Hommel G, Kraemer I, Otto G. Tacrolimus monotherapy without steroids after liver transplantation--a prospective randomized double-blinded placebo-controlled trial. Am J Transplant. **2007**;7:1616–1623.

Eason JD, Nair S, Cohen AJ, Blazek JL, Loss GE. Steroid-free liver transplantation using rabbit antithymocyte globulin and early tacrolimus monotherapy. Transplantation. **2003**;75:1396–1399.

Belli LS, de Carlis L, Rondinara G, Alberti AB, Bellati G, De Gasperi A, Forti D, Idèo G. Early cyclosporine monotherapy in liver transplantation: a 5-year follow-up of a prospective, randomized trial. Hepatology. **1998**;27:1524–1529.

De Carlis L, Belli LS, Rondinara GF, Alberti A, Sansalone CV, Colella G, Aseni P, Slim AO, Forti D. Early steroid withdrawal in liver transplant patients: final report of a prospective randomized trial. Transplant Proc. **1997**;29:539–542.

Romani F, Belli LS, De Carlis L, Rondinara GF, Alberti A, Sansalone CV, Bellati G, Zavaglia C, Fesce E, Ideo G. Cyclosporin monotherapy (after 3 months) in liver transplant patients: a prospective randomized trial. Transplant Proc. **1994**;26:2683–2685.

Schlitt HJ, Barkmann A, Böker KH, Schmidt HH, Emmanouilidis N, Rosenau J, Bahr MJ, Tusch G, Manns MP, Nashan B, et al. Replacement of calcineurin inhibitors with mycophenolate mofetil in liver-transplant patients with renal dysfunction: a randomised controlled study. Lancet. **2001**;357:587–591.

Schmeding M, Kiessling A, Neuhaus R, Heidenhain C, Bahra M, Neuhaus P, Neumann UP. Mycophenolate mofetil monotherapy in liver transplantation: 5-year follow-up of a prospective randomized trial. Transplantation. **2011**;92:923–929.

Liver transplant; adults and children, tacrolimus versus cyclosporine

Haddad et al, 2006, Cyclosporin versus tacrolimus for liver transplanted patients [90]

The SR included the following 16 RCTs:

European FK506 Multicentre Liver Study Group. Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. Lancet 1994;344:423-8. [MEDLINE: 7520105]

Fisher RA, Ham JM, Marcos A, Shiffman ML, Luketic VA, Kimball PM, et al. A prospective randomized trial of mycophenolate mofetil with neoral or tacrolimus after orthotopic transplantation. Transplantation 1998;66(12):1616-21. [MEDLINE: 9884248]

Fisher RA, Stone JJ, Wolfe LG, Rodgers CM, Anderson ML, Sterling RK, et al. Four-year follow-up of a prospective randomized trial of mycophenolate mofetil with cyclosporine microemulsion or tacrolimus following liver transplantation. Clinical Transplantation 2004;18(4):436-72. [MEDLINE: 15233827]

Fung J, Abu-Elmagd K, Jain A, Gordon R, Tzakis A, Todo S, et al. A randomized trial of primary liver transplantation under immunosuppression with FK 506 vs cyclosporine. Transplantation Proceedings 1991;23(6):2977-83. [MEDLINE: 172133]

Fung JJ, Eliasziw M, Todo S, Jain A, Demetris AJ, McMichael JP, et al. The Pittsburgh randomized trial of tacrolimus compared to cyclosporine for hepatic transplantation. Journal of the American College of Surgeons 1996;183(2):117-25. [MEDLINE: 8696542]

Grazi GL, Levy G, Wu Y, Marotta P, Boillot O, Sanjuan F, et al. 12-month follow-up data from a randomized multicentre, prospective study of cyclosporine C2 monitoring versus tacrolimus in liver transplantation (LIS2T). American Journal of Transplantation 2004;4(Suppl 8):268.

Levy G, Villamil F, Samuel D, Sanjuan F, Grazi GL, Wu Y, et al. Results of LIS2T, a multicenter, randomized study comparing cyclosporine microemulsion with C2 monitoring and tacrolimus with C0 monitoring in de novo liver transplantation. Transplantation 2004;77(11):1632-8. [MEDLINE: 15201658]

Greig P, Lilly L, Scudamore C, Erb S, Yoshida E, Kneteman N, et al. Early steroid withdrawal after liver transplantation: the Canadian tacrolimus versus microemulsion cyclosporin A trial. 1-year follow-up. Liver Transplantation 2003;9(6):587-95. [MEDLINE: 12783400]

Kelly D, Jara P, Rodeck B, Lykavieris P, Burdelski M, Becker M, et al. Tacrolimus and steroids versus ciclosporin microemulsion, steroids, and azathioprine in children undergoing liver transplantation: randomised European multicentre trial. Lancet 2004;364:1054-61. [MEDLINE: 15380964]

Klupp J, Glanemann M, Bechstein WO, Platz KP, Langrehr JM, Keck H, et al. Mycophenolate mofetil in combination with tacrolimus versus neoral after liver transplantation. Transplantation Proceedings 1999;31:1113-4. [MEDLINE: 10083497]

Martin P, Busuttil RW, Goldstein RM, Crippin JS, Klintmalm GB, Fitzsimmons WE, et al. Impact of tacrolimus versus cyclosporine in hepatitis C virus-infected liver transplant recipients on recurrent hepatitis: a prospective randomized trial. Liver Transplantation 2004;10(10):1258-62. [MEDLINE: 15376310]

Muehlbacher FF, for the European Liver Transplantation Tacrolimus vs Cyclosporin Microemulsion Study Group. Tacrolimus versus cyclosporin microemulsion in liver transplantation: results of one-year follow-up. 10th ESOT & 12th ETCO Congress 2001, October 6-11, 2001, Lisboa, Portugal. 2001.

Muhlbacher F, European Liver Transplantation Tacrolimus vs Cyclosporin Microemulsion Study Group. Tacrolimus versus cyclosporin microemulsion in liver transplantation: results of a 3-month study. Transplantation Proceedings 2001;33(1-2):1339-40. [MEDLINE: 11267317]

O'Grady JG, Burroughs A, Hardy P, Elbourne D, Truesdale A, The UK and Republic of Ireland Liver Transplant Study Group. Tacrolimus versus microemulsified ciclosporin in liver transplantation: the TMC randomised controlled trial. Lancet 2002;360:1119-25. [MEDLINE: 12387959]

Rolles K, Davidson BR, Burroughs AK. A pilot study of immunosuppressive monotherapy in liver transplantation: tacrolimus versus microemulsified cyclosporin. Transplantation 1999;68(8):1195-209. [MEDLINE: 10551650]

Stegall M, Wachs ME, Everson G, Steinberg T, Bilir B, Shrestha R, et al. Prednisone withdrawal 14 days after liver transplantation with mycophenolate: a prospective trial of cyclosporine and tacrolimus. Transplantation 1997;64(12):1755-60. [MEDLINE: 9422416]

Therapondos G, Flapan AD, Dollinger MM, Garden OJ, Plevris JN, Hayes PC. Cardiac function after orthotopic liver transplantation and the effects of immunosuppression: a prospective randomized trial comparing cyclosporin (Neoral) and tacrolimus. Liver Transplantation 2002;8(8):690-700. [MEDLINE: 12149762]

Timmermann W, Erhard J, Lange R, Reck T, Kockerling F, Muller A, et al. A randomised trial comparing the efficacy and safety of tacrolimus with microemulsified cyclosporine after liver transplantation. Transplantation Proceedings 2002;34(5):1516-8. [MEDLINE: 12176463]

The US Multicentre FK506 Study Group. A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation. New England Journal of Medicine 1994;331(17):1110-5. [MEDLINE: 7523946]

Zervos XA, Weppler D, Fragulidis GP, Torres MB, Nery JR, Khan MF, et al. Comparison of tacrolimus with microemulsion cyclosporine as primary immunosuppression in hepatitis C patients after liver transplantation. Transplantation 1998;65(8):1044-6. [MEDLINE: 9583863]

Liver transplant; adults and children; tacrolimus vs cyclosporin

McAlister et al, 2006, Cyclosporin versus Tacrolimus as Primary Immunosuppressant After Liver Transplantation: A Meta-Analysis [91]

The SR included 16 RCTs.

European FK506 Multicentre Liver Study Group. Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. Lancet **1994**; 344: 423– 428.

The US Multicentre FK506 Study Group. A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation. N Engl J Med **1994**; 331: 1110–1115.

O'Grady JG, Burroughs A, Hardy P, Elbourne D, Truesdale A, The UK and Republic of Ireland Liver Transplant Study Group. Tacrolimus versus microemulsified ciclosporin in liver transplantation: The TMC randomised controlled trial. Lancet **2002**; 360: 1119– 1125.

Timmermann W, Erhard J, Lange R et al. A randomised trial comparing the efficacy and safety of tacrolimus with microemulsified cyclosporine after liver transplantation. Transplant Proc **2002**; 34: 1516– 1518.

Stegall M, Wachs ME, Everson G et al. Prednisone withdrawal 14 days after liver transplantation with mycophenolate: A prospective trial of cyclosporine and tacrolimus. Transplantation **1997**; 64: 1755– 1760.

Fisher RA, Ham JM, Marcos A et al. A prospective randomized trial of mycophenolate mofetil with neoral or tacrolimus after orthotopic transplantation. Transplantation **1998**; 66: 1616– 1621.

Fung J, Abu-Elmagd K, Jain A et al. A randomized trial of primary liver transplantation under immunosuppression with FK 506 vs cyclosporine. Transplant Proc **1991**; 23: 2977– 2983.

Grazi GL, Levy G, Wu Y et al. 12-month follow-up data from a randomized multicentre, prospective study of cyclosporine C2 monitoring versus tacrolimus in liver transplantation (LIS2T). Am J Transplant **2004**; 4 (Suppl 8): 268.

Greig P, Lilly L, Scudamore C et al. Early steroid withdrawal after liver transplantation: The Canadian tacrolimus versus microemulsion cyclosporin a trial: 1-year follow-up. Liver Transpl **2003**; 9: 587– 595.

Klupp J, Glanemann M, Bechstein WO et al. Mycophenolate mofetil in combination with tacrolimus versus neoral after liver transplantation. Transplant Proc **1999**; 31: 1113– 1114.

Therapondos G, Flapan AD, Dollinger MM, Garden OJ, Plevris JN, Hayes PC. Cardiac function after orthotopic liver transplantation and the effects of immunosuppression: a prospective randomized trial comparing cyclosporin (neoral) and tacrolimus. Liver Transpl **2002**; 8: 690– 700.

Kelly D, Jara P, Rodeck B et al. Tacrolimus and steroids versus ciclosporin microemulsion, steroids, and azathioprine in children undergoing liver transplantation: Randomised European multicentre trial. Lancet **2004**; 364: 1054– 1061.

Martin P, Busuttil RW, Goldstein RM et al. Impact of tacrolimus versus cyclosporine in hepatitis C virus-infected liver transplant recipients on recurrent hepatitis: a prospective randomized trial. Liver Transpl **2004**; 10: 1258– 1262.

Muhlbacher F. European Liver Transplantation Tacrolimus vs Cyclosporin Microemulsion Study Group. Tacrolimus versus cyclosporin microemulsion in liver transplantation: results of a 3-month study. Transpl Proc **2001**; 33: 1339– 1340.

Rolles K, Davidson BR, Burroughs AK. A pilot study of immunosuppressive monotherapy in liver transplantation: Tacrolimus versus microemulsified cyclosporin. Transplantation **1999**; 68: 1195– 1209.

Zervos XA, Weppler D, Fragulidis GP et al. Comparison of tacrolimus with microemulsion cyclosporine as primary immunosuppression in hepatitis C patients after liver transplantation. Transplantation **1998**; 65: 1044– 1046.

Lung transplant

Lung transplant; adults; tacrolimus vs cyclosporin

Penninga et al, 2013, Tacrolimus versus cyclosporin as primary immunosuppression for lung transplant recipients [92]

The SR included 3 RCTs

Hachem 2007

Hachem RR, Chakinala MM, Yusen RD, Aloush AA, Patterson GA, Trulock EP. A prospective randomized study of tacrolimus versus cyclosporine after lung transplantation. Journal of Heart & Lung Transplantation 2006;25(2 Suppl 1):S127.

Hachem RR, Yusen RD, Chakinala MM, Meyers BF, Lynch JP, Aloush AA, et al. A randomized controlled trial of tacrolimus versus cyclosporine after lung transplantation. Journal of Heart & Lung Transplantation 2007;26(10):1012-8. [MEDLINE: 17919621]

Treede 2012

Reichenspurner H, Glanville A, Christina A, Lama R, Carlos B, Marc E, et al. Complete 3 year analysis of a prospective randomized international multi-center investigator driven study comparing tacrolimus and cyclosporin A, both in combination with MMF and steroids after

lung transplantation in 249 patients [abstract]. Journal of Heart & Lung Transplantation 2008;27(2 Suppl 1):S205-6.

Reichenspurner H, Glanville A, Klepetko W, Lama R, Verleden GM, Bravo C, et al. One year complete follow-up of a prospective randomized international investigator driven study comparing Tac and CsA (+MMF/steroids) after lung transplantation in 274 patients [abstract]. Journal of Heart & Lung Transplantation 2005;24(2 Suppl 1):S82.

Reichenspurner H, Glanville A, Klepetko W, Lama R, Verleden GM, Bravo C, et al. Prospective randomized international multi-center investigator driven study comparing Tac and CsA (+MMF/steroids) after lung transplantation - interim analysis of 110 patients [abstract]. Journal of Heart & Lung Transplantation 2003;22(1 Suppl 1):S77.

Reichenspurner H, Klepetko W, Aboyoun C, Bravo C, Estenne M, Hirt S, et al. Final 3 year analysis of a prospective randomized international multicenter investigator driven study comparing Tac and CsA (+ MMF/steroids) after lung transplantation in 274 patients [abstract]. Journal of Heart & Lung Transplantation 2007;26(2 Suppl 1):S211.

Treede H, Glanville A, Klepetko W, Lama R, Bravo C, Estenne M, et al. Risk of bronchiolitis obliterans syndrome is twice as high in cyclosporine treated patients in comparison to tacrolimus 3 years after lung transplantation: Results of a prospective randomized international trial of 248 patients. Journal of Heart & Lung Transplantation 2010;29(2 Suppl 1):S39. [EMBASE: 70194242]

Treede H, Glanville AR, Klepetko W, Aboyoun C, Vettorazzi E, Lama R, 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. Journal of Heart & Lung Transplantation 2012;31(8):797-804. [PUBMED: 22554673]

Treede H, Klepetko W, Glanville A, Lama R, Bravo C, Estenne M, et al. Tacrolimus reduces the risk for bronchiolitis obliterans syndrome 3 years after lung-transplantation by 50% in comparison to cyclosporine in a prospective randomized international trial of 248 patients. Transplant International 2009;22(Suppl 2):54.

Zuckermann 2003

Klepetko W, Reichenspurner H, Zuckermann A, Meiser B, Birsan T, Treede H, et al. Prospective randomized two-center trial comparing cyclosporine A (CsA) versus tacrolimus

(Tac), in combination with mycophenolate mofetil (MMF) and steroids after lung transplantation (LTX) [abstract]. Journal of Heart & Lung Transplantation 1999;18(1):45-6.

Treede H, Klepetko W, Reichenspurner H, Zuckermann A, Meiser B, Birsan T, et al. Tacrolimus versus cyclosporine after lung transplantation: a prospective, open, randomized two-center trial comparing two different immunosuppressive protocols. Journal of Heart & Lung Transplantation 2001;20(5):511-7. [MEDLINE: 11343977]

Zuckermann A, Reichenspurner H, Birsan T, Treede H, Deviatko E, Reichart B, et al. Cyclosporine A versus tacrolimus in combination with mycophenolate mofetil and steroids as primary immunosuppression after lung transplantation: one-year results of a 2-center prospective randomized trial. Journal of Thoracic & Cardiovascular Surgery 2003;125(4):891-900. [MEDLINE: 12698153]

Zuckermann A, Reichenspurner H, Jaksch P, Treede H, Wisser W, Groetzner J, et al. Long term follow-up of a prospective randomized trial comparing tacrolimus versus cyclosporine in combination with MMF after lung transplantation. Journal of Heart & Lung Transplantation 2003;22(1 Suppl 1):S76-7.

Lung transplant; adults; tacrolimus vs cyclosporine

Fan et al, 2009, Tacrolimus Versus Cyclosporine for Adult Lung Transplant Recipients: A Meta-Analysis [93]

The SR included 3 RCTs.

Zuckermann A, Reichenspurner H, Birsan T, et al: Cyclosporine A versus tacrolimus in combination with mycophenolate mofetil and steroids as primary immunosuppression after lung transplantation: one-year results of a 2-center prospective randomized trial. J Thorac Cardiovasc Surg 125:891, 2003.

Keenan RJ, Konishi H, Kawai A, et al: Clinical trial of tacrolimus versus cyclosporine in lung transplantation. Ann Thorac Surg 60:580, 1995.

Hachem RR, Yusen RD, Chakinala MM, et al: A randomized controlled trial of tacrolimus versus cyclosporine after lung transplantation. J Heart Lung Transplant 26:1012, 2007.

Heart transplant

Heart transplant; adults and children, tacrolimus vs cyclosporine

Penninga et al, 2020, Tacrolimus versus cyclosporine as primary immunosuppression after heart transplantation: systematic review with meta-analyses and trial sequential analyses of randomised trials [94]

The SR included 11 RCTs; data from 11 RCTs were published in 25 publications:

Grimm M, Rinaldi M, Yonan NA et al (**2006**) Superior prevention of acute rejection by tacrolimus vs. cyclosporine in heart transplant recipients—a large European trial. Am J Transplant 6:1387–1397

Kobashigawa J, Patel J, Furukawa H et al (**2006**) Five-year results of a randomized, single-center study of tacrolimus vs microemulsion cyclosporine in heart transplant patients. J Heart Lung Transplant 25:434–439

Kobashigawa JA, Miller LW, Russell SD (**2004**) A randomized, prospective, multicenter comparison of tacrolimus, mycopholate mofetil (mmf) and steroids vs cyclosporine microemulsion, mmf and steroids vs tacrolimus, sirolimus and steroids in de novo cardiac transplantation recipients—6 month report. 3rd International Congress on Immunosuppression, San Diego

Kobashigawa JA, Patel JK, Furukawa H, Marquez A, Oeser BT, Laks H (**2004**) Five-year results of a randomized single center study of tacrolimus versus microemulsion cyclosporine in heart transplant patients. 3rd International Congress on Immunosuppression, San Diego

Kobashigawa JA, Miller LW, Russell SD et al (**2006**) Tacrolimus with mycophenolate mofetil (MMF) or sirolimus vs. cyclosporine with MMF in cardiac transplant patients: 1-year report. Am J Transplant 6:1377–1386

Meiser BM, Groetzner J, Kaczmarek I et al (**2004**) Tacrolimus or cyclosporine: which is the better partner for mycophenolate-mofetil in heart transplant recipients? Transplantation 78:591–598

Meiser BM, Scheersoi T, Pfeiffer M et al (**2000**) Comparison of trough level adjusted MMF application in combination with either cyclosporine or tacrolimus in a randomized study after heart transplantation. Transplantation 69:695

Meiser BM, Uberfuhr P, Fuchs A et al (**1996**) Comparison between tacrolimus (FK506) and cyclosporin A (CyA) after heart transplantation: a randomised, controlled clinical study. Zeitschr Kardiol 85 [Suppl 2]:133

Meiser BM, Uberfuhr P, Fuchs A et al (**1998**) Single-center randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of acute myocardial rejection. J Heart Lung Transplant 17:782–788

Reichart B, Meiser B, Vigano M et al (**1998**) European multicenter tacrolimus (FK506) heart pilot study: one-year results—European tacrolimus multicenter heart study group. J Heart Lung Transplant 17:1998

Pollock-BarZiv SMD, Dipchand AI, McCrindle BW, Nalli N, West LJ (**2005**) Randomized clinical trial of tacrolimus- vs cyclosporine-based immunosuppression in pediatric heart transplantation: preliminary results at 15-month follow-up. J Heart Lung Transplant 24:190–194

Rinaldi M, Pellegrini C, Martinelli L et al (**1997**) FK506 effectiveness in reducing acute rejection after heart transplantation: a prospective randomized study. J Heart Lung Transplant 16:1001–1010

Taylor DO, Barr ML, Radovancevic B et al (**1999**) A randomized, multicenter comparison of tacrolimus and cyclosporine immunosuppressive regimens in cardiac transplantation: decreased hyperlipidemia and hypertension with tacrolimus. J Heart Lung Transplant 18:336–345

Wang CH, Ko WJ, Chou N, Wang SS (**2004**) Efficacy and safety of tacrolimus versus cyclosporine microemulsion in primary cardiac transplant recipients: 6-month results in Taiwan. Transplant Proc 36:2384–2385

Wang CH, Ko WJ, Chou N, Wang SS (**2004**) Therapeutic drug monitoring of tacrolimus in cardiac transplant recipients: a comparison with cyclosporine neoral. Transplant Proc 36:2386–2387

Wang SS, Chou NK, Chi NH et al (**2008**) Heart transplantation under cyclosporine or tacrolimus combined with mycophenolate mofetil or everolimus. Transplant Proc 40:2607–2608

Groetzner J, Meiser BM, Schirmer J et al (**2001**) Tacrolimus or cyclosporine for immunosuppression after cardiac transplantation: which treatment reveals more side effects during long-term follow-up? Transplant Proc 33:1461–1464

Groetzner J, Meiser B, Schirmer J et al (**2001**) Tacrolimus/mycophenolate mofetil vs cyclosporine/mycophenolate mofetil: comparison of mycophenolate mofetil acid trough levels and coronary vasomotor function. J Heart Lung Transplant 20:191

Groetzner J, Meiser B, Schirmer J et al (**2002**) Tacrolimus/mycophenolate mofetil vs cyclosporine/mycophenolate mofetil: impact on infections following cardiac transplantation. J Heart Lung Transplant 21:120

Schirmer J, Meiser B, Kadner A et al (**2001**) Tacrolimus versus cyclosporine after HTX: comparison of long-term effects. J Heart Lung Transplant 20:191

Grimm M, Rinaldi M, Yonan NA (**2003**) Efficacy and safety of tacrolimus (TAC) vs. cyclosporine microemulsion (CME) in de novo cardiac transplant recipients: 6-month results. J Heart Lung Transplant 22:S92

Taylor DO, Barr ML, Radovancevic B et al (**1997**) A comparison of tacrolimus- and cyclosporine-based immunosuppression in cardiac transplantation. J Heart Lung Transplant 16:72

Petrakopoulou P, Anthopoulou L, Muscholl M et al (**2006**) Coronary endothelial vasomotor function and vascular remodeling in heart transplant recipients randomized for tacrolimus or cyclosporine immunosuppression. J Am Coll Cardiol 47:1622–1629

von Steinbüchel N, Limm H, Leopold C, Carr D (**2000**) Assessment of health-related quality-of-life in patients after heart transplantation under therapy with tacrolimus or cyclosporine. Transpl Int 13 [Suppl 1]:S609–S614

Reichart B, Meiser B, Vigano M et al (**2001**) European multicenter tacrolimus heart pilot study: three year follow-up. J Heart Lung Transplant 20:249–250

Heart transplant; adults and children; tacrolimus versus cyclosporine microemulsion

Fan et al, 2009, Tacrolimus Versus Cyclosporine Microemulsion for Heart Transplant Recipients: A Meta-analysis [95]

The SR included 7 RCTs.

Mehra M.R. et al. Ethnic disparity in clinical outcome after heart transplantation is abrogated using tacrolimus and mycophenolate mofetil-based immunosuppression. Transplantation. **2002**; 74: 1568-1573.

Meiser B.M. et al. Tacrolimus or cyclosporine: which is the better partner for mycophenolate mofetil in heart transplant recipients?. Transplantation. **2004**; 78: 591-598.

Wang C.H. et al. Efficacy and safety of tacrolimus versus cyclosporine microemulsion in primary cardiac transplant recipients: 6-month results in Taiwan. Transplant proc. **2004**; 36: 2384-2385.

Pollock-Barziv S.M. et al. Randomized clinical trial of tacrolimus- vs cyclosporine-based immunosuppression in pediatric heart transplantation: preliminary results at 15-month follow-up. J Heart Lung Transplant. **2005**; 24: 190-194.

Grimm M. et al. Superior prevention of acute rejection by tacrolimus vs. cyclosporine in heart transplant recipients--a large European trial. Am J Transplant. **2006**; 6: 1387-1397.

Kobashigawa J.A. et al. Tacrolimus with mycophenolate mofetil (MMF) or sirolimus vs. cyclosporine with MMF in cardiac transplant patients: 1-year report. Am J Transplant. **2006**; 6: 1377-1386.

Kobashigawa J.A. et al. Five-year results of a randomized, single-center study of tacrolimus vs microemulsion cyclosporine in heart transplant patients. J Heart Lung Transplant. **2006**; 25: 434-439.

Diabetes mellitus onset; adults; tacrolimus vs cyclosporine

Heisel et al, 2004, New Onset Diabetes Mellitus in Patients Receiving Calcineurin Inhibitors: A Systematic Review and Meta-Analysis [98]

The SR included 56 publications; 35 for kindey transplant patiens, 16 for liver transplant, 4 for heart transplant and 1 for lung transplant.

Kidney transplant studies:

Baid S, Rubin N, Delmonico FL et al. Tacrolimus-associated posttransplant diabetes in renal transplant reciepients: an analysis of risk factors and role of hepatitis C infection. American Transplant Congress, Abstract 57, **2002**.

Bloom RD, Rao V, Weng F, Grossman RA, Cohen D, Mange KC. Association of hepatitis C with posttransplant diabetes in renal transplant patients on tacrolimus. J Am Soc Nephrol **2002**; 13: 1374– 1380.

Van Duijnhoven EM, Christiaans MH, Boots JM, Nieman FH, Wolffenbuttel BH, Van Hooff JP. Glucose metabolism in the first 3 years after renal transplantation in patients receiving tacrolimus versus cyclosporine-based immunosuppression. J Am Soc Nephrol **2002**; 13: 213–220.

First MR, Gerber DA, Hariharan S, Kaufman DB, Shapiro R. Posttransplant diabetes mellitus in kidney allograft recipients: incidence, risk factors, and management. Transplantation **2002**; 73: 379– 386.

Johny KV, Nampoory MRN, Costandi JN et al. High incidence of post-transplant diabetes mellitus in Kuwait. Diabetes Res Clin Pract **2002**; 55: 123– 130.

Markell M, Salifu M, Stratilatova M et al. Comparison of risk for post-transplant diabetes (PTDM) in age-stratifies cyclosporine and tacrolimus-treated patients. American Transplant Congress, Abstract 208, **2002**.

Mysore S, Kumar A, Fa K et al. Steroid avoidance (SA) in kidney transplant recipients treated with simulect (Bmab), Neoral (CsA) and cellcept (MMF) – a randomized prospective controlled clinical trial. American Transplant Congress, Abstract 1012, **2002**.

Panz VRBR, Raal FJ, Maher H, Hsu HC, Joffe BI. Diabetogenic effect of tacrolimus in South African patients undergoing kidney transplantation. Transplantation **2002**; 73: 587– 590.

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