CHAPTER 4.2 Immunosuppressive maintenance therapy

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1 Introduction

Immunosuppressive therapy after kidney transplantation is carried out with a combination of drugs that affect the immune system at different points in the cascade of lymphocyte activation and proliferation. It is therefore useful to combine these drugs. In this way, the dose of the individual drug can be reduced and side effects avoided or at least reduced. Drugs used for maintenance immunosuppression include calcineurin inhibitors (tacrolimus, cyclosporin A), mycophenolate mofetil (MMF) or enteric-coated mycophenolate sodium as a more effective replacement for azathioprine, glucocorticoids and, for specific indications, mammalian target of rapamycin (mTOR) inhibitors such as everolimus and sirolimus. To avoid both under- and over-immunosuppression, the dosage of immunosuppressive drugs must be adjusted individually. This is usually done by measuring blood levels (therapeutic drug monitoring, see also Chapter 4.3) and adjusting the dosage of the drugs used accordingly. The *de novo* appearance of donor-specific HLA antibodies can be interpreted as a biomarker for under-immunosuppression. Various biomarkers are currently being investigated in transplantation medicine to enable even better individualisation of immunosuppressive therapy in the future.

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2 Tacrolimus

Tacrolimus is a more potent immunosuppressant than cyclosporin A. A randomised prospective study of the efficacy and safety of tacrolimus compared with cyclosporin A in paediatric kidney transplant recipients showed a lower rate of rejection, better GFR and also better graft survival at 4 years in the tacrolimus group (Filler et al 2005), so most paediatric kidney transplant centres internationally now use tacrolimus as the primary immunosuppressant.

Immediate-release tacrolimus (Prograf®, 0.5, 1 and 5 mg capsules; Modigraf®, 0.2 mg granules for oral suspension)

Dosage:
- Children < 40 kg: 0.3 mg/kg body weight (bw) per day p.o. in 2 divided doses,
- Children > 40 kg: 0.2 mg/kg bw per day p.o. in 2 divided doses.
- Start within 6 hours of transplantation. Tacrolimus dose adjustment according to whole blood trough level 12 hours after intake immediately before morning administration.
- In the UK, tacrolimus is prescribed (initial dosing) at 0.15 mg/kg twice daily with a maximum initial dose of 5 mg twice daily for all children and adolescents, regardless of weight (Dudley et al 2021)

Target trough levels (measured in whole blood by mass spectrometry), if given in combination with MMF or azathioprine:
- Day 0–21: 8–12 ng/mL
- Day 22–month 6: 7–10 ng/mL
- Month 6–12: 5–8 ng/mL (depending on overall immunosuppression and individual immunological risk)
- After month 12: 5–8 ng/mL

UK target tacrolimus levels:
- Day 0–56: 8–12 ng/mL
- Day 57–365: 5–8 ng/mL
- Beyond the first year, tacrolimus levels may be individualized (e.g., 3–5 ng/mL)

Dose adjustments: Usually in 25% increments, with a maximum of 2 dose adjustments per week (long half-life of approximately 16 hours). However, in the early post-transplant period and in individual cases, however, daily dose adjustments may be required.

Living kidney donation: Tacrolimus dosing may be started 5 days before transplant; target trough level before transplant: 8–12 ng/mL.

Tacrolimus Monitoring by Mini-AUC (Limited Sampling Strategy (LSS))
Indication: Patients, in whom trough levels in the target range cannot be achieved with a relatively high body weight-based dose (in children < 40 kg, > 0.3 mg tacrolimus/kg per day; in children > 40 kg > 0.2 mg tacrolimus/kg per day); i.e., tacrolimus rapid metabolisers, infants and young children. In this situation, a more accurate determination of tacrolimus exposure using a mini-AUC should be performed to avoid toxicity or underexposure.

Practical implementation: A light, low-fat breakfast is permitted on the day of the mini-AUC; no large meal should be eaten in the first hour after taking tacrolimus. A blood sample is taken (via an indwelling intravenous catheter) before tacrolimus administration (C_0) and 1 (C_1), 2 (C_2) and 4 hours (C_4) after oral administration.

Algorithm for calculating the mini-AUC:
Tacrolimus-AUC = 4.15390 + 3.17385 x C0 + 1.28131 x C1 + 0.75475 x C2 + 5.35301 x C4 [Filler G et al 2002]

Target tacrolimus exposure (target AUC)
The target tacrolimus exposure depends on the time period post-transplant and the immunological or infectious risk:
Week 1–4 (early post-transplant period): 150–200 µg · h/L (in conjunction with an MPA-AUC > 40 mg · h/L) [Scholten EM et al., 2005, Lee and Butani 2007]
Month 1–3: 120–150 µg · h/L
> Month 3 (stable period): 75–150 µg · h/L

Modigraf® 0.2 mg and 1 mg for suspension preparation
For young children who cannot swallow Prograf® capsules, use Modigraf® granules for oral suspension. Modigraf® should be dissolved in a minimum of 2 mL

and a maximum of 50 mL of liquid. This suspension can also be used for administration by nasogastric tube.

Intravenous administration of tacrolimus
Only in exceptional cases, when oral or enteral therapy by gastric tube is not possible, intravenous continuous infusion of 0.06 mg/kg per day over 24 hours. During this time, the tacrolimus blood levels should be between 10–25 ng/mL.

Premedication for intravenous administration due to possible anaphylactic reaction:
Clemastine (Tavegil®) 0.04 mg/kg; Esomeprazole (Nexium®), dosage: patients aged 1–11 years or 10–20 kg b.w.: 10 mg esomeprazole per day; patients > 20 kg b.w.: 10–20 mg esomeprazole per day, patients aged 12–18 years: 20–40 mg esomeprazole per day as a short infusion over 30 minutes.

- Avoid intravenous administration of tacrolimus for more than 3 days due to increased risk of PTLD.
- After intravenous administration, give the first oral dose 12 hours after stopping the infusion.
- If repeat intravenous therapy is required, 20% of the previous p.o. dose should be given.

Common side effects of tacrolimus
Metabolic acidosis, hyperkalaemia, hypomagnesaemia, hyperuricaemia, bone pain, impaired renal function, hypertension, neurological complications (headaches, tremor), gastrointestinal complaints, blood count changes, diabetes mellitus (dose-dependent, generally reversible), etc. (see Drug product information package insert).

- Caution in EBV-seronegative children < 5 years of age receiving a kidney transplant from an EBV-positive donor, as there is an increased risk of PTLD in the event of seroconversion.
- Caution: Paradoxical increase in tacrolimus exposure (trough levels) with severe diarrhoea (gastroenteritis); therefore, close monitoring of tacrolimus trough levels is recommended.

Relative contraindications (cautions) for tacrolimus: Diabetes mellitus (DM) type I (possibly also type II) or disturbed glucose tolerance (consider also DM in first-degree relatives), cardiomyopathy or prolonged QT interval.

Pharmacokinetics

- Rapid absorption after oral administration, t_{max} 1.5–3 hours.
- Take at least 1 hour before or 2 hours after a meal (not with grapefruit juice!).
- Note large inter-individual variability in bioavailability, therefore individualised dosing based on measured blood levels is required.
- 95% of tacrolimus is bound to erythrocytes, 5% bound to plasma proteins. Only the unbound fraction is pharmacologically active, and this is subject to considerable variability without changing of the concentration in whole blood. For example, the amount of unbound tacrolimus is increased in anaemia, hypalbuminaemia or uraemia. Caution: Toxic reactions are possible despite whole blood concentrations in the therapeutic range.
- Half-life approximately 16–43 hours depending on the amount of unbound fraction. Steady state is only reached after approx. 2–3 days, therefore no more than 2 dose changes per week.

Frequency of trough level monitoring:
There is some between centre variability here and clinician discretion is required, however, as a guide:

- First week post-transplant: once daily (in some cases twice daily)
- 2nd and 3rd week: every other day
- Months 2 to 6: once a week
- Beyond 6 months: every other week (or less often)

- Dose-related side effects respond to dose reduction only after a few days.
- Dose changes are usually in 25% increments of the initial dose.
- Tacrolimus clearance decreases in the first few months posttransplant, and dose reductions of up to 33% of the initial dose may be necessary.
- Hepatic metabolism and biliary excretion. With cholestasis, the proportion of pharmacologically predominantly inactive metabolites in the measured blood level is approximately 20%.
- Metabolism via the cytochrome P450 3A4 and 3A5 system in the liver. Decreased metabolism in severe hepatic impairment.

Possible mechanisms of drug interactions:
Induction or inhibition of the cytochrome P450 3A4/3A5 system by other drugs, thereby lowering or increasing blood levels (see Drug product information package insert).

- Drugs that increase tacrolimus blood levels include: Diltiazem, clotrimazole, fluconazole, ketoconazole, danazol, amoxicillin, macrolide antibiotics (erythromycin, clarithromycin, but not azithromycin or roxithromycin), imipenem, ibuprofen.
- Drugs that lower tacrolimus blood levels include: Rifampicin, carbamazepine, phenobarbital, phenytoin.

Prolonged-release and extended-release tacrolimus formulations
A prolonged-release tacrolimus formulation ((Advagraf™ in Europe, Astagraf™ in the United States) for older children and adolescents allows once daily dosing, which reduces the pill burden and may improve adherence. Comparative pharmacokinetic studies have shown that stable paediatric transplant recipients can be converted from immediate-release to prolonged-release-tacrolimus at the same total daily dose, using the same therapeutic drug monitoring method.

Extended-release, melt-dose tablets (LCP-Tac, Envarsus XR; Cary, NC: Veloxis USA, Inc.) is currently under investigation also in paediatric patients. LCP-Tac is a new formulation with improved bioavailability and lower maximum concentrations compared to immediate release tacrolimus. Preliminary data suggest that the daily dose of LCP tacrolimus should be 0.7 (70%) of the previous dose of immediate-release or extended-release tacrolimus.

3 Mycophenolate mofetil (MMF, CellCept®)

MMF dosage for co-medication with tacrolimus
Some centres use the same body surface-based dose of MMF for all paediatric patients, some centres stratify as follows:

Below 6 years of age:
Day 0–14: 800 mg/m² body surface area (BSA) per day in 2 divided doses p.o.;
After day 14: 600 (up to 900) mg/m² per day in 2 divided doses

Above 6 years of age:
Day 0–14: 1200 mg/m² per day in 2 divided doses;
After day 14: 600 (up to 900) mg/m² per day in 2 divided doses.

In the UK, MMF is given for all ages as part of an early steroid withdrawal regimen as follows (Dudley et al 2021):

Day 0–14: 1200 mg/m² per day in 2 divided doses;
After day 14: 600 mg/m² per day in 2 divided doses.

MMF dosage for co-medication with cyclosporine:
Below 6 years of age:
Day 0–14: 1200 mg/m² BSA per day in 2 doses p.o.
After day 14: 1200 mg/m² per day in 2 divided doses.

Above 6 years of age:
Day 0–14: 1800 mg/m² BSA per day in 2 doses p.o.
After day 14: 1200 mg/m² per day in 2 divided doses.

Living donor kidney transplantation: MMF may be started 5 days pre-transplant, MMF dose see above; reduce MMF dose by 50% for dialysed patients (poorer tolerability).

MMF suspension and i.v.-administration
- MMF suspension for young children who cannot swallow capsules and or tablets; the suspension also allows for more flexible dosing. If the MMF dose cannot be administered within ± 10% of the desired dose with 250 mg capsules, the use of MMF suspension should also be considered.
- If oral administration is not possible, MMF can be given intravenously on a temporary basis.

MMF-related side effects
Leukopenia: Reduce the MMF dose by 50% if leukopenia < 4000/µl or neutropenia < 1600/µl. If leukopenia < 2000/µl or neutropenia < 1300/µl, discontinue MMF treatment.

Diarrhoea: If diarrhoea persists for more than 3 days and is not due to another cause (e.g., infection), consider giving 3–4 times daily (same total daily dose).

If this is not successful consider reducing the MMF dose by 50% (consider increasing the (methyl)prednisolone dose at the same time). If the diarrhoea does not resolve, consider switching to everolimus, sirolimus or azathioprine, depending on the immunological risk.

If the MMF dose is reduced within the first 3 months after transplantation (e.g., due to diarrhoea), dual immunosuppression with CNI and steroids should be intensified (e.g., steroid dose doubled) to prevent rejection. If diarrhoea is severe, intravenous methylprednisolone should be considered.

Relative contraindications to MMF:
- Serological evidence of active HIV, hepatitis B or C infection
- Patients with severe systemic infection
- Leukopenia < 2500/µl or anaemia < 5 g/dL.

Absolute contraindication: If pregnancy is planned, MMF should be stopped at least 12 weeks before conception. Consider switching to azathioprine.

Therapeutic drug monitoring of MPA, the active moiety of MMF
Target pre-dose MPA plasma level (12 hours after oral intake of MMF): 1.5–4 mg/L (by mass spectrometry).
Pre-dose MPA plasma levels are a rather imprecise marker of MPA exposure (MPA-AUC_{0-12}); the determination of a mini-AUC of MPA by a limited sampling strategy (LSS) is preferable.

Mini-AUC of MPA using a limited sampling strategy (LSS)
Significance: MPA underexposure is associated with a higher incidence of acute rejection episode.
Time points: Day 7 post-transplant, day 14–21 post-transplant, months 3, year 1 (during the annual transplant follow-up visit), in the event of a relevant change in immunosuppressive co-medication
Blood sampling (via indwelling intravenous catheter): before MMF administration (C_0), at 0.5 ($C_{0,5}$) and at 2 hours (C_2) after oral MMF administration.

Algorithms for calculating the MPA-AUC:
MMF therapy in conjunction with tacrolimus: MPA-AUC =
$10.01391 + 3.94791 \times C_0 + 3.24253 \times C_{0.5} + 1.0108 \times C_2$; $r^2 = 0.81$

MMF therapy in conjunction with cyclosporine: MPA-AUC = 18.609 + 4.309 x C_0 + 0.536 x $C_{0.5}$ + 2.148 x C_2; r^2 = 0.72.

MMF therapy without calcineurin inhibitor co-medication: use the same algorithm as for tacrolimus co-medication.

Target MPA-AUC: > 40 mg*h/L (in conjunction with a calcineurin inhibitor)

Enteric-coated mycophenolate sodium (Myfortic®)
Mycophenolate mofetil (CellCept®) and enteric-coated (delayed-release) mycophenolate sodium (EC-MPS) (Myfortic®) are not equivalent. Mycophenolate mofetil 500 mg is considered equivalent to mycophenolate sodium 360 mg. In adolescent patient on MMF and marked upper gastrointestinal side effects, switch from MMF to EC-MPS at a molecularly equivalent dose is an option. The rate of lower gastrointestinal side effects (diarrhoea) of MMF and EC-MPS is comparable. Because of the delayed-release formulation of EC-MPS and the highly variable absorption of the drug and day-to-day fluctuation in enterohepatic cycling of MPA, therapeutic drug monitoring with a limited sampling strategy over the first 2 hours after dosing, as recommended for MMF, is not possible for EC-MPS; 3–4 or more concentration measures over the first 6 hours after dosing are necessary (Bergan et al 2021).

4 Methylprednisolone (Urbason®) or prednisolone (Solu-Decortin H®)

4 mg methylprednisolone is equivalent to 5 mg prednisolone. The dose information below refer to methylprednisolone.

Day 0: 300 mg/m^2 or 10 mg/kg b.w. as a short infusion over 30 minutes, at least 1 hour before reperfusion of the renal graft.
Day 1: 48 mg/m^2 p.o. in 2 doses
Days 2–7: 32 mg/m^2 p.o. in 2 doses
Week 2: 24 mg/m^2 p.o. in 1 dose in the morning
Week 3–4: 16 mg/m^2 p.o. in 1 dose in the morning
Week 5–6: 8 mg/m^2 p.o. in 1 dose in the morning
From week 7: 3–4 mg/m^2 p.o. in 1 ED, maximum 5 mg per day
(round doses up or down to a practical tablet size).

In the UK; prednisolone is prescribed as below (Dudley et al 2021):
Day 0: 600 mg/m² (maximum dose 500 mg) at induction or reperfusion of the renal graft.
Day 1–2: 60 mg/m² (maximum dose 60 mg) p.o. once daily
Days 3–7: 40 mg/m² (maximum dose 40 mg) p.o. once daily
Days 8–14: 30 mg/m² (maximum dose 30 mg) p.o. once daily
Days 15–21: 20 mg/m² (maximum dose 20 mg) p.o. once daily
Days 21–28: 10 mg/m² (maximum dose 10 mg) p.o. once daily
Days 29–90: 10 mg/m² (maximum dose 10 mg) p.o. on alternate days
Day 91 onwards: 5 mg/m² (maximum dose 5 mg) p.o. on alternate days

For early or late steroid withdrawal see Chapter 5.1.

5 Cyclosporin A (Sandimmun Optoral®)

Second-line calcineurin inhibitor, if tacrolimus is contraindicated or not tolerated.

Dosage:
Day 0: 400–500 mg/m² body surface area per day in 2 divided doses p.o., starting 6 hours after transplantation.
From day 1 onwards: 300 mg/m² BSA per day in 2 single doses p.o.
Dose adjustment according to whole blood trough levels (C_0) and 2 hour-blood levels (C_2).
If given intravenously, give 30% of the single oral dose over 4 hours (caution: nephrotoxicity).

Target whole blood trough level (by mass spectrometry):
Months 0–3: 120–200 ng/mL
Beyond month 4: 80–160 ng/mL

Target range 2 hour-level (C_2):
Weeks 0–4: 800–1400 ng/mL
Months 1–6: 800–1200 ng/mL
Months 7–12: 600–1000 ng/mL
Beyond month 12: 400–800 ng/mL

6 Azathioprine (Imurek®)

Indication
In case of intolerance or contraindication to MMF in patients at low immunological risk. Infants receiving MMF are particularly susceptible to MMF-related adverse events such as poor appetite or diarrhoea. In the UK, azathioprine is routinely prescribed as part of a steroid-maintenance regimen (Dudley et al 2021).

Dosage
2 mg azathioprine/kg per day as a single dose.
Approximately 10% of patients have reduced activity of the enzyme thiopurine methyltransferase (TPMT) due to genetic polymorphism. Azathioprine metabolism is impaired, particularly in homozygous carriers, and there is an increased risk of myelotoxic effects. Testing for a TPMT deficiency is recommended for those with evidence of myelotoxicity (Ma et al 2016) and may be considered before starting therapy.

Side effects
Myelosuppression (especially with concomitant drugs such as olsalazine, mesalazine and sulphasalazine, which inhibit the enzyme TPMT). Concomitant use of azathioprine and drugs with myelosuppressive properties such as penicillamine and cytostatics may increase myelotoxic effects and should be avoided. If allopurinol, oxipurinol or thiopurinol are taken concomitantly, the dose of azathioprine should be reduced to a quarter of the normal dose. Special care is needed when using azathioprine with tubocurarine and succinylcholine as the effect of depolarising muscle relaxants may be increased. There is an increased risk of myelosuppression when azathioprine is used with trimethoprim/sulfamethoxazole, cimetidine, indomethacin or the ACE inhibitor captopril.

7 Everolimus (Certican®)

mTOR inhibitor that inhibits activated T cells. Everolimus is usually given with low-dose CNI.
Half-life approx. 28 hours, steady state reached after approx. 4 days

Indication: MMF intolerance in patients with standard or high immunological risk, CNI toxicity, PTLD/malignancies, intolerance to primary immunosuppression. Some centres switch patients at high risk of CMV infection (donor CMV seropositive, recipient CMV seronegative) to low-dose CNI and everolimus at 4 weeks post-transplant, because everolimus has a direct anti-CMV effect.

Relative contraindications: High proteinuria, hyperlipidaemia, risk of impaired wound healing. Significantly impaired renal function (GFR < 35 ml/min/1.73 m^2).

Contraindication: If pregnancy is planned, everolimus therapy should be discontinued at least 12 weeks prior to conception.

Dosage:
If co-administered with *tacrolimus:*
Infants, children and adolescents: 2 x 2 mg/m^2 BSA per day p.o.

If co-administered with *cyclosporine:*
Infants and young children: 2 x 0.8 mg/m^2 BSA per day or 0.05 mg/kg per day p.o.
Adolescents: 2 x 0.75 mg absolute per day p.o.

Target trough levels:
If co-medicated with calcineurin inhibitor: Months 2–6: 3–8 ng/mL; from month 7: 2–5 ng/mL
Without calcineurin inhibitor: 6–8 ng/mL

Adverse reactions:
Leukopenia; reduce dose of everolimus by 50% if leukopenia < 4000/µl or neutropenia < 1600/µl. Discontinue everolimus if leukopenia < 2000/µl or neutropenia < 1300/µl. Hyperlipidaemia, impaired wound healing, proteinuria, myelosuppression, aphthae.

Cyclosporine dose and target trough levels in combination with everolimus:
Cyclosporine dose:
Weeks 1 and 2 posttransplant: 400 mg/m² BSA per day p.o. in 2 divided doses
Week 3 and beyond: 200 mg/m² BSA per day p.o. in 2 divided doses

Cyclosporine target trough level
Cyclosporine trough levels:
Weeks 1 and 2: 200–250 ng/mL
Week 3 to month 6: 50–100 ng/mL
Beyond month 6: 30–75 ng/mL

Tacrolimus dose and target trough levels in combination with everolimus:
Children < 40 kg: 0.3 mg/kg per day in 2 divided doses p.o.,
Children ≥ 40 kg: 0.2 mg/kg per day in 2 divided doses p.o.

Tacrolimus target trough levels:

Time post-transplant	Tacrolimus target trough level (ng/mL) in combination with everolimus	Tacrolimus trough level (ng/mL) in combination with MMF or azathioprine
Weeks 0–3	5–8	8–12
Week 4 – month 4	4–6	7–10
Months 4–6	4–6	7–10
Months 6–12	2–4	5–8
Beyond month 12	2–4	5–8

In patients at increased immunological risk, tacrolimus trough levels should be aimed at the upper target range. For standard or low immunological risk patients, the sum of the tacrolimus trough level and the everolimus trough level should be approximately 10 ng/mL in the first 6 months post-transplant.

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