Chapter 3: Long-Term Maintenance Immunosuppressive Medications

3.1: We suggest using the lowest planned doses of maintenance immunosuppressive medications by 2–4 months after transplantation, if there has been no acute rejection. *(2C)*
3.2: We suggest that CNIs be continued rather than withdrawn. *(2B)*
3.2: If prednisone is being used beyond the first week after transplantation, we suggest prednisone be continued rather than withdrawn. *(2C)*

CNI, calcineurin inhibitor.

Background

Using high doses of immunosuppressive medications early after transplantation when the risk of acute rejection is highest, but then reducing doses later when the risk of acute rejection is lower, has been used empirically as the mainstay of long-term immunosuppressive medication management since the advent of kidney transplantation. However, there are no randomized trials testing this therapeutic strategy.

Rationale

- If low-dose CNI was not implemented at the time of transplantation, CNI dose reduction >2–4 months after transplantation may reduce toxicity yet prevent acute rejection.
- RCTs show that CNI withdrawal leads to increased acute rejection, without altering graft survival.
- RCTs show that steroid withdrawal more than 3 months after transplantation increases the risk of acute rejection.
- Different immunosuppressive medications have different toxicity profiles and patients vary in their susceptibility to adverse effects.

CNI dose reduction

Although there are no RCTs comparing dose reduction with maintaining initial high doses and target levels, this dose reduction strategy has been successfully adopted in most RCTs. The assumption is that the immune system gradually adapts to the foreign antigens in the graft, and that the need for immunosuppression is thereby reduced. There is great individual variation, and some patients with a high risk for immunological complications (acute and chronic rejection) may need to continue on higher doses of immunosuppression compared to the majority of patients.

A range of trial designs have directly and indirectly compared the effects of different CNI dose, usually as measured by different target levels. In RCTs in which CNI has been combined with mTORi (eight RCTs, 1178 patients), as either low-dose mTORi with standard CNI or higher mTORi and lower CNI, standard-dose CNI was associated with lower rates of acute rejection (RR 0.67) but lower GFR (9 mL/min/1.73 m^2). Such trials are clearly confounded, but do suggest that variable CNI exposure leads to competing benefits and harm. Graft function may be improved by minimizing CNI, leading to reduced CAI, but may be worsened if acute rejection occurs.

The strongest evidence comes from RCTs that have directly compared low vs. high CNI doses (four RCTs, 1256 patients). In these trials, there were no differences in outcomes (including graft survival) except for GFR, which favored low CNI in two of the four studies. Low-quality evidence suggests no net benefit or harm of low- vs. standard-dose CNI (see Evidence Profile and accompanying evidence in Supporting Tables 27–29 at http://www3.interscience.wiley.com/journal/118499698/toc).

Using indirect comparisons of trials of different CNI doses, the risk of diabetes and graft loss was reduced with lower doses. However, there are sparse data on the relative effects of specific CNI target values from head-to-head trials, apart from the broad category of high vs. low.

Low-dose CNI maintenance

The notion of complete CNI withdrawal, after the peak period for immunologically mediated complications (3 months) is attractive, considering the long-term complications of CNI exposure. However, RCTs of complete CNI withdrawal show that, although some small benefit in graft function results, the risk of acute rejection is significantly increased without a clear benefit on improved graft survival (eight RCTs, 1891 patients). As described above, CNI toxicity can be minimized by administering low-dose CNI, while ensuring sufficient immunosuppression is provided. Moderate-quality evidence shows a net harm to CNI withdrawal (see Evidence Profile and accompanying evidence in Supporting Tables 30–32).

Steroid withdrawal

Long-term steroid administration may lead to hypertension, NODAT, osteoporosis, fractures and dyslipidemia, all

Table 2: Toxicity profiles of immunosuppressive medications

Adverse effect	Steroids	CsA	Tac	mTORi	MMF	AZA
New-onset diabetes mellitus	↑	↑	↑↑	↑		
Dyslipidemias	↑	↑		↑↑		
Hypertension	↑↑	↑↑	↑			
Osteopenia	↑↑	↑	(↑)			
Anemia and leucopenia				↑	↑	↑
Delayed wound healing				↑		
Diarrhea, nausea/vomiting			↑		↑↑	
Proteinuria				↑↑		
Decreased GFR		↑	↑			

AZA, azathioprine; CsA, cyclosporine A; GFR, glomerular filtration rate; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitor(s); Tac, tacrolimus.
↑ indicates a mild-moderate adverse effect on the complication.
↑↑ indicates a moderate-severe adverse effect on the complication.
(↑) indicates a possible, but less certain adverse effect on the complication.

of which may affect graft survival. However, long-term steroid administration prevents acute rejection and immunologically mediated graft loss. In six RCTs of 1519 KTRs, steroid withdrawal led to increased acute rejection, without a clear benefit for improved patient or graft outcomes, except for a reduction in total cholesterol levels in the steroid-withdrawal group. Low-quality evidence suggests net harm of steroid withdrawal (see Evidence Profile in Supporting Table 33).

Individual tailoring of immunosuppressive medication to the patient's risk profile

Although tailoring immunosuppressive therapies to the individual patient's risk profile (both risk for acute rejection and risk for adverse effects) is considered standard practice, there are few studies that suggest how this should be done. There are some data on the relative incidence and severity of adverse effects, collected in clinical trials and observational studies (Table 2). However, standard definitions have not been used to define adverse effects of immunosuppressive medications. Data collection has generally relied on spontaneous investigator reporting, which can lead to serious under-reporting. For these and other reasons, the quality of data on adverse drug effects is very low.

Withdrawal of a specific drug in an individual patient with an adverse drug effect may or may not result in clinical improvement. Nevertheless, drug withdrawal or substitution is a logical course of action if the benefits (reducing symptoms) appear to outweigh the harm (acute rejection).

- NODAT may be caused or exacerbated by corticosteroids, tacrolimus, mTORi and, to a lesser extent, by CsA. In patients with impaired glucose tolerance or NODAT, steroid reduction or withdrawal may be beneficial. If this is not sufficient, a switch from tacrolimus to CsA-ME may be considered.
- Dyslipidemia may be caused or exacerbated by corticosteroids, CsA and especially by mTORi. Patients with significant dyslipidemia before or after transplantation should probably avoid mTORi.
- Hypertension may be caused or exacerbated by corticosteroids, CsA and, to a lesser extent, tacrolimus. In patients, who are not normotensive after transplantation, despite adequate antihypertensive treatment, reduction or withdrawal of steroid or CNI may be beneficial.
- Osteopenia may be caused or exacerbated by corticosteroids, and possibly CsA and tacrolimus. Steroid reduction or withdrawal may be helpful.
- Bone marrow suppression may be caused or exacerbated by MMF, azathioprine and mTORi. Monitoring of the mycophenolic acid (MPA) area under the concentration–time curve (AUC), and probably reduction of the dose of MMF or azathioprine, are the first suggested actions in case of anemia or leucopenia.
- Delayed wound healing may be caused or exacerbated by mTORi. Patients who have delayed wound healing on an mTORi may benefit from switching the mTORi to a CNI.
- Diarrhea, nausea and vomiting may be caused or exacerbated by MMF and tacrolimus. Monitoring MPA, AUC and tacrolimus C_0 levels may help to reduce these complications. However, it is important to rule out treatable, underlying causes other than the immunosuppressive medication. In a recent study, about half of the patients were cured by treatment of an infection (58). Only after ruling out other underlying causes should reducing the MMF, or changing MMF to azathioprine, be considered.
- Proteinuria may be caused or exacerbated by mTORi. Consider avoiding an mTORi in a patient with persistent urinary protein excretion of more than 500–1000 mg/day.
- Decreased kidney function may be caused or exacerbated by CsA and tacrolimus. See Chapter 7 regarding treatment of chronic CNI nephrotoxicity.