Chapter 2: Initial Maintenance Immunosuppressive Medications

2.1: We recommend using a combination of immuno-suppressive medications as maintenance therapy including a CNI and an antiproliferative agent, with or without corticosteroids. (1B)

2.2: We suggest that tacrolimus be the first-line CNI used. (2A)

2.2.1: We suggest that tacrolimus *or* CsA be started before or at the time of transplantation, rather than delayed until the onset of graft function. (2D tacrolimus; 2B CsA)

2.3: We suggest that mycophenolate be the first-line antiproliferative agent. (2B)

2.4: We suggest that, in patients who are at low immunological risk and who receive induction therapy, corticosteroids could be discontinued during the first week after transplantation. (2B)

2.5: We recommend that if mTORi are used, they should not be started until graft function is established and surgical wounds are healed. (1B)

CNI, calcineurin inhibitor; CsA, cyclosporine A; mTORi, mammalian target of rapamycin inhibitor(s).

Background

Maintenance immunosuppressive medication is a long-term treatment to prevent acute rejection and deterioration of graft function. Treatment is started before or at the time of transplantation, and the initial medication may or may not be used with induction therapy. Agents are used in combination to achieve sufficient immunosuppression, while minimizing the toxicity associated with individual agents. Since the risk for acute rejection is highest in the first 3 months after transplantation, higher doses are used during this period, and then reduced thereafter in stable patients to minimize toxicity. In these guidelines, antiproliferative agents refer specifically to azathioprine or mycophenolate (either MMF or enteric-coated mycophenolate sodium [EC-MPS]).

Corticosteroids have traditionally been a mainstay of maintenance immunosuppression in KTRs. However, adverse effects of corticosteroids have led to attempts to find maintenance immunosuppression regimens that do not include corticosteroids. Terminology has often been confusing, but 'steroid avoidance' is used here to refer to protocols that call for the initial use of corticosteroids, which are then withdrawn sometime during the first week after

transplantation. In contrast, 'steroid-free' protocols do not routinely use corticosteroids as initial or maintenance immunosuppression. 'Steroid withdrawal' refers to protocols that discontinue corticosteroids after the first week post-transplant. Similar definitions have been applied to the use of CNIs.

Rationale

- Used in combination and at reduced doses, drugs that have different mechanisms of action may achieve additive efficacy with limited toxicity.
- The earlier that therapeutic blood levels of a CNI can be attained, the more effective the CNI will be in preventing acute rejection.
- There is no reason to delay the initiation of a CNI, and no evidence that delaying the CNI prevents or ameliorates DGF.
- Compared to CsA, tacrolimus reduces the risk of acute rejection and improves graft survival during the first year of transplantation.
- Low-dose tacrolimus minimizes the risk of new-onset diabetes after transplantation (NODAT) compared to higher doses of tacrolimus.
- Compared with placebo and azathioprine, mycophenolate reduces the risk of acute rejection; there is some evidence that mycophenolate improves long-term graft survival compared with azathioprine.
- Avoiding the use of maintenance corticosteroids beyond the first week after kidney transplantation reduces adverse effects without affecting graft survival.
- Mammalian target of rapamycin inhibitors (mTORi) have not been shown to improve patient outcomes when used either as replacement for antiproliferative agents or CNIs, or as add-on therapy, and they have important short- and long-term adverse effects.

Calcineurin Inhibitors

Timing of initiation

In theory, the earlier that therapeutic blood levels of a CNI can be attained, the more effective the CNI is likely to be in preventing acute rejection. However, there are also theoretical reasons that the early use of CNIs might increase the incidence and severity of DGF. As a result, RCTs have compared early vs. delayed CNI initiation after transplantation. In three RCTs (N = 338), there was no difference

in the incidence of DGF with early vs. delayed CsA initiation. In five RCTs (N = 620), there were no differences in acute rejection, graft failure or kidney function in early vs. delayed CsA initiation. Altogether, these RCTs suggest that there is no reason to delay the initiation of CsA. There are no similar studies using tacrolimus, but it is suggested that, with a regimen including induction and reduced-dose tacrolimus, the risk for early CNI nephrotoxicity is minimized and optimal prevention of acute rejection can be achieved. There is moderate-quality evidence that, in CsA-containing regimens, there is no net benefit or harm of early vs. delayed CsA; the evidence is of low quality for CNIs in general, because of a lack of data for tacrolimus-containing regimens (see Evidence Profile and accompanying evidence in Supporting Tables 11–13 at http://www3.interscience.wiley.com/journal/118499698/toc).

Tacrolimus vs. cyclosporine

A meta-analysis of RCTs reported reduced acute rejection and better graft survival with tacrolimus compared to CsA (22). For every 100 patients treated for the first year with tacrolimus rather than CsA, 12 would be prevented from having acute rejection, two would be prevented from having graft failure, but five would develop NODAT. The RCTs in the meta-analysis combined studies of patients receiving the original CsA preparation and cyclosporine A microemulsion (CsA-ME). This study also showed that lower tacrolimus were associated with higher relative risk of graft loss, while higher levels of tacrolimus were associated with an increased risk for NODAT.

Randomized controlled trials comparing tacrolimus with CsA-ME using concomitant azathioprine and corticosteroids, but no induction, have shown reduced acute rejection with tacrolimus; for example, 22% vs. 42% at 12 months, respectively (p < 0.001) (23). The difference in acute rejection between the two CNIs could no longer be observed with concomitant induction and MMF instead of azathioprine; for example 4% vs. 6%, for tacrolimus vs. CsA-ME, respectively (24) or 7% vs. 10% at 6 months, respectively (25) when C_2 monitoring of CsA was also employed. Furthermore, there is evidence that subclinical rejection (acute rejection changes in protocol biopsy not indicated by a change in kidney function) is more effectively prevented by tacrolimus and MMF compared to CsA and MMF; 15% vs. 39% (p < 0.05) (26).

A very large multicenter RCT in de novo KTRs (n = 1645; the Symphony study) showed superior graft function, better prevention of acute rejection (12.3%) and superior graft survival (96.4%) at 12 months with daclizumab induction and low-dose tacrolimus (C_0 3–7 ng/mL). The comparator groups included low-dose CsA and low-dose sirolimus, both with daclizumab induction and standard-dose CsA without induction. All patients received MMF (2 g/day) and corticosteroids (27).

There is no uniform definition of NODAT used in the literature. Therefore, the reported incidences of NODAT vary to a great extent. Studies reporting a difference between tacrolimus and CsA in the incidence of NODAT, impaired glucose tolerance, or the use of antidiabetic treatment, favor CsA; for example 17% vs. 9% (p < 0.01; tacrolimus vs. CsA) (25). Others have found lower incidences and no significant difference (24,28). One reason for the variation in findings may be differences in the use of corticosteroids as maintenance medication and treatment of acute rejection. Indeed, use of a steroid-free regimen has been associated with a lower incidence of NODAT (29).

Overall, there is moderate-quality evidence for a net benefit of tacrolimus vs. CsA (see Evidence Profile and accompanying evidence in Supporting Tables 8–10). There is no clear evidence of differences in terms of patient mortality, incidence of malignancy, infection, delayed onset of graft function or blood pressure. There is evidence that cholesterol, low-density lipoprotein cholesterol (LDL-C) (but not high-density lipoprotein cholesterol [HDL-C]), acute rejection and graft loss are higher with CsA vs. tacrolimus. However, there is also evidence that NODAT is more common with tacrolimus than CsA, so that there is clear trade-off in the different patient-relevant outcomes with these two CNIs.

Dosing of CNI

Dosing of CNI is important, but is a relatively under-researched area. There are few trials that compare the effects of different doses or target levels of the same drugs in which baseline immunosuppression is kept constant across both arms. Indirect comparisons and case series have shown that high doses might increase adverse events and low doses might increase acute rejection. Standard-dose tacrolimus may be defined as it is recommended by the producer (Astellas Pharma, Tokyo, Japan); the dose achieving 12-h trough levels (C_0) of 10 (5–15) ng/mL. A low-dose tacrolimus has recently been introduced in the Symphony study and was defined as C_0 of 5 (3–7) ng/mL (27). Standard-dose CsA may be defined as the dose achieving C_0 of 200 (150–300) ng/mL (30) or C_2 1400–1800 ng/mL early and 800–1200 ng/mL later after transplantation (25). Low-dose CsA has been used in some recent clinical studies (27,30) and was defined as achieving C_0 of 75 (50–100) ng/mL.

Mycophenolate Mofetil

Randomized controlled trials have shown that MMF (2 or 3 g, but not 1 g daily) is significantly better in preventing acute rejection than placebo. This was seen in studies using steroids as concomitant medication and either tacrolimus or CsA (31,32). For example, acute rejection at 6 months was reduced from 55% with placebo to 30% and 26% with MMF 2 and 3 g daily doses (31). There were 5–7% improvements of graft survival at 12 months with MMF, but the studies were not powered to evaluate

this difference. There were no significant differences in patient survival, graft function, malignancy, NODAT, infection rates or gastrointestinal adverse events such as diarrhea, although there might be evidence that higher doses of MMF cause more diarrhea than lower doses of MMF. More bone marrow suppression was seen with MMF compared to placebo. Overall, there is moderate-quality evidence of a net benefit of MMF over placebo to prevent acute rejection, but low-quality evidence for all graft and patient outcomes overall (see Evidence Profile and accompanying evidence in Supporting Tables 14–15).

Randomized controlled trials comparing outcomes between MMF vs. azathioprine have shown some important inconsistencies. In a recent meta-analysis of 19 trials and 3143 patients, MMF was associated with less acute rejection (RR 0.62, 95% confidence interval [CI] 0.55–0.87) and improved graft survival (RR 0.76, 0.59–0.98) (33). However, there were no differences in patient survival or kidney function (33). There were also no differences in major adverse effects (e.g. infections, CMV, leucopenia, anemia and malignancies) between MMF and azathioprine, but diarrhea was more common with MMF (RR 1.57; 95% CI 1.33–28.6) (33). In several RCTs, MMF reduced the incidence of acute rejection at 6 months; for example from 36% with azathioprine (100–150 mg/day) to 20% with MMF (2 g/day) using CsA and steroids as concomitant medication (34) and from 38% to 20% with the addition of concomitant induction (35). Also, a reduction in acute rejection from 29% to 7% was seen with concomitant tacrolimus, steroids and induction in using MMF 2 g, but not 1 g (36). Conversely, another study showed a smaller reduction in acute rejection at 6 months from 23% with azathioprine (100–150 mg/day) to 18% with MMF (2 g/day), a difference that was not statistically significantly (37). These patients were also treated with CsA-ME and steroids. However, using the same concomitant medication, including CsA-ME, other investigators found a significant reduction of acute rejection at 12 months from 27% with azathioprine to 17% with MMF 2 g (38). In a third arm of this latter study, patients received MMF from day 0 to day 90 and thereafter azathioprine, and the acute rejection rate was the same, 17%, as for those receiving MMF for the entire study period of 12 months. Thus, high-quality evidence finds a net benefit of MMF over azathioprine to prevent acute rejection, but moderate-quality evidence exists for patient-level outcomes. Because of the substantially increased cost of MMF compared with azathioprine and increased side effects compared with azathioprine, there is no clear net benefit, but a decision based upon trade-offs is required (see Evidence Profile and accompanying evidence in Supporting Tables 16–18).

Analyses of observational registry data have shown either a small 4% improvement in graft survival with MMF vs. azathioprine (39) or, more recently, no improvement in graft survival (40). However, for a number of reasons, the re-sults of retrospective analyses of observational registry data need to be interpreted cautiously (41).

MMF Compared to EC-MPS

One RCT compared MMF 2 g daily vs. EC-MPS 1.44 g daily with CsA-ME, steroids, with or without induction (42). There were no significant differences in acute rejection (24% vs. 23%), patient or graft survival or rates of malignancy or infection. There was no difference in rates of gastrointestinal disorders (80% vs. 81%) despite the fact that the potential reduction of gastrointestinal adverse events has been the incentive for the development of EC-MPS. Another study (43) tested the crossover between the two formulations and also found no differences in any of the outcome parameters. A summary of the RCTs on MMF vs. EC-MPS is available in Supporting Tables 25–26.

Steroid avoidance or withdrawal

The rationale for minimizing corticosteroid exposure is compelling and provided by well-established risks of osteoporosis, avascular necrosis, cataracts, weight gain, diabetes, hypertension and dyslipidemia. Such risk is not constant, and varies with comorbidities such as preexisting metabolic syndrome and age. On the other hand, corticosteroids have been the mainstay of immunosuppression for KTRs for decades, and trial data evaluating minimization of steroid exposure are sparse compared to the large number of trials that have included steroids in the regimens being evaluated. In addition, many of the adverse effects attributed to corticosteroids were observed with high doses. Whether or not low doses (e.g. 5 mg prednisone per day) that are commonly used for long-term maintenance immunosuppression are associated with major adverse effects is less clear.

Randomized controlled trials have shown that the withdrawal of corticosteroids from maintenance immunosuppressive medication regimens, when carried out weeks to months after transplantation, is associated with a high risk of acute rejection (44,45). More recent studies have examined whether steroid avoidance (discontinuing corticosteroids within the first week after transplantation) can be done safely. These studies have generally shown higher rates of acute rejection, but lower rates of long-term adverse effects (12,29,46–48). Unfortunately, these trials have had design limitations that make the interpretation of their results difficult.

Overall, there is moderate-quality evidence for trade-offs between steroid avoidance or withdrawal compared to steroid maintenance, with a higher rate of steroid-sensitive acute rejections but avoidance of steroid-related adverse effects (see Evidence Profile and accompanying evidence in Supporting Tables 19–21).

Mammalian target of rapamycin inhibitor(s)

Regimens using the mTORi sirolimus and everolimus have been compared to a number of different regimens in clinical trials in KTRs, for example as replacement for azathioprine, MMF or CNIs, and in combination with CNIs (both at high and low dose). The use of mTORi in the setting of chronic allograft injury (CAI) is described in Chapter 7. mTORi have a number of adverse effects that limit their use, including dyslipidemia and bone marrow suppression (49–56). Although they have been compared with many other regimens in RCTs, in none of these RCTs was there an improvement in graft or patient survival.

mTORi as replacement for antiproliferative agents

In a meta-analysis of 11 RCTs with 3966 KTRs evaluating mTORi as replacement for azathioprine or MMF, there were no differences in graft or patient survival (57). mTORi appear to reduce the risk of acute rejection (RR 0.84, 95% CI 0.71–0.99; p = 0.04), but graft function and LDL-C outcomes were generally better with azathioprine or MMF (57).

mTORi as replacement for CNIs

In a meta-analysis of eight RCTs with 750 patients evaluating mTORi as replacement for CNIs, there were no differences in acute rejection, CAN, graft survival or patient survival (57). mTORi were associated with higher glomerular filtration rate (GFR), but also with increased risk of bone marrow suppression and dyslipidemia (49,57).

mTORi in combination with CNIs

The combined use of mTORi and CNIs should be avoided, because these agents potentiate nephrotoxicity, particularly when used in the early post-transplant period (57). When used as long-term maintenance, mTORi have been used in two different regimens in combination with CNIs. Eight RCTs involving 1360 patients have evaluated low-dose mTORi and standard-dose CNI compared with standard-dose mTORi and low-dose CNI (57). Overall, the low-dose, CNI-standard dose mTORi regimen is associated with a 30% increased risk of rejection with no difference in graft survival. An additional 10 RCTs involving 3175 patients have evaluated the effects of high- vs. low-dose mTORi in combination with fixed-dose CNI, showing less rejection but lower GFR with higher-dose therapy, but no improvement in patient outcomes.

Moderate-quality evidence for sirolimus finds net harm without improved graft or patient survival; CNI toxicity is potentiated when used in combination with sirolimus (see Evidence Profile and accompanying evidence in Supporting Tables 22–24).

Research Recommendations

- A long-term RCT that has adequate statistical power to detect differences in acute rejection and major adverse events is needed to determine whether the benefits of steroid avoidance outweigh the harm.