Chapter 5: Monitoring Immunosuppressive Medications

5.1: We recommend measuring CNI blood levels (*1B*), and suggest measuring at least:
- **every other day during the immediate post-operative period until target levels are reached *(2C)*;**
- **whenever there is a change in medication or patient status that may affect blood levels *(2C)*;**
- **whenever there is a decline in kidney function that may indicate nephrotoxicity or rejection. *(2C)***

5.1.1: We suggest monitoring CsA using 12-h trough (C_0), 2-h post-dose (C_2) or abbreviated AUC. *(2D)*

5.1.2: We suggest monitoring tacrolimus using 12-h trough (C_0). *(2C)*

5.2: We suggest monitoring MMF levels. *(2D)*

5.3: We suggest monitoring mTORi levels. (*2C*)

AUC, area under concentration–time curve; CNI, calcineurin inhibitor; CsA, cyclosporine A; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitor(s).

Background

Cyclosporine A has a narrow therapeutic window and variable absorption characteristics, even with the microemulsion formulation (CsA-ME). Therefore, the CsA dosage must be individualized to find a balance between high levels that may be toxic and low levels that may be insufficient to prevent rejection. Variability in absorption is greatest during the first 4 h after dosing, and during the first few weeks after transplantation. There are no RCTs comparing monitoring with no monitoring; however, the fact that different target levels influence efficacy and toxicity is strongly suggestive that monitoring is beneficial (82).

The C_0 is the measured concentration after the dosing interval (e.g. 12 h after dosing if the dosing interval is every 12 h), C_2 the concentration 2 h after dosing and $AUC_{0–4}$ is the AUC during the first 4 h after dosing. Fewer data are available to guide blood-level monitoring of tacrolimus compared to CsA. MPA is the active metabolite of MMF and the molecule generally used for monitoring of MMF. The half-lives of mTORi are greater than 48 h, making anything but monitoring of C_0 unlikely to be useful. There are no clinical methods for monitoring corticosteroid blood levels.

There continues to be widespread interest in pharmcodynamic assays for monitoring immunosuppressive medication and adjusting dosing accordingly. However, there are insufficient data demonstrating the efficacy of pharmacodynamic monitoring.

Rationale

CsA monitoring

Cyclosporine A absorption may increase substantially during the first 1–2 weeks after transplantation. In KTRs, absorption stabilizes by approximately the end of the first month. Common factors that might change CsA blood levels are the use of other drugs affecting cytochrome P450 3A4 (CYP3A4) and/or P-glycoprotein, diet and intestinal motility. There are no studies comparing one schedule of monitoring vs. another; however, tailoring the monitoring schedule to the expected absorption variability is a reasonable, empirical approach. There are no data to suggest whether monitoring blood levels in stable patients beyond the first few weeks after transplantation is beneficial.

There are few RCTs to define optimal target blood levels. Target levels should generally reflect the overall immunosuppressive medication regimen, and therefore target levels may vary accordingly. For example, it may be prudent to use lower early posttransplant target blood levels when an induction antibody is used. In any case, blood-level monitoring with predetermined targets can be effectively used to balance the risk for rejection with the risk for toxicity.

Cyclosporine A C_0 has often been used for therapeutic drug monitoring, but C_0 does not correlate closely with $AUC_{0–4}$. Blood levels at 2 h after drug administration (C_2), instead of at 12 h (C_0 if the dosing interval is 12 h), have been used to monitor CsA therapy with the CsA-ME formulation. Although C_2 levels appear to correlate more closely with $AUC_{0–4}$, no differences have been observed in two RCTs between the incidence of acute rejection, graft loss or adverse events whether patients were monitored by $AUC_{0–4}$ or C_2 or C_0 levels (83). Overall, a very low strength of evidence suggests uncertain trade-offs between using C_0 or C_2 (see Evidence Profile and accompanying evidence in Supporting Tables 34–36 at http://www3.interscience.wiley.com/journal/118499698/toc); therefore, either C_0 or C_2 blood levels are acceptable.

Tacrolimus monitoring

There have been fewer studies with blood-level monitoring for tacrolimus than for CsA. However, available evidence

suggests that the benefits and harm of therapeutic drug monitoring for these two CNIs are similar. Tacrolimus C_0 is correlated with the AUC of tacrolimus (generally $r > 0.8$) (84,85). This relationship appears to be better during the first few months after transplant than later; however, there is high inter- and intrapatient variability. As is the case for CsA, there are no studies comparing one schedule of monitoring tacrolimus vs. another; however, tailoring the monitoring schedule to the expected absorption variability is a reasonable, empirical approach. Target levels for tacrolimus should reflect the patient's overall immunosuppressive drug regimen and risk for rejection, with higher targets early after transplantation, and lower targets later.

MMF monitoring

The AUC is widely regarded as the best measure of overall drug exposure of MPA. Pharmacokinetic studies have demonstrated poor correlation of C_0 with the full AUC (86). The inability of single-point sampling strategies, particularly those in the early postdose period, to effectively predict the AUC has resulted in a number of studies investigating the use of limited sampling strategies. These strategies use a number of sampling points, usually between 2 and 4 h, to predict the AUC (87).

Mycophenolate mofetil has conventionally been administered at a fixed dose without routinely monitoring MPA blood levels. Therapeutic drug monitoring during MMF therapy remains controversial. Available studies have serious limitations and report conflicting results. Early after transplantation, MPA AUC might be correlated with a lower risk of acute rejection than C_0, but this is supported by only a single RCT (88). There are two RCTs showing that targeting different MPA AUC resulted in different rates of acute rejection (89,90). Several observational studies have also shown that MPA AUC early after transplantation correlates with acute rejection (91–93). Most studies showed little correlation between MPA pharmacokinetic parameters and adverse effects (89–93). In addition, there is an important intrapatient variability of MPA pharmacokinetics and an increasing number of different drug combinations, which may affect MPA bioavailability. The proposed therapeutic window of the MPA $AUC_{0–12}$ (30–60 μg·h/mL) is restricted to the early posttransplant period and when MMF is used in combination with CsA. In general, MPA C_0 1.0–3.5 mg/L correlates with MPA $AUC_{0–12}$ (30–60 μg·h/mL) in patients treated with CsA. A summary of the RCTs about MPA monitoring is provided in Supporting Table 37.

mTORi monitoring

The pharmacokinetics of mTORi sirolimus and everolimus differ substantially (94). Although the time to peak concentration is similar between the two mTORi, the half-life of sirolimus is about 60 h in adults (10–24 in children), while that of everolimus is 28–35 h (95,96). In general, C_0 correlates well with $AUC_{0–12}$ (95,97). Therefore, C_0 is probably adequate for monitoring mTORi levels. There are limited observational data suggesting that mTORi C_0 correlate with adverse effects (98). There are no RCTs demonstrating that monitoring mTORi C_0 reduces acute rejection or adverse effects.

Research Recommendations

- RCTs with adequate statistical power are needed to determine the cost-effectiveness of therapeutic drug monitoring for all immunosuppressive agents with measurable blood levels.