Appendix

Guidance for the Investigator on Dose Adjustment for Patients in the Concentration-Controlled Arm of the Study

Throughout the study at six time points after transplantation (day 3, day 10, week 4, month 3, month 6, and month 12) abbreviated AUCs will be determined for patients in the concentration-controlled group. Each abbreviated AUC consists of three samples, drawn within the first 2 hr (0, 30 min, and 120 min) after MMF administration. Adult patients and pediatric patients treated with cyclosporin A and MMF should be fasted; however, pediatric patients treated with tacrolimus and MMF should receive a meal before their AUC assessments are performed. From the three MPA values obtained during patient sampling a 12-hr MPA-AUC will be predicted using a defined algorithm. The target MPA-AUC for all time points is between 30 and 60 mg/L h. We ask you to stay as close to the middle of this range as possible, that is, 45 mg/L h.

What factors should be kept in mind in adjusting the dose:

1. MPA exposure changes over time, especially within the first 3 months. This means that even without a dose change exposure may increase over time. It is extremely difficult to predict this change in PK over time for individual patients. It is advised that the dose should be changed if the measured AUC is more than 20% from the desired 45 mg/L h. It is likely that, for a significant number of patients, the dose of MMF will increase after measurement of the first two or three AUCs, whereas dose reductions are likely after measurement of the final AUCs.
2. Cyclosporin A-treated patients need more MMF to reach target, compared with tacrolimus-treated patients. We ask you to start MMF treatment in adult patients with 1000 mg twice daily and pediatric patients with 600 mg/m^2 twice daily. In patients treated with cyclosporin A considerable dose increase may be necessary in the first 2 or 3 AUCs to reach target. We expect patients on tacrolimus co-treatment to reach the target with fewer or smaller dose increases. However, for individual patients this general rule may not seem to be applicable, and we ask you to take a close look at the AUC values obtained and change the dose if the target is not reached. Please take care in documenting on eCRF whether a patient is being treated with cyclosporin A or tacrolimus.
3. Low- versus high-risk patients. In some transplanted patients the risk of acute rejection is higher than in others. The steering committee has discussed the need for other target values for MPA-AUC in certain subsets of patients. However, in the literature there is insufficient data to establish other target values for high- or low-risk patients. The range of values from 30 to 60 mg/L h is broad, and will leave you the flexibility to aim for the higher part of this range (e.g., in African Americans) or the lower part of the range (e.g., in older patients in whom the risk of rejection is low and the risk of infection high).
4. Influence of delayed graft function. In patients with impaired renal function the free fraction of the drug is higher. It has been shown that the increase in free MPA-AUC is most pronounced in patients with delayed graft function. If it is true that the free fraction of the drug is the best predictor of biologic activity of the drug, the higher free fraction during delayed graft function may be useful, as delayed graft function is often associated with an increased risk of acute rejection.
5. Methodology causes a small bias. The use of EMIT methodology will result in MPA concentrations that are 10% to 20% higher than those using HPLC. The bias is larger when there are high levels of Ac-MPAG, which could be anticipated in patients with renal dysfunction.
6. In the fixed-dose group MPA concentrations should not be taken into account. Patients in the fixed-dose group will be sampled at the same time points (0, 30 min, 120 min) as patients in the concentration-controlled group. The results of the MPA measurements should not be available to clinical staff and should not influence the treatment of fixed-dose patients at any time throughout the trial. Please carefully record the times blood samples are collected.
7. Logistics influence choice of sampling day. It is important to reach target levels as soon as possible. Therefore, we have included two sampling days within the first 2 weeks. Samples for the first time point (day 3) can be collected after the patient has had 5 doses of MMF. Remember to consider the impact of assay turnaround time. If samples are drawn on a Friday (day 3) and determined only on Monday or Tuesday of the following week, this may delay implementation of a dose change. Similar considerations apply to day 10 sampling, especially if there has been a delay in implementing a dose change from the Day 3 AUC. Centers that have to ship their samples to a regional laboratory must also consider these logistic factors, as a delay in shipping the samples or in sample analysis could have serious implications for the timing of dose changes.