TACROLIMUS LEVELS IN LIVER TRANSPLANT; INDIAN STUDY

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Introduction:
Tacrolimus

- Is a product of soil fungus *streptomyces tsukubaensis*.
- Is a hydrophobic macrolide antibiotic (mol.wt.821Da) with an immunosuppressive potency (10-100 fold greater than cyclosporin on molar basis).
- Has high absorption rate and variable between individuals and may be influenced by diet.
- Has half life of 4-41 hours.
- Decreases lymphocyte proliferation when complexed with immunophilin FK binding protein (FK BP12).

In liver transplant, immunosuppression using single agent has become standard practice. Tacrolimus (FK 506) has emerged as a key agent because of properties of prophylaxis against acute acellular rejection (ACR) as well as its ability to treat early rejection.

Between 3 and 89% of oral tacrolimus doses reaches the systemic circulation as a result of variations in hepatic and intestinal clearance and there is a corresponding 30 fold range in dosage requirement in stable liver graft recipients. For these reasons, there is no direct, real time assay of immunosuppression, nor any adequate dynamic biomarker of its efficacy and side effects, monitoring of tacrolimus in blood is essential. Monitoring also checks for patient non-compliance and provides reassurance during management.

Dosage is adjusted so that tacrolimus trough levels (before taking proGraf dose /FK 506) falls within the therapeutic range (5-15 ng/ml) because acute rejection and toxic side effects. (e.g.: nephrotoxic, neuropathy, seizures, tremors, diabetes, hypertension, hyperkalemia, headache, insomnia) are increasingly prevalent at the respective lower and upper extremes of this range.

Material and Methods:
Four patients (3 adults and 1 Child) who had undergone liver transplants were followed for 94 days. These patients were on proGraf (Tacrolimus /FK 506) 1 mg BD-3.5 mg BD. The does was initiated on second day of liver transplant. In the immediate post operative period, due to cover of I.V. Methylprednisolone, chance of ACR is little.
The whole blood was collected in EDTA and Plain vacationers before proGraf dose (trough levels), on 4th, 10th, 17th, 21th, 25th, 31th, 35th, 52nd, 60th and 94th day post liver transplant.

Urea and Creatinine were estimated from serum by using urease, Jeff kinetic methods respectively.

Tacrolimus from whole blood was extracted by using myethylene chloride. (Digestive Reagent consist of bacterial Protein kinase K and subtilisin in Tris buffer containing seponin) and then measured using ELISA kit from DiaSorin. Inc.

**RESULTS:**

- In the period of three months, two patients developed hypertension (both were having premorbid hypertension), One developed diabetes mellitus (had premorbid diabetes mellitus). All three adult patients developed mild tremors.

- The tacrolimus levels for all patients was in the range of 3.6 – 14 ng/ml.

- The tacrolimus levels were reflective of the dose of proGraf.

- Urea levels were elevated for first 15 days post liver transplant in two adult patients and reached to normal levels in 30 days.

- Creatinine levels in two patients were peaked on day 4 post liver transplant and reached to normal levels by day 10 of post lever transplant.

- One patient had elevated urea & creatinine, which was related to high levels of tacrolimus and was decreased, as well as preexisting hepato-renal syndrome.

- In the child patient urea and creatinine was within normal limits.

- Flexibility dosing in the early period, post liver transplant so that by day 5 (when methylprednisolone is withdrawn) tacrolimus levels of 8-12 ng/ml are aimed for but our results were in the range of 8.6 – 16 ng/ml. Then dose of proGraf was reduced from 2 mgBD to 1 mgBD and the 6.6 ng/ml mean tacrolimus level was achieved.

- At the time of discharge from hospital the mean tacrolimus level was 10.8 ng/ml with minimum dosage. (2-7.0 mg/day)

**CONCLUSION:**

Tacrolimus (FK506) is effective in the early liver transplant period when the risk of ACR is highest.

The nephrotoxic side effect (elevated levels of urea and creatinine) of tacrolimus was countered by lowering the dose of proGraf (tacrolimus/FK506).

Single drug immunosuppression is optimal in patients undergoing liver transplant.
TACROLIMUS MEAN DOSES AND LEVELS IN LIVER Tx PATIENTS

dose of proGraf in mg BD

Creatinine response to tacrolimus dose

post liver Tx days