# LIMITED SAMPLING STRATEGIES FOR PREDICTING TACROLIMUS EXPOSURE WITH ONCE DAILY EXTENDED FORMULATION IN KIDNEY TRANSPLANT RECIPIENTS AND OPTIMAL PRE-DOSING SCHEDULE


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## Objectives:

Recently, once-daily tacrolimus extended-release formulation (TACER) has been world widely accepted in kidney transplantation, but its pharmacokinetics (PK) and optimal dosing are not well evaluated and may be different optimal trough level of tacrolimus from the immediate-release (twice-daily) formulation.

We have validated the optimal dosage of TACER and the use of single and limited sampling strategies ( SSS and LSS) to estimate tacrolimus exposure with TACER.

## Methods:

Between September 2009 and October 2010 33 de novo Kidney transplant recipients with ABO compatible/ mismatch and DSA negative transplant were treated with immunosuppression protocol using TACER as Figure 1 and evaluated retrospectively.

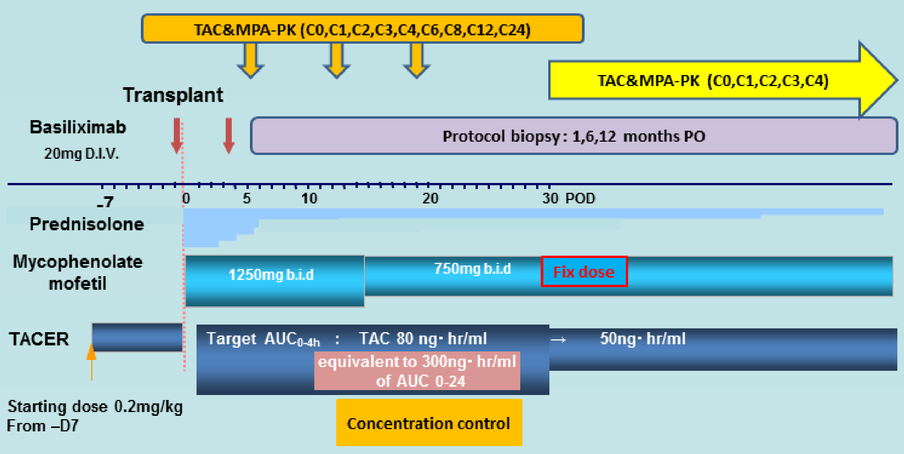



*Figure 1. Immunosuppression protocol with TACER*

### Recipient's characteristics

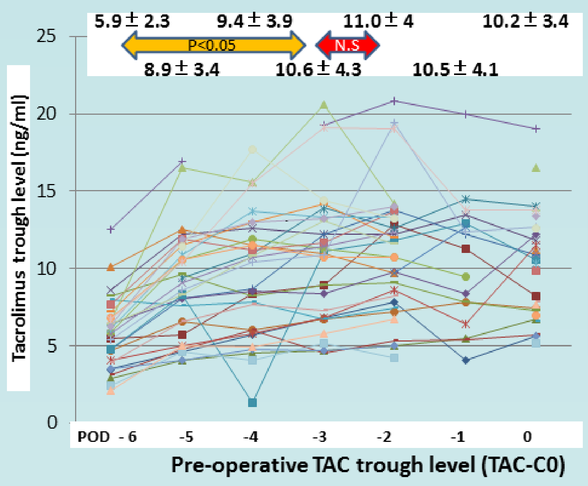
| Number of patients | 33 | Mean ± SD |
|---|---|---|
| Sex (M/F) | 8/ 25 | |
| Age | 18 – 69 yo | 45.6±13.4 |
| Observation time | 43 – 56 months | 48± 4 |
| Recipient's BMI | 15.7～30.8 kg/m² | 21.3 ±4.1 |

### Donor's characteristics

| | | Means |
|---|---|---|
| Sex (M/F) | 9/ 24 | |
| Age | 37-78 yo | |
| Relationship | Spouse 12 (36.4%)<br>Parents 12 (36.4%)<br>Sibling 8 (24.2%)<br>Aunt 1 (3.0%) | |
| HLA mismatch Class I | 0-4 | 2.1± 0.9 |
| HLA mismatch Class II | 0-2 | 1.1± 0.8 |

## Results:

### 1. Evaluation of optimal duration of pre-dosing of TECER



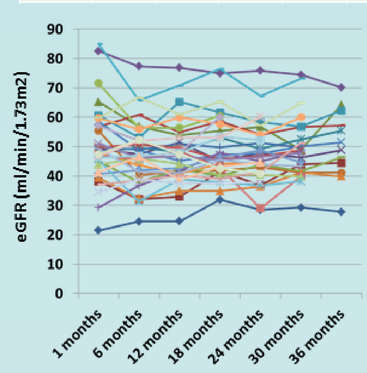

**Saturated TAC trough level were obtained after four does of TACER**

### 2. Clinical Efficacy & Adverse events

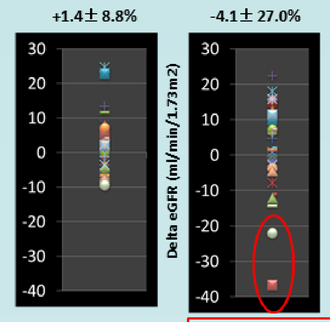
| | incidence | detail |
|---|---|---|
| Graft survival | 100% (33/33) | |
| Patient survival | 100% (33/33) | |
| TACER withdrawal due to nephrotoxicity | 6.1% (2/33) | Conversion to twice-daily formulation |
| Acute T cell mediated Rejection (ATMR) | 12.1% (4/33)<br>Subclinical ATMR : 2 (6.1%)<br>Clinical ATMR: 2 (6.1%) | 2 Subclinical by 6M protocol Bx<br>2 Clinical at 2M& 6M P |
| Acute antibody mediated Rejection (AAMR) | 3.0% (1/33) | POD 2<br>Antigen unknown<br>(Non HLA Ab) |
| CNI toxicity findings in protocol biopsy | 7/33 (21.2%) | Protocol biopsy At 6&12 M |
| Donor specific antibody production (DSA) | 2/33 (6.1%) | Anti-HLA Class II Ab |

### Graft function – eGFR-

| | 1m | 6m | 12m | 18m | 24m | 30m | 36m |
|---|---|---|---|---|---|---|---|
| eGFR | 50.3 | 47.4 | 47.8 | 49.1 | 47.3 | 49.3 | 50.7 |
| SD | 13.3 | 11.0 | 10.8 | 10.7 | 10.2 | 10.6 | 11.9 |



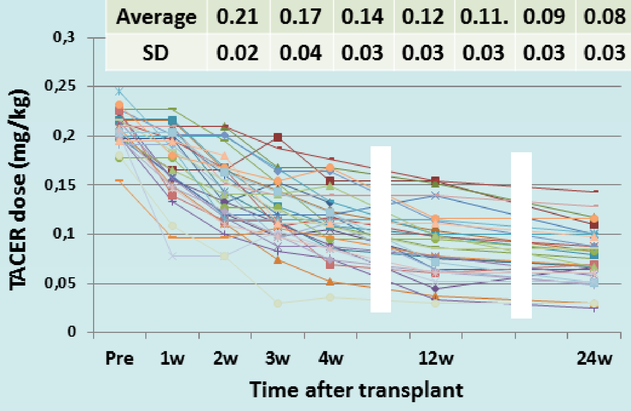

| Delta eGFR 6-12 months | Delta eGFR 6-24 months |
|---|---|
| +1.4± 8.8% | -4.1± 27.0% |




### 3. Pharmacokinetics study of tacrolimus

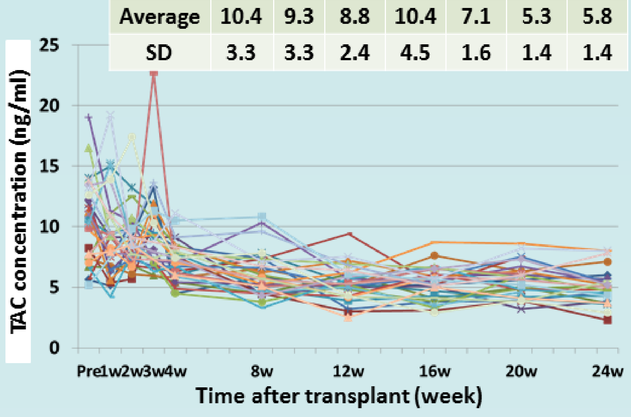
#### Change in TACER dosage

| | Pre | 1w | 2w | 3w | 4w | 12w | 24w |
|---|---|---|---|---|---|---|---|
| Average | 0.21 | 0.17 | 0.14 | 0.12 | 0.11. | 0.09 | 0.08 |
| SD | 0.02 | 0.04 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 |




#### Post-operative TAC trough level until 6months after transplant

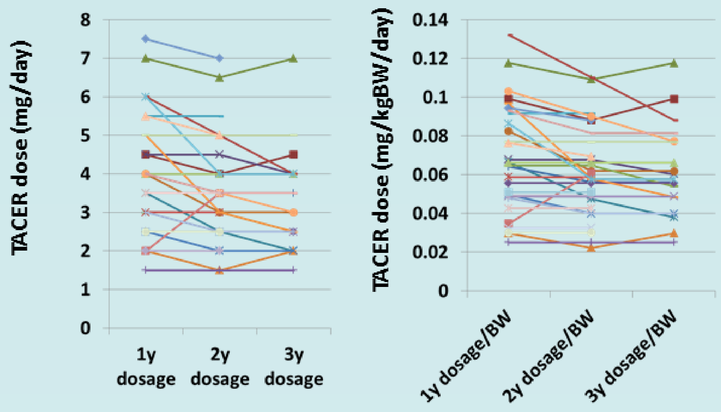
| | Pre | 1w | 2w | 3w | 4w | 12w | 24w |
|---|---|---|---|---|---|---|---|
| Average | 10.4 | 9.3 | 8.8 | 10.4 | 7.1 | 5.3 | 5.8 |
| SD | 3.3 | 3.3 | 2.4 | 4.5 | 1.6 | 1.4 | 1.4 |



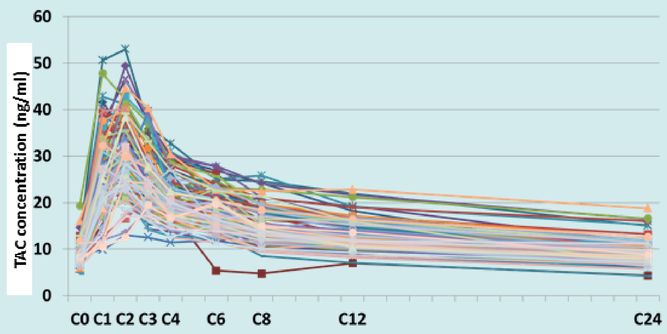

#### Change in TACER dosage

| 1y PO | 2yPO | 3yPO |
|---|---|---|
| 3.8±1.6 | 3.5±1.4 | 3.3±1.3 |

| 1y PO | 2yPO | 3yPO |
|---|---|---|
| 0.07±0.03 | 0.06±0.02 | 0.06±0.02 |



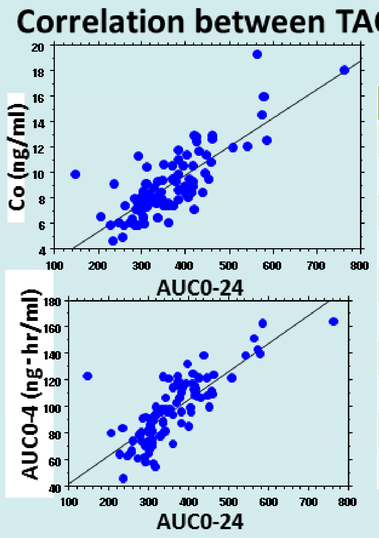

#### TAC-PK profile at 1,2,3w after transplant




Actual TAC-AUC0-24

| 1st week | 2nd week | 3rd week |
|---|---|---|
| 388 ± 97 (205-585) | 358 ± 67 (255-579) | 334 ± 97 (145-764) |

#### Correlation between TAC-cAUC0-24 and Cx




| Sampling point | R2 |
|---|---|
| C0 | 0.621 |
| C1 | 0.266 |
| C2 | 0.525 |
| C3 | 0.589 |
| C4 | 0.636 |
| C6 | 0.748 |
| C8 | 0.790 |
| C12 | 0.903 |
| C24 | 0.766 |
| AUC 0-4 | 0.620 |

#### Correlation between TAC-AUC0-24 and Abbreviation formula by Limited samplings strategy

| Sampling points | $R^2$ | Formula |
|---|---|---|
| C0,C1,C2,C3,C4 | 0.773 | AUC0-24=24.582+15.556xC0-0.039XC1 +2.350XC2 +0.490XC3+5.412XC4 |
| C0,C1,C2,C3 | 0.749 | AUC0-24=38.007+17.468xC0+0.349XC1 +2.850XC2 +2.732XC3 |
| C0,C1,C2 | 0.742 | AUC0-24=46.394+19.696xC0+0.066XC1 +4.443XC2 |

## Conclusions:

1) **Optimal duration of pre-dosing of TECER:** *4 predosing were required to obtain the saturated level of TAC*

2) **Clinical Efficacy & Adverse events:** Excellent efficacy (*Graft and Patient survival 100% and ATMR rate 6.7%*), but higher adverse events such as *CMV infection (30%) and CNI toxicity (22%) on protocol biopsy up to 1 year after transplant*.

3) **TAC-PK study:** C0 did not correlated with AUC0-24 (R=0.79), nor other single sampling data. Limited sampling strategy principles with sampling data of C0, C1 and C2 (or plus C3) well correlated with AUC 0-24 .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