

## Long Term Cyclosporin A Blood Level after Kidney Transplantation, Revisited

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### Introduction

Cyclosporin A blood level is not clearly determined lately post-transplantation (i.e. after many years), and all the recommendations are anecdotal and non-consensual. It is well known that the therapeutic effect of CNIs is variable and largely depending on the enzymatic activity in the intestinal wall and the hepatic cytochrome p450 activity which is inherently different both intra and inter-individually, thereby the readjustment of the dose of CNIs is recommended to be instituted frequently, especially after the first month post transplantation, and it has been reported to be quite stable after three months post transplantation, though it has been recommended in several laboratory references to have lower C2 blood level after the first year post transplantation. herewith we are reporting on six patients who were attending the nephrology clinic for allograft dysfunction, All of them have had renal allograft transplanted for many years (5-15 years), and presented with comparable cyclosporine blood level (C2 varied between 0.35-0.65). They were on maintenance immunosuppressive protocols consisting of

- 1-Neoral, cellcept, prednisolon two patients.
- 2-Neoral,Azathioprim, Prednisolon, two patients.
- 3-Neoral, Rapaimmune and prednisolon, two patients.

### Acute Rejection vs Cyclosporin Toxicity

Considering the first two patients presented with allograft dysfunction. Their C2 Neoral blood level was hovering between (0.4-0.5 Mg/ml) which is quite low for the recommended C2 blood level for the corresponding post transplantation period of 0.8-1 Mg/ml, they have since had normal kidney function, normal blood pressure and unremarkable urinary findings. The history of all of them was neither remarkable for allograft rejection nor for opportunistic infection. Allograft biopsy was contemplated in all of them

There upon we have made a conclusion spawned from the general outcome of the changeable C2 blood level and thereof the allograft function. In two of the patients, they had been reported to have deteriorated allograft function with prominent anemia and recent deterioration of hypertension control, C2 Cyclosporin blood level was reported to be higher than it was before, in one of them C2 blood level was 0.65 Mg/ml, and similarly it was 0.60 Mg/ml in the other patient (primarily it was 0.5 and 0.48 Mg/ml respectively). Thereupon we had inclined to the suspicion of CNI acute nephrotoxicity based on the differential C2 blood level in the two occasions and the event consequent to it. Thereby Neoral dose was reduced to 125mg per day divided doses, equivalent to 1.6mg per Kg body weight (primarily was 150 mg per day), subsequently renal function improved quite effectively and eGFR had improved to 62 ml/min, and further improved to 75 ml/min, after having been readjusted to 50 mg twice daily. Meanwhile the second patient Neoral dose had been reduced to

75 mg daily in divided doses (primarily was 100 mg per day), equivalent to 1.04 mg/kg body weight, accompanied by close observation of the kidney function. Consequently allograft function has improved promptly within few days confirming the primary presumable diagnosis of CNI acute nephrotoxicity mostly secondary to drug-drug interaction. On the reverse in another two patients, having been evaluated for acute allograft dysfunction of uncertain etiology and who had been reported to have prior Neoral C2 blood level of (0.4-0.5 Mg/ml), acute rejection was concluded in both of them after being indicated to have normal transplanted kidney in radiology scanning, unremarkable urinary findings, progressive elevation of the blood urea nitrogen and serum creatinin, and low blood Neoral C2 level (it was reported to be 0.3 Mg/ml, and 0.25 Mg/ml respectively) with findings consistent with acute cellular rejection on allograft biopsy. Prompt anti-rejection therapy was instituted with intravenous Methylprednisolon 1 gm per day for three successive days,accompanied by readjustment of Neoral dose to attain the prior blood level, and prednisolon tablets to be tapered within two weeks to its original dose. Third group was consisting of two patients who had been maintained on Neoral, and Rapaimmune inhibitors (Sirolimus and Everolimus respectively) plus prednisolon. Both of them were reported to have allograft dysfunction of uncertain etiology for a variable length of time (months to one year), ultrasonic study showed normal size and texture of the transplanted kidney, urine test was unremarkable for proteinuria or active sediment, blood C2 Neoral level was 0.35 Mg/ml, and 0.4 Mg/ml respectively. Despite the fact that it was within its recommended blood level, its combination with Rapaimmune is an exceptional reason to consider readjustment of Neoral to lower level. Thereupon Neoral dose has been lowered to 75 Mg per day (prior dose was 100 Mg a day), subsequently blood Neoral C2 level went down to 0.24 mg/ml and consequently creatinin normalized to its preceding blood level. Which is explicitly elaborating on the combined regimen, featuring the risk of having allograft dysfunction with the mutual effect of both. The other appreciable issue is to exploit whether it is comparable for being on the aforementioned regimen rather than the other conventional regimens in the sense of long term outcome.

### Highlight

Cyclosporin A is well known for its powerful immunosuppressive effect, and it is proved to be pivotal in the first year post transplantation pertaining to its selective immune modulation through inhibitory effect on Calcineurin and consequently interleukin 2 production. However the role of Cyclosporin A later post transplantation is still debatable, giving the reported adverse effects its casting on the allograft function later on.

## Conclusion

The long term cyclosporin blood level is still a debatable issue which reflects the interplay of several factors in the forefront to govern the allograft function including the other interacting immunosuppressant

medications particularly mTOR inhibitors. It is still recommended to reassess and readjust the level of cyclosporin after many years of applying the immunosuppressant protocol in order to reach to a level that is suitable and unique for each individual patient.