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Editorial Open Access

mTORi and CNIs Liaison, Revisited

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Editorial

The combination of Mammalian Target of Rapa inhibitors (mTORi) and Calcineurin inhibitors (CNI) is still a desirable approach aiming at reducing the Calcineurin inhibitors toxicity and improving the long term outcome of the kidney transplantation, nevertheless this seemingly profitable combination is not without a flip side that is the risk of having an allograft dysfunction [1]. Although the exact mechanism is still tenuous and vastly underexploited, the event of having an allograft dysfunction is increasingly encountered in the daily practice. Herewith we are reporting on two patients who had presented with allograft dysfunction that had been proven later to be secondary to CNI nephrotoxicity. First patient is having an acute allograft nephropathy, because he had had the allograft dysfunction very early in the post transplantation period (within weeks after the institution of the Everolimus), whilst the other patient has had a long term history of allograft dysfunction, dated to early post-transplantation period, and it has been reported for three years.

Given the fact that the residual blood level of mTORi and peak level of Neoral were at its normal limits, it's explicitly countless for being related to the toxic blood level of either. And it is still controversial whether it's mTORi or CNI nephrotoxicity, and is there any de novo intracellular effect that might be different from or unrelated to the blood levels. Is it different with Tacrolimus, and what would be the appropriate blood level of Neoral or Tacrolimus when either is combined with mTORi? Having all these considerations, we are sharing with you our experience.

History of Illness

First patient: 50 year old male of Indian descent ,who had been in renal failure for long time of unknown etiology , and has had transplanted kidney from a related donor for the past 6 months ,and he had been reported having allograft dysfunction(serum creatinin of 1.8, GFR of 35 ml/min) since the first post-operative month . The allograft dysfunction was non progressive and was not associated with active urinary sediment. The immunosuppresive regimen was consistent of Tacrolimus capsules 1 mg twice daily, Everolimus 0.5 mg twice daily and Mycophenolate Mofetil 500 mg twice daily, and apart from prominent anemia and hypertension that he was having, rest of medical history was unremarkable. Primary evaluation revealed blood Everolimus trough level of 6.1ug/l (3-15 ug/l) ,blood Tacrolimus trough level was 5.8 mg/l (5.0-20 mg/l) .Urine test was unremarkable, ultra-sonic examination showed normal texture allograft with no evidence of hydronephrosis, Doppler study was not done. The patient was reported to have neither post operative delayed graft function nor episode of acute rejection earlier to his latest presentation, or was there any general medical illness.

Second patient: 36 year old female who is an allograft recipient since 2005. Her primary renal disease is unknown, the donor was unrelated donor, and she denies having had any Postoperative delayed graft function, or acute rejection episode. She was maintained on Neoral 50 mg twice daily, Rapamycin 1 mg once daily and prednisolon 2.5mg per day. She was reported to have an allograft dysfunction for the last three years seemingly attributed to chronic allograft nephropathy. Investigations revealed serum creatinin of 3.2 mg/dl, GFR of 25 ml/min, ultrasound study showed normal sized allograft with normal texture and corticomedullary differentiation. Blood trough level of Sirolimus was 9.4 mg/l, and Neoral C2 blood level was 0.3 Mg/ml. Urinary finding was unremarkable neither for active sediments nor for proteinuria, but serum uric acid was elevated at 10.5 mg/dl. No allograft biopsy was done for either of them. GFR, blood pressure, urinary parameters have since followed in both the patients for the subsequent six months.

Discussion

Having had the allograft dysfunction in the setting of maintenance immune suppression protocol consisting of mTORi and CNIs is immediately apparent as the inadvertent outcome of the combination. Despite the fact that for both of them blood levels were within the therapeutic ranges, I had inclined to the diagnosis of allograft dysfunction secondary to drug-drug interaction. The dose of CNI was reduced in both of the patients with close follow up of the renal function. Therefor Tacrolimus was reduced to 1 mg in the morning and 0.5 mg in the evening, and Neoral was reduced to 50 mg in the morning and 25 mg in the evening, respectively. No change in the dose of mTORi was considered. Surprisingly within few days a dramatic improvement in the renal function was noticed in both of the patients, creatinine was normalized to 1.1 and GFR improved to 77 ml/min in the first patient (with concomitant improvement in the hypertension and the anemia), whilst the second patient serum creatinine has dropped to 1.5 and eGFR has risen up to 60 ml/min henceforth, with concomitant improvement of serum uric acid level (from 10.5 to 7.4 mg/dl).Subsequent blood trough level of Tacrolimus was 3.8 mg/l and Neoral blood C2 level was 0.2 mg/ml. No change in the blood trough level of mTORi was notable meanwhile.

The History of the Two Patients Would Highlight the Following Points:

Despite the fact that its still debatable whether to withdraw CNIs (within few months after the institution of combined CNI and mTORi protocol in low risk patients and after one year in high risk patients), or to continue, it's still often seen the maintenance of immune suppression protocol that is consistent of combination of both.

blood levels were in the therapeutic range), however its well known that CNIs inhibit the cytochrome P450 and elevate the serum level of mTORi. It's not yet clear whether it's basically mTORi, or CNIs induced nephrotoxicity, though in both of the patients, the sole reduction of the dose of the CNIs, and consecutively their blood level, has led to a dramatic improvement of the allograft function. The toxicity is not apparently related to the duration of insult, and is apparently reversible whatever the duration of allograft dysfunction is (highlighting the fact that it's rather a hemodynamic than a chronic structurally mediated allograft dysfunction). In the protocols that imply combined mTORi and CNIs, it's not well established the exact appropriate blood levels of CNIs. Meanwhile it's recommended to adjust the dose of CNIs to lower limits in order to avoid the prominent complications that are integral to the long term administration of CNIs combined with mTORi, particularly the nephrotoxicity, hypertension and tremor, a substantive potential that is seemingly underestimated. It's not yet distinctive whether the outcome is better with protocol combining Tacrolimus and mTORi. And similarly would it be contemplated for the other member of mTORi (Everolimus) combined with CNIs. Being absolutely reversible and hemodynamicaly mediated is consistent with CNI acute nephrotoxicity that is inflicted by the inherent glomerular afferent arteriolar vaso¬constrictive propensity of the CNIs. And the absence of significant proteinuria and the normalization of blood pressure after adjustment of CNIs dosages have denoted the aforementioned proposition. Despite the fact that mTORi are reported to be the culprit for maintaining allograft injury in the particular setting of post transplantation delayed graft function and in impairing the recovery of the tubular function caused by CNIs related acute tubular necrosis . And being an impediment for the spontaneous recovery of the ongoing kidney damage, promptly attributed to its integral propensity to arrest cell cycle. And ultimately the absence of proteinuria which is the sin qua non of mTORi nephrotoxicity due to the debatable de novo tubular or glomerular injury, mTORi are unlikely to be the underlying etiology for the allograft dysfunction in both of the patients presented. Although the commonly held idea that the combination of Tacrolimus and mTORi is more appropriate and allograft function saving than to combine Neoral and Sirolimus, yet it is still a potential risk factor for allograft dysfunction as it has been shown in the patient we are presenting (although Tacrolimus was at its lowest recommended blood level), and subsequent minimization of the tacrolimus dose was profitable to improve the kidney function. Meanwhile its reduction was not affecting the trough blood level of Everolimus, and the serum creatinin and GFR was improved and vastly stable through out the subsequent six months of follow up. And the normalization of serum uric acid is in line with the hemodynamic improvement of the glomerular perfusion. Therefor I think that the most appropriate Tacrolimus blood trough level is less than 5.8 mg/l when it's involved in a protocol combining it with mTORi as a maintenance regimen. Similarly Neoral C2 blood level of less than 0.2 mg/l was most appropriate for long term combined regimen for being associated with constant improvement of the GFR from base line of 25 ml/min to 60 ml/min over the subsequent six months.

Giving the fact that GFR had been improving with the minimization of CNIs blood level, and maintaining it at its nadir, is seemingly an intriguing approach to hold off the CNIs altogether and to rely on the mTORi in combination with mycophenolic acid and prednisolon as a triple maintenance therapy, especially with patients in the late post transplantation period without a history of prior rejections, and with normal level of panel reacting antibody. It's still early to opine on the benefit of one protocol over another and particularly in the presence of the conflicting recommendations of the guidelines regarding the implication of mTORi in transplantation.

References

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