Nuggehally R Srinivas /J. Pharm. Sci. & Res. Vol.3(3), 2011,1093-1095

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Clinical Therapy with Immunosuppresants/Calcineurin Inhibitors – Dilemma and Challenges from a Pharmacokinetic Perspective

Nuggehally R Srinivas
Vanthys Pharmaceutical Development Pvt [Ltd], #46, 3rd Floor, Phoenix Pinnacle,
Ulsoor Road, Bangalore 560 042

Abstract

Polypharmacy has become a common practice in today's disease management and hence, it introduces a risk of some overt safety issues if proper attention is not paid to the prescription pattern(s). In addition, given the re-purposing of many approved drugs for other indications have also been widely followed, it may also open avenues for drug-drug interaction that may have not been anticipated. This communication attempts to cover challenges associated in clinical therapy with the popular calcineurin inhibitors as their use has now extended beyond the indications that would need immunosuppresion. Also, it covers certain strategies that could be easily put in place to avoid the risk(s) and/or mitigate the risk in a proactive manner.

The emergence of several immunosuppressants/ calcineurin based inhibitors has revolutionized the area of transplantation and has served the field well in spite of challenges imposed on their use due to its increased vulnerability to cytochrome P450 enzymes (CYPs) and/or drug transporter systems [1, 2, 3, 4, 5]. However, careful dose selection, monitoring of patients and adherence to strict therapeutic drug monitoring have been the key milestones of the clinical therapy in order to balance the risk:benefit profiles of many of the agents in its clinical use.

The present day use of many of the agents for re-purposing clinical programs, namely the use of everolimus, sirolimus, temsirolimus, ridaforolimus etc , as potential mTor inhibitors for several oncology indications [6, 7, 8, 9], adds another degree of complexity relating to the issues of both CYPs and transporters because today's cancer therapy involves combination of agents with various mechanisms which may also bring induction/inhibition liabilities of enzymes and/or transporters.

The intent of this communication is to bring into light some additional perspectives to enable the clinician and the medical practitioner to make the right decision either when adding a newer drug to the existing regimen and/or replacing the drug with another drug in the existing dosing regimen and/or making a judicious decision for a switch of the combination regimen – these are very relevant in today's clinical therapy of many disease areas which involve combination of many therapeutics.

Addition of tigecycline to cyclosporine treatment: In order to manage infection in a transplant patient on active oral therapy with cyclosporine, intravenous tigecyline was coadministered [10]. In spite of the different route of administration, the presence of tigecycline caused an increased exposure of cyclosporine in the patient leading to safety issues that necessitated dose reduction of cyclosporine when tigecycline was continued to treat the infection.[10] The increased exposure of cyclosporine was due to the result of blockade of biliary excretion of cyclosporine due to the coadministered tigecyline [11].

Replacement of cyclosporine with tacrolimus in patients with continuous everolimus therapy: In this interesting study, it was documented that withdrawal of cyclosporine and replacement by tacrolimus in transplant patients resulted in a drastic reduction of the exposure of everolimus such that its predose levels, mean peak concentration and overall extent of absorption were almost halved [12]. This interaction could be explained by the fact that stoppage of cyclosporine caused a removal of the perturbation in the CYP system such that it was now fully available to metabolize everolimus leading to decreased blood levels of everolimus in the patients.

Dual replacement of cyclosporine/fluvastatin with tacrolimus/atorvastatin in dyslipidema: In an interesting report a transplant patient who

was treatment refractory to fluvastatin was switched into a more effective atorvastatin [13]. However, given the status of his transplant, it was also important to switch the immunosuppressant to a more neutral one to prevent any anticipated pharmacokinetic drug-drug interaction that is known to occur between atorvastatin and cyclosporine.[13]While atorvastatin has been shown to marginally effect the pharmacokinetics of cyclosporine via CYP3A4 pathway [14], cyclosporine in turn can have a significant impact on the hepatic uptake of atorvastatin which is drastically increased through organic anion transporter 1AB1 protein [15].

Thus in the first two interesting cases presented, cyclosporine is a victim and a perpetrator, respectively. In the third case, however, cyclosporine can be classified as both a victim and a perpetrator as one examines the nature of the interaction. Interestingly, as evident in another case study, one has to pay attention for the potency of the perpetrator within the same class of agents [16]. In this case, although tacrolimus dose was reduced in the presence of co-administration of azole anti-fungal agents in the patient, fluconazole vs voriconazole produced some interesting differences in the plasma levels of tacrolimus [16]. This study also indicated that it may not be not just enough to dose reduce tacrolimus but also pay attention to the azole agent and if necessary switch to a less potent azole [16].

As is typically seen in clinical practice one has to be vigilant when drug combination options are used and/or newer drugs or replacement drugs needs to be added to the regimen to ensure the pharmacokinetic liabilities, if any, are adequately addressed in not only the appropriate selection of the agent(s).

It is the opinion of the author that development of sound strategies to address such drug-drug interaction risks is developed in a proactive fashion. Firstly, the institution of limited pharmacokinetic measurements may be required to mitigate the risks involved during the coadministration of calcineurin based inhibitors in either clinical practice or when carrying out clinical investigations. While singe point drug measurements, although ideal for therapeutic drug monitoring, may not provide enough clarity on the quantum of interaction, it may ideal to have a limited sampling strategy to compute a partial AUC (AUC up to 4 hours or 6 hours) when the drug combinations are initiated. Since these calcineurin based inhibitors act upon both gut CYP3A4 and uptake transporters rather acutely, a partial AUC determination may provide a basis to gauge the likelihood/quantum of the pharmacokinetic interaction. Secondly, where the interaction of calcineurin drugs with the coadministered drug is imminent through prior literature knowledge of similar class of agents, it may be important to implement a CYP3A4/5 genotyping protocol as a de-risking strategy to keep such patients away from the combination and/or chose a dose reduction strategy in lieu of the genotype data. Thirdly, it may be a good idea to start the administration of the two agents as a single dose combination on the first day and only after ascertaining lack of significant drug drug interaction via the partial AUC approach or a standard whole blood measurements or even measuring intracellular concentration using PBMCs, ramping up to multiple (repeated) dose paradigm. Fourthly, based on individual patient CYP3A4/5genotypes, if available and/or known severity of the likely interaction of the two agents in combination is confirmed (in vitro, preclinical or clinical evidence), it may be important to either stratify patients into various tiers of risks and appropriate risk management strategy should be instituted. Such strategies could involve reduced daily doses of one or both agents, change in frequency of dosing or switching of the agent itself to another agent that has lesser propensity for drug drug interaction.

REFERENCES

[1]. Staatz CE, Goodman LK, Tett SE [2010] Effect of CYP3A and ABCB1 single nucleotide polymorphisms on the pharmacokinetics and pharmacodynamics of calcineurin inhibitors: Part I. *Clin Pharmacokinet.* 49:141-175.

[2]. Staatz CE, Goodman LK, Tett SE [2010] Effect of CYP3A and ABCB1 single nucleotide

polymorphisms on the pharmacokinetics and pharmacodynamics of calcineurin inhibitors: Part II. *Clin Pharmacokinet.* 49: 207-221.

[3]. Pourfarziani V, Taheri S [2009] Mycophenolate sodium increases cyclosporine blood levels in renal transplant recipients. *Saudi J Kidney Dis Transpl.* 20:991-994

[4]. Vicari-Christensen M, Repper S, Basile S, Young D [2009] Tacrolimus: review of pharmacokinetics, pharmacodynamics, and pharmacogenetics to facilitate practitioners' understanding and offer strategies for educating patients and promoting adherence. *Prog Transplant.* 19:277-284.

[5]. Felipe CR, Park SI, Pinheiro-Machado PG, Garcia R, Casarini DE, Moreira S, Tedesco-Silva H Jr, Medina-Pestana JO [2009] Cyclosporine and sirolimus pharmacokinetics and drug-to-drug interactions in kidney transplant recipients. *Fundam Clin Pharmacol.* 23:625-631.

[6]. Jerusalem G, Fasolo A, Dieras V, Cardoso F, Bergh J, Vittori L, Zhang Y, Massacesi C, Sahmoud T, Gianni L [2011] Phase I trial of oral mTOR inhibitor everolimus in combination with trastuzumab and vinorelbine in pre-treated patients with HER2-overexpressing metastatic breast cancer. *Breast Cancer Res Treat.* 125:447-455.

[7]. Gerullis H, Ecke TH, Eimer C, Heuck CJ, Otto T [2010] Mycophenolate sodium increases cyclosporine blood levels in renal transplant recipients. mTOR-inhibition in metastatic renal cell carcinoma. Focus on temsirolimus: a review. *Minerva Urol Nefrol.* 62:411-423.

[8]. Perotti A, Locatelli A, Sessa C, Hess D, Viganò L, Capri G, Maur M, Cerny T, Cresta S, Rojo F, Albanell J, Marsoni S, Corradino I, Berk L, Rivera VM, Haluska F, Gianni L [2010] Phase IB study of the mTOR inhibitor ridaforolimus with capecitabine. *J Clin Oncol.* 28:4554-4561.

[9]. Flaig TW, Costa LJ, Gustafson DL, Breaker K, Schultz MK, Crighton F, Kim FJ, Drabkin H [2010] Safety and efficacy of the combination of erlotinib and sirolimus for the treatment of metastatic renal cell carcinoma after failure of sunitinib or sorafenib. *Br J Cancer* 103:796-801.

[10]. Stumpf AN, Schmidt C, Hiddemann W, Gerbitz A [2009] High serum concentrations of cyclosporin related to administration of tigecycline. *Eur J Clin Pharmacol.* 65:101-103.

[11]. Srinivas NR [2009] Tigecycline and cyclosporine interaction-an interesting case of biliary-excreted drug enhancing the oral bioavailability of cyclosporine. *Eur J Clin Pharmacol.* 6:543-544.

[12]. Brandhorst G, Tenderich G, Zittermann A, Oezpeker C, Koerfer R, Oellerich M, Armstrong VW [2008] Everolimus exposure in cardiac transplant recipients is influenced by concomitant calcineurin inhibitor. *Ther Drug Monit.* 30:113-116.

[13]. Skalicka B, Kubanek M, Malek I, Vymetalova Y, Hoskova L, Podzimkova M, Kautzner J [2009] Conversion to tacrolimus and atorvastatin in cyclosporine-treated heart transplant recipients with dyslipidemia refractory to fluvastatin. *J Heart Lung Transplant.* 28:598-604.

[14]. Taylor PJ, Kubler PA, Lynch SV, Allen J, Butler M, Pillans PI [2004] Effect of atorvastatin on cyclosporine pharmacokinetics in liver transplant recipients. *Ann Pharmacother.* 38:205-208.

[15]. Amundsen R, Christensen H, Zabihyan B, Asberg A [2010] Cyclosporine A, but not tacrolimus, shows relevant inhibition of organic anion-transporting protein 1B1-mediated transport of atorvastatin. *Drug Metab Dispos.* 38:1499-1504.

[16]. Pea F, Baccarani U, Tavio M, Cojutti P, Adani GL, Londero A, Baraldo M, Franceschi L, Furlanut M, Viale P [2008] Pharmacokinetic interaction between everolimus and antifungal triazoles in a liver transplant patient. *Ann Pharmacother.* 42:1711-1716.