

Brief Report

DOI: 10.5582/bst.2011.v5.5.189

Implications of integrase inhibitors for HIV-infected transplantation recipients: Raltegravir and dolutegravir (S/GSK 1349572)**Kayo Waki^{1,2,*}, Yasuhiko Sugawara³**¹ Department of Diabetes and Metabolic Diseases, The University of Tokyo Hospital, Tokyo, Japan;² Department of Ubiquitous Health Informatics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan;³ Division of Artificial Organ and Transplantation, Department of Surgery, The University of Tokyo, Tokyo, Japan.**Summary**

In the modern era of highly active antiretroviral therapy (HAART), reluctance to perform transplantation (Tx) in HIV-infected individuals is no longer justified. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs), the current first line regimens of HAART, are metabolized by the cytochrome P450 family (CYP3A4). Most NNRTIs induce CYP3A4, whereas PIs inhibit it. Calcineurin inhibitors (CNIs), which are mandatory for Tx, need the same enzyme complex for their clearance. Therefore, a significant drug-drug interaction (DDI) is encountered between current HAART and CNIs. This results in extreme difficulty in adjusting the optimal dose of CNIs, for which the therapeutic range is narrow. Of interest, integrase inhibitors (INIs) – novel, potent anti-HIV drugs – are mainly metabolized by uridine diphosphate glucuronosyltransferase (UGT) 1A1 and do not induce or inhibit CYP3A4. DDI is presumably absent when NNRTIs or PIs are replaced by INIs. Raltegravir (RAL), a first generation INI, has been introduced into kidney and liver Tx. There is increasing evidence that rejection is well controlled without renal impairment due to CNI over-exposure while persistent, robust suppression of HIV is achieved. Global phase III clinical trials of dolutegravir (DTG), a second generation INI, are currently in progress. *In vitro* data has suggested that DTG may be less prone to resistance than RAL (referred to as having a higher genetic barrier). The time has come to extensively discuss the implications of INIs in Tx for HIV positive patients.

Keywords: Liver transplantation, kidney transplantation, drug-drug interaction (DDI), highly active antiretroviral therapy (HAART)

In the modern era of highly active antiretroviral therapy (HAART), which consists of non-nucleoside reverse transcriptase inhibitors (NNRTIs) or boosted protease inhibitors (PIs), reluctance to perform transplantation (Tx) in HIV-infected individuals is no longer justified (1,2). No fewer than 20-30% of HIV-positive patients are co-infected by HCV, and end-stage renal disease caused by HIV-associated nephropathy develops in as many as 5-10% of HAART-treated patients (2,3). As a result, HIV-positive patients are much more likely

to receive needed liver or kidney Tx than are the HIV-negative. Recently, though, integrase inhibitors (INIs) have emerged. They are novel, potent anti-HIV drugs characterized by a distinct metabolic pathway; they include raltegravir (RAL, Isentress, Merck & Co., Inc., New Jersey, USA) and dolutegravir (DTG, S/GSK1349572, ViiV Healthcare/Shionogi, Middlesex, UK/Osaka, Japan) (4,5). Currently, their implications in the setting of Tx for HIV positive patients are being actively discussed.

To maintain undetectable plasma HIV-RNA, the current first line regimens of HAART consist of a PI boosted by ritonavir or a non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitors (NRTIs) as described above (2). PIs and NNRTIs require metabolism by the cytochrome P450 family (2). Ritonavir and the

*Address correspondence to:

Dr. Kayo Waki, Department of Ubiquitous Health Informatics, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo Bunkyo-ku, Tokyo 113-8655, Japan.

e-mail: kwaki-tyk@umin.ac.jp

other PIs are potent inhibitors of CYP3A4, while most NNRTIs are its inducers (2). The same enzyme complex is responsible for the clearance of calcineurin inhibitors (CNIs); the mainstay of current immunosuppression (IS) – e.g. cyclosporine (Neoral, Novartis International AG, Basel, Switzerland) and tacrolimus (Prograf, Astellas Pharma Inc., Tokyo, Japan) (2). Thus, a significant drug-drug interaction (DDI) exists between current HAART and IS (2). In the presence of PIs, a reciprocal DDI can potentially lead to CNI over-exposure and renal toxicity. This results in difficulty in adjusting optimal dosage of CNIs characterized by a narrow therapeutic range, or the requirement of transient discontinuation of HAART during the peri-Tx period (2,6). However, interruption of HAART may result in the accumulation of resistance-associated mutations. Earlier re-introduction of HAART can positively affect anti-HCV therapy after liver Tx for HCV diseases (6). Such a complex scenario warrants development of HAART that exhibits no DDI with CNIs (Figure 1).

Integrase inhibitors (INIs) are mainly metabolized by uridine diphosphate glucuronosyltransferase (UGT) 1A1. These INIs are neither inducers nor inhibitors of CYP3A4 (4,5). Therefore, they presumably do not interact with CNIs (2). RAL, a first generation INI, has been introduced into HIV-positive Tx mainly due to its distinct metabolic pathway and remarkable efficacy. PI-sparing, RAL-based HAART does not require either dose adjustment of CNIs or discontinuation of HAART early post-Tx. There is increasing evidence that RAL is effective in preventing renal toxicity while maintaining potent and sustained antiretroviral properties (7,8) (Figure 1). It has been reported that the negative impacts of abacavir sulfate/lamivudine (NRTIs) (Epzicom, ViiV healthcare, Middlesex, UK) on the kidney are smaller than those of tenofovir disoproxil fumarate/emtricitabine (NRTIs) (Truvada, Gilead Science, Inc., California, USA) (2). Some researchers advocate that HAART regimens – RAL, a key drug, used with Epzicom as a backbone therapy – would be the best option for HIV-positive kidney Tx (2) (Figure 1).

DTG is a second generation INI (5). Its global phase III trials are currently in progress. During a phase II trial with HAART-naïve subjects, its non-inferior efficacy was demonstrated to be not inferior to that of efavirenz (NNRTI) (Sustiva, Bristol-Myers Squibb Pharma Company, New York, USA) (5). *In vitro* studies have raised the curious possibility that DTG could have the potential of a higher genetic barrier to resistance than RAL, in the setting of INI-naïve patients (9) (Figure 1). No serious drug-induced adverse effects were observed throughout phase II trials, and its tolerability was excellent (10). A slight self-limiting serum creatinine (Cr) elevation was observed. An *in vitro* study strongly suggested that such a Cr elevation was merely a sequel to a non-pathologic decrease in Cr secretion *via* the proximal tube, but did not represent renal toxicity (5).

Ideal anti-retroviral therapy for HIV positive transplant

To provide sustained viral suppression while minimizing drug interactions and toxicity, a regimen should:

- 1) Be potent and have a high genetic barrier to resistance
- 2) Not induce or inhibit metabolism of calcineurin inhibitors (CNIs)
- 3) Not have overlapping toxicities with immunosuppression (IS)
- 4) Have minimal impact on graft function
- 5) Have excellent tolerability and ease of dosing

Figure 1. Ideal anti-retroviral therapy for HIV positive transplants. (Beatty G, personal communication, American Transplant Congress April 30-May 4, 2011, Philadelphia, PA, USA)

This accords well with a recent phase I study in which administration of DTG in healthy individuals did not negatively affect the glomerular filtration rate (GFR) (11).

Once-daily DTG proved satisfactorily efficacious in the phase II trial for naïve subjects cited above, while RAL must be administered *b.i.d.* (4,5). This advantage may act in favor of using DTG (Figure 1). In support, a switch to (*q.d.*) modified release tacrolimus (Advagraf, Astellas Pharma Inc., Tokyo, Japan) from conventional *b.i.d.* (Prograf) increased using by Tx patients (12). Of note, several cases of rhabdomyolysis were observed in RAL-treated subjects. One must pay attention to concomitant use of RAL with other drugs (e.g. statins) that can cause rhabdomyolysis (13-17). In addition, one can not entirely exclude the possibility that the concern for rhabdomyolysis caused by concomitant use of RAL and statins may be further enhanced by CNIs due to disturbance of statin uptake into the liver by organic anion transporting polypeptides (18). On the other hand, one case of grade 4 CPK elevation was observed during phase II trials of DTG, but it was exercise-related, transient, and asymptomatic (10). Even so, a caution is still needed before sufficient cases are accumulated during phase III trials and at post-market phase.

More accumulated experience using RAL is needed to fully understand the implications of INIs in HIV-infected Tx recipients. Meanwhile, the efficacy, safety, and tolerability of DTG must be carefully analyzed in comparison to those of RAL, PIs and NNRTIs during the phase III studies. Finally, the authors propose to discuss the possibility of using DTG in Tx, taking its attractive *in vitro* and *in vivo* characteristics into account.

Acknowledgements

The authors thank Dr. J Parker for manuscript preparation.

References

1. Qiu J, Terasaki PI, Waki K, Cai J, Gjertson DW. HIV-

- positive renal recipients can achieve survival rates similar to those of HIV-negative patients. *Transplantation*. 2006; 81:1658-1661.
2. Trullas JC, Cofan F, Tuset M, Ricart MJ, Brunet M, Cervera C, Manzardo C, López-Dieguez M, Oppenheimer F, Moreno A, Campistol JM, Miro JM. Renal transplantation in HIV-infected patients: 2010 update. *Kidney Int*. 2011; 79:825-842.
 3. Soriano V, Mocroft A, Rockstroh J, Ledergerber B, Knysz B, Chaplinskas S, Peters L, Karlsson A, Katlama C, Toro C, Kupfer B, Vogel M, Lundgren J; EuroSIDA Study Group. Spontaneous viral clearance, viral load, and genotype distribution of hepatitis C virus (HCV) in HIV-infected patients with anti-HCV antibodies in Europe. *J Infect Dis*. 2008; 198:1337-1344.
 4. Nguyen BY, Isaacs RD, Tepler H, *et al*. Raltegravir: The first HIV-1 integrase strand transfer inhibitor in the HIV armamentarium. *Ann N Y Acad Sci*. 2011; 1222:83-89.
 5. Lenz JC, Rockstroh JK. S/GSK1349572, a new integrase inhibitor for the treatment of HIV: Promises and challenges. *Expert Opin Investig Drugs*. 2011; 20:537-548.
 6. Tsukada K, Sugawara Y, Kaneko J, Tamura S, Tachikawa N, Morisawa Y, Okugawa S, Kikuchi Y, Oka S, Kimura S, Yatomi Y, Makuuchi M, Kokudo N, Koike K. Living donor liver transplantations in HIV- and hepatitis C virus-coinfected hemophiliacs: Experience in a single center. *Transplantation*. 2011; 91:1261-1264.
 7. Moreno A, Pérez-Elías MJ, Casado JL, Fortún J, Bárcena R, Quereda C, Del Campo S, Gutiérrez C, Pastor O, Nuño J, Fernandez A, Moreno S. Raltegravir-based highly active antiretroviral therapy has beneficial effects on the renal function of human immunodeficiency virus-infected patients after solid organ transplantation. *Liver Transpl*. 2010; 16:530-532.
 8. Tricot L, Teicher E, Peytavin G, *et al*. Safety and efficacy of raltegravir in HIV-infected transplant patients cotreated with immunosuppressive drugs. *Am J Transplant*. 2009; 9:1946-1952.
 9. Kobayashi M, Yoshinaga T, Seki T, *et al*. *In vitro* antiretroviral properties of S/GSK1349572, a next-generation HIV integrase inhibitor. *Antimicrob Agents Chemother*. 2011; 55:813-821.
 10. Min S, Carrod A, Curtis L, Stainsby C, Brothers C, Yeo J, Nichols G. Safety profile of dolutegravir (DTG, S/GSK1349572), in combination with other antiretrovirals in antiretroviral (ART)-naïve and ART-experienced adults from phase IIB studies. [abstract No TUPE238]. 6th International AIDS Society (IAS) conference on HIV pathogenesis, treatment, and prevention; 2011.
 11. Koteff J, Borland J, Chen S, Song I, Peppercorn A, Koshiba T, Cannon C, Muster H, Piscitelli S. An Open Label, Placebo-Controlled Study to Evaluate the Effect of Dolutegravir (DTG, S/GSK1349572) on Iohexol and Para-Aminohippurate Clearance in Healthy Subjects. [abstract A1-1728]. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2011.
 12. Doesch AO, Mueller S, Konstandin M, Celik S, Erbel C, Kristen A, Frankenstein L, Koch A, Dengler TJ, Ehlermann P, Zugck C, De Geest S, Katus HA. Increased adherence after switch from twice daily calcineurin inhibitor based treatment to once daily modified released tacrolimus in heart transplantation: A pre-experimental study. *Transplant Proc*. 2010; 42:4238-4242.
 13. Zembower TR, Gerzentshtein L, Coleman K, Palella FJ Jr. Severe rhabdomyolysis associated with raltegravir use. *AIDS*. 2008; 22:1382-1384.
 14. Dori L, Buonomini AR, Viscione M, Sarmati L, Andreoni M. A case of rhabdomyolysis associated with raltegravir use. *AIDS*. 2010; 24:473-475.
 15. Masiá M, Enríquez R, Sirvent A, Gutiérrez F. Severe acute renal failure associated with rhabdomyolysis during treatment with raltegravir. A call for caution. *J Infect*. 2010; 61:189-190.
 16. Croce F, Vitello P, Dalla Pria A, Riva A, Galli M, Antinori S. Severe raltegravir-associated rhabdomyolysis: A case report and review of the literature. *Int J STD AIDS*. 2010; 21:783-785.
 17. Reust CE. Common adverse effects of antiretroviral therapy for HIV disease. *Am Fam Physician*. 2011; 83:1443-1451.
 18. Moreno A, Fortún J, Graus J, Rodríguez-Gandía MA, Quereda C, Pérez-Elías MJ, Nuño J, Wikman P, Moreno S, Bárcena R. Severe rhabdomyolysis due to rosuvastatin in a liver transplant subject with human immunodeficiency virus and immunosuppressive therapy-related dyslipidemia. *Liver Transpl*. 2011; 17:331-333.

(Received September 11, 2011; Revised September 29, 2011; Accepted October 4, 2011)