Pharmacokinetics and Dolutegravir in HIV Treatment Research

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Abstract

Dolutegravir (DTG) is the fourth integrase inhibitor approved by the Food and Drug Administration for use in HIV treatment at a dosage of 50 mg PO once daily (FDA, 2018). This review addresses research into the safety and pharmacokinetics of DTG. Using clinical trials with healthy subjects for pharmacokinetic investigation of DTG, research has observed the primary metabolic pathway and the primary elimination pathway as fecal elimination (Castellino et al. 2013). This same research observed the half-life and absorption rate to be approximately 15 hours and .5 -1.25 hours, respectively (Castellino et al. 2013). Other research tested the efficacy of DTG tested in HIV-positive adults, finding it to lower HIV-RNA concentrations in the blood (Letendre et al. 2014; Min et al. 2011) and cerebrospinal fluid (Letendre et al. 2014), while increasing the subjects' CD4 counts (Letendre et al. 2014), which was also observed in HIV-positive adolescents (Viani et al. 2015). DTG was also observed to pass through the placenta in HIV-positive pregnant women with an initially low concentration that rose over time (Mulligan et al. 2018). Several studies then tested the safety of DTG coadministration with other treatment drugs for HIV (Anderson et al. 2017; Ford et al. 2013), Hepatitis C (Johnson et al. 2014; Khatri et al. 2016; Ross et al. 2016), and other HIV side effects (Song et al. 2013), and only coadministration with carbamazepine was deemed unsafe (Song et al. 2013). However, these coadministration experiments were only done with healthy subjects, and women were underrepresented in DTG testing overall, having either tight requirements to meet for participation (Song et al. 2013; Ross et al. 2016) or being excluded altogether (Castellino et al. 2013).

Introduction

In its latest report, the Center for Disease Control (2016) reported the Human Immunodeficiency Virus (HIV) to have infected approximately 1.1 million people in the United States age 13 and older. In this fight against HIV, a plethora of drugs have been tested as treatments to fight it, and the most common targets are three specific HIV enzymes: reverse transcriptase, integrase, and protease (Castellino et al. 2013). Integrase allows viral DNA to integrate into the host cell DNA, while reverse transcriptase initiates retroviral RNA replication, and protease separates the necessary proteins from the initially long polypeptide chain produced from translation of the DNA code.

This article discusses experiments testing Dolutegravir (DTG), an integrase strand transfer inhibitor (Khatri et al. 2016), the second approved by the FDA at a recommended dose (50 mg PO once daily) in 2013 after its predecessor, Raltegravir (FDA 2018). As the name implies, DTG fights HIV infection by targeting HIV integrase to prevent HIV DNA integration into host DNA, subsequently stopping viral reproduction and the spread of the HIV retrovirus. However, DTG alone will not properly fight HIV, nor will it fight any coinfections or simultaneous medical conditions, such as hepatitis C (HCV), which coinfects roughly 1 in 3 HIV infected individuals (Ross et al. 2016) due to similar infection pathways. Thus, researchers have used pharmacokinetics as a basis of investigation.

Pharmacokinetics allow researchers to observe drug movements and pathways of drugs through the body, and they play an important role in testing for the safety and efficacy of drug administration alone and in coadministration with other treatment drugs. Pharmacokinetic research will explore the safety of DTG as a treatment drug by assessing its pharmacokinetic characteristics when by itself and when coadministered with other treatment drugs. Additionally, this research will aid medical professionals in knowing when to prescribe DTG for HIV-positive patients. This literature review will investigate the pharmacokinetics research done on DTG.

Inclusion Criteria

Inclusion criteria has remained consistent between the Dolutegravir drug interaction studies. Each of the drug interaction studies utilized healthy subjects (Anderson et al. 2017; Ford et al. 2013; Johnson et al. 2014; Khatri et al. 2016; Ross et al. 2016; Song et al. 2013), and nearly every one specified a body-mass index (BMI) of 18.5 to 31.0 kg/m^2 (Ford et al. 2013; Johnson et al. 2014; Ross et al. 2016; Song et al. 2013) save for Khatri et al. (2016) who specified an 18.0 to 30.0 kg/m^2 range, and Anderson et al. (2017) who used the 18.5 to 32 kg/m2 range. However, in the studies collecting base information on DTG pharmacokinetics in different subjects, the inclusion criteria chosen by researchers tended to vary more. Most studies used HIV seropositive adults (Letendre et al. 2014; Min et al. 2011; Mulligan et al. 2018), while Castellino et al. (2013) used healthy adults, Weller et al. (2014) used renally impaired adults, and Viani et al. (2015) used HIV seropositive adolescents aged 12 to 18 years old. Not only that, most studies disregarded BMI as an inclusion criterion (Letendre et al. 2014; Min et al. 2011; Mulligan et al. 2018; Viani et al. 2015), and some raised the BMI requirement, with Castellino et al. (2013) using the 18.5 to 31.0 kg/m2 range and Weller et al. (2014) raising it to 19 to 38 kg/m2.

However, the most interesting variation within these experiments has to do with women. Some studies asked women participating in the study to use non-hormonal or study-approved birth control methods (Song et al. 2013; Ross et al. 2016). Considering the nature of pharmacokinetics research, hormonal level is an important variable to consider in this research, which is why Ross et al. (2016) also requested that the women take pregnancy tests. Another study required women to have non-child-bearing potential (Ford et al. 2013), which included having undergone a tubal ligation or a hysterectomy,

or being post-menopausal. Additionally, Castellino et al.'s (2013) study completely excluded women.

Since women are largely underrepresented as test subjects in HIV research (Curno et al. 2016), this important medical research needs to include more women. Female biology is different from men's, and it presents challenges when it comes to variable control. In particular, during women's menstrual cycles, as hormones are produced, hormones have potential to affect drug studies, creating an uncontrollable variable (Curno et al. 2016). However, since this vein of pharmacokinetic research is all about the interactions of drugs in the human body, the research should investigate pharmacokinetics in female biology as well. Additionally, the study of DTG creates the potential to further test coadministration of DTG and other HIV treatment drugs with hormonal birth control, as Song et al. (2015) have begun by investigating the pharmacokinetic effects a birth control treatment could have on test drugs. Drug treatments, not just for HIV, but for any other coinfections or concurrent conditions, could be improved with a better understanding of how female biology affects them.

Dolutegravir Pharmacokinetics

Various studies have investigated the pharmacokinetics of Dolutegravir with a variety of subjects. In an open-label, phase I, single-dose mass balance study, Castellino et al. (2013) investigated the metabolism, excretion pathway, and pharmacokinetics of DTG in healthy adult male subjects (Ages 30-55). To help identify DTG metabolites, Castellino et al. tagged the 20 mg DTG PO once daily doses with 0.96 mSv of radioactivity, and they took blood, plasma, urine, and feces samples at specified intervals. Using High Performance Liquid Chromatography (HPLC), Castellino et al. (2013) found that out of the four metabolites observed, Metabolite 2 (M2) was the metabolite with the most radioactivity recovery, at 18.9% primarily though urine, with Metabolites 1, 3, and 4, recovering 4.9%, 3.0%, and 1.8% of the dose respectively. These results suggest M2 is the product of the predominant biotransformative metabolism pathway for DTG, glucuronidation by UGT1A1 (Castellino et al. 2013). Additionally, using Liquid Scintillation Counting (LSC) to determine DTG concentrations, Castellino et al. (2013) found that feces held the highest concentration of DTG among the subjects, counting for elimination of 60% of the dose and supporting fecal elimination as the primary route of DTG elimination.

Despite renal elimination being the least used elimination pathway for DTG (Castellino et al. 2013), Weller et al. (2014) tested the DTG pharmacokinetics in severely renally impaired participants, with their definition of severe renal impairment being creatine clearance (CLcr) of <30 mL/min. The experiment was a phase 1, single dose (50 mg DTG PO once daily), open label study using HPLC to measure DTG concentration followed by noncompartmental methods of pharmacokinetic analysis. While some non-renally excreted drugs may have their pharmacokinetics affected by renal impairment, which would lead to an increase in DTG exposure, the results of the study showed a decrease in DTG exposure (C_{max} 23% decreased, AUC(0-∞) 40% decreased) (Weller et al. 2014), indicating renal impairment likely does not affect DTG pharmacokinetics.

Additionally, using Liquid Chromatography and Tandem Mass Spectrometry (LC-MS-MS) to analyze the Dolutegravir concentrations in Plasma, Castellino et al. (2013) created data showing support for claims that Dolutegravir has a fast absorption rate (0.5 h to 1.25 h). Castellino et al. has suspected this absorption rate to be lowered in patients with renal impairment, based on previous literature supporting alterations in transit time with severe renal impairment (Lefebvre et al. 2001;Strid et al. 2003). Weller et al. (2014)'s results of lower exposure in severely renally impaired subjects conflicting with expected higher exposure for non-renally cleared drugs. In general, both Weller et al. (2014) and Castellino et al. (2013) found that Dolutegravir was well tolerated, which is supported by phase 1 studies with various conditions and coadministrations (Anderson et al. 2017; Ford et al. 2013; Johnson et al. 2014; Khatri et al. 2016; Letendre et al. 2014; Ross et al. 2016; Song et al. 2013; Weller et al. 2014; Viani et al. 2015). Additionally, the phase II study done by Min et al. (2011) found DTG to be well tolerated in the short term by HIV seropositive adults. Castellino et al. (2013) also determined DTG's average half-life to be approximately 15.6 hours in their 30-55 year old adult male participants, consistent with the 15.4-hour half-life observed by Weller et al. in their control group (2014). In this study, Weller et al. (2014) found the half-life to be shorter in renally impaired subjects, the median sitting at 12.7 hours compared to their control value of 15 hours. This research established basic pharmacokinetic information about DTG as a control in healthy subjects to aid predictions and provide a point of comparison for DTG when administered in different subjects and under different conditions.

Another set of studies tested the effectiveness and toxicity of Dolutegravir in HIV seropositive subjects. In a phase IIa, randomized, double-blind, dose ranging study, Min et al. (2011) tested the efficacy of DTG in HIV seropositive adults, and Min et al. observed the DTG exposure with once daily DTG doses of 2, 10, and 50mg compared to a placebo group, as well as HIV-1 RNA concentrations. Min et al. used LC-MS-MS to determine DTG concentrations, the COBAS test to determine HIV-1 RNA levels, and noncompartmental methods of pharmacokinetic analysis in order to correlate the rise of DTG doses and the subsequent rise in exposure to the significant reduction in plasma HIV-1 RNA levels (2011). This correlation led Min et al. (2011) to conclude good short-term tolerability for DTG. In another study, Letendre et al. tested DTG in HIV seropositive adult participants at 50 mg PO daily, monitoring the DTG concentrations, along with HIV-1 RNA concentrations in the plasma and cerebrospinal fluid (2014). Letendre used HPLC for analysis of DTG concentrations in both plasma and cerebrospinal fluid, and an HIV-1 Superlow Assay to determine HIV-1 RNA levels in plasma and cerebrospinal fluid (2014), observing a rapid decrease in CSF HIV-1 RNA (%). Additionally, they observed a lower DTG concentration in CSF with all subjects at <50 copies/mL at week sixteen, Plasma DTG concentrations to decrease to <50 copies/mL in 77% of participants by week sixteen and CD4 cell counts to rise an average of roughly 226 cells/mm^3, which is particularly important for an immunocompromising infection like HIV. This effect was echoed in adolescents, who also experienced a rise in CD4 cell counts with DTG administration (50 mg PO daily for children >40 kg, 35 mg PO daily for children between 30-40 kg) in Viani et al. (2015)'s study experiment. In this study, Viani et al. (2015) observed a faster rate of viral decay in adolescents than that in adults with an efficacy of DTG that was approximately equivalent to that in adults.

Another study on HIV positive pregnant women showed DTG concentrations (from a 50 mg PO once daily dose) rise over time, with concentrations observed at 37% and 29% lower than postpartum values in the second and third trimesters, respectively (Mulligan et al. 2018). This study attributed this initial lowering of DTG concentrations, in part, to high progesterone levels (Mulligan et al. 2018), as progesterone induces UGTlAl, which is a major protein in the metabolism of DTG. The researchers also suspected increased hormone levels played a part as well, binding to plasma proteins that DTG normally binds to. No infants in the study acquired HIV, and the comparable DTG concentrations between mothers and newborns supported easy passage of DTG through the placenta (Mulligan et al. 2018). This study observed half-lives as well, but due to the study design, the study questioned the accuracy of this observation. Regardless of potential accuracy issues, Mulligan et al. (2018) observed a shortening of DTG half-life during pregnancy, which is consistent with their proposed explanation for the lowering of Dolutegravir concentrations.

HCV Coinfection

Another area of concern with HIV is various coinfections and the difficult task of balancing medications for HIV with medications for concomitant conditions. One of the most common coinfections for HIV, at approximately 1 in 3 HIV infected patients (Johnson et al. 2014), is the Hepatitis C virus (HCV). As such, Dolutegravir has been tested as a potential concomitant option with HCV treatment drugs. In an open label, 3 period, crossover study, Ross et al. (2016) tested the concomitant administration of DTG (50 mg PO once daily) with Daclatasvir (60 mg PO daily), an inhibitor of the HCV nonstructural protein NS5A (Ross et al. 2016) in healthy adult subjects. After taking blood and plasma samples and examining them through Purified Protein Derivative methods, Ross et al. (2016) analyzed the pharmacokinetics of DTG and Daclatasvir using noncompartmental methods. The results showed that neither DTG nor Daclatasvir had significant pharmacokinetic effects from coadministration. During coadministration, DTG Half-life ($T_{1/2}$), Maximum concentration ($C_{max)}$, Area Under the Curve from the beginning to the end of the test interval ($AUC_{0\text{-}t}$), and Concentration at the end of the study (C_t) increased, while the Apparent Oral Clearance from Plasma (CL/F) decreased compared to DTG alone, supporting clinically insignificant, but present, changes (Ross et al. 2016). Additionally, Daclatasvir pharmacokinetics experienced an increase in C_t, CL/F, $T_{1/2}$, C_{max}, and a decrease in $AUC_{0\text{-}t}$ compared to Daclatasvir alone (Ross et al. 2016). With no significant changes observed, Ross et al. (2016) concluded the coadministration can be done with no need for dose adjustments.

Khatri et al. (2016) tested DTG (50 mg PO once daily) coadministration with a 3-Direct-Acting-Antiviral Regimen tested with healthy adult subjects in a Phase 1, single center, open label, multiple dose study as a viable option for HIV and HCV coinfection. The regimen included Ombitasvir, an NS5A protease inhibitor (25 mg PO once daily); Dasabuvir, a nonnucleoside NS5B RNA polymerase inhibitor (250 mg PO twice daily); Paritaprevir, a Nonstructural 3/4a Protease Inhibitor (150 mg PO once daily); and Ritonavir, an additional protease inhibitor (100 mg PO once daily)

(Khatri et al. 2016). After using validated LC-MS-MS to determine the concentrations of the study drugs, Khatri et al. (2016) used noncompartmental methods to assess the pharmacokinetic parameters of each experimental drug. DTG experienced an increase in lowest concentration between doses (C_{min}), C_{max}, AUC, while time until C_{max} (T_{max}) and $T_{1/2}$ were unaffected during coadministration with the 3-direct-acting-antiviral regimen (Khatri et al. 2016). The 3-direct-acting-antiviral regimen experienced minimal effects, including decreases in C_{trough} for Paritaprevir, Dasabuvir and Ritonavir, and a 7% change in Dasabuvir C_{max} and AUC. Not only did Khatri et al. determine these changes not to be clinically significant (2016), they also concluded that no dose adjustment would be necessary for coadministration.

Johnson et al. coadminstered DTG with Boceprevir and Telaprevir, respectively. Using LC-MS-MS to evaluate the test drug concentrations in plasma samples, and noncompartmental analysis method for the pharmacokinetic parameters of the test drugs, Johnson et al. (2014) examined the pharmacokinetic interactions between DTG (50 mg PO once daily) and Boceprevir (800 mg PO every 8 hours) or Telaprevir (750 mg PO every 8 hours) in a single center, randomized, open label, two cohort, two-period, one way study with healthy adult subjects. During coadministration with Boceprevir, each pharmacokinetic parameter assessed for DTG had changes of less than 10% compared to DTG alone, and the plasma exposure and other pharmacokinetic values of Boceprevir were not significantly affected by DTG (Johnson et al. 2014). Coadministration of DTG with Telaprevir modestly increased the plasma exposure of DTG with an increase of AUC(0-t), C_{max}, C_t values by 25%, 19&, and 37% higher, respectively (Johnson et al. 2014). Telaprevir pharmacokinetic values were not significantly affected by coadministration with Dolutegravir either. Based on these results, Johnson et al. (2014) concluded that DTG coadministration with Telaprevir or Boceprevir is safe and can be done without dose adjustments. Each of these studies has opened up possibilities for treatment of coinfection of HIV and HCV by testing the safety and pharmacokinetic interactions between various treatment drugs. However, each of these studies was performed using healthy adult subjects, and it would be beneficial to test the treatments on HIV infected and/or HCV infected subjects, as well as adolescent subjects, who are vulnerable to low treatment adherence (Viani et al. 2015).

Additional HIV Treatment Support

HCV is not the only condition that can affect HIV seropositive patients, and treatment drugs for HCV are not the only drugs that could impede Dolutegravir efficacy. For example, in a Phase 1, single site, open-label, fixed sequence, crossover study done Song et al. (2013) observed the pharmacokinetic interactions between DTG (50 mg PO once daily) and Carbamazepine (CBZ) (100, 200, or 300 mg PO daily) in healthy adult subjects. CBZ helps treat side effects of neurological HIV manifestations, which can cause neuropathic pain, seizures, and psychiatric disorders (Song et al. 2013). Using HPLC methods for DTG analysis and noncompartmental methods of pharmacokinetic analysis, Song et al. (2013) concluded DTG pharmacokinetic characteristics Ct, Cmax, AUC(0-t), experience a decrease in value of 73%, 33%, and 49% respectively. This

observation led Song et al. (2013) to recommend an increase in DTG dose when it is coadministered with CBZ (Song et al. 2013). This recommendation for increasing the dosage is likely due to CBZ induction of UGT1A1, which is mainly responsible for DTG metabolism, and CYP3A, another notable metabolic enzyme for DTG (Reese et al. 2013).

Additionally, conflicts with other HIV treatment drugs must be monitored in order to prescribe an effective regimen. For example, nonnucleoside reverse transcriptase inhibitors (NNRTIs) are an important type of drug for HIV infection: researching effective coadministration of NNRTIs with other HIV treatment drugs, such as an INI like Dolutegravir, may be a key to HIV treatment. In a phase 1, open label, two-panel, single-sequence, crossover study in healthy adult subjects, Ford et al. (2013) investigated the coadministration of the NNRTI Rilpivirine (RPV) (25 mg PO once daily) with DTG (50 mg PO once daily) and GSK1265744 (30 mg PO once daily) respectively, which are both INIs that have approximately the same function. Monitoring drug concentrations with HPLC-MS-MS and analyzing pharmacokinetic parameters using noncompartmental methods, Ford et al. (2013) observed DTG to be unaffected by RPV, with the only notable change being an increase in Ct of 22%. Similarly, Ford et al. (2013) observed RPV to be likewise unaffected by DTG, with only an increase in Ct (21%) being notable. Additionally, the researchers found GSK1265744 to decrease RPV Ct, and to have no effect on the other RPV pharmacokinetic parameters, while GSK1265744 was also unaffected by RPV (Ford et al. 2013). Ford et al. deemed that no changes were clinically significant and recommended no dose adjustment for either combination.

In a phase 1, open label, three-period, fixed sequence study with healthy adult subjects, Anderson et al. (2017) observed the coadministration of DTG (50 mg PO once daily) with Doravirine (200 mg PO once daily), an NNRTI using Reversed-phase Ultra-performance Liquid Chromatography with Tandem Mass Spectrometry for drug concentration detection and noncompartmental methods of pharmacokinetic analysis. DTG AUC0-24, C24, and C_{max} experienced an increase during Doravirine coadministration, while Doravirine remained unaffected by DTG (Anderson et al. 2017). These two studies open up more possibilities for HIV treatment regimens, as the GSK1265744 and RPV combination can be administered infrequently, the DTG and RPV combination could be easily taken at low doses once a day (Ford et al. 2013), and Doravirine's ability to be safely coadministered with DTG presents Doravirine as a possible alternative for NNRTI resistant patients.

Conclusion

In the fight against HIV, vital treatment options are being explored and administered for the many unique infection statuses of HIV infected individuals. One such option is DTG, and though much research has been done on this drug, much study involving it remains to be done. First and foremost, while the many drug coadministrations tested have been determined as safe, many of the drug-drug interaction studies with DTG have been tested only in healthy adults (Anderson et al. 2017; Ford et al. 2013; Johnson et al. 2014; Khatri et al. 2016; Ross et al. 2016; Song et al. 2013). This lack presents an opportunity to test not just the safety, but the efficacy of DTG

drug coadministrations in HIV seropositive subjects, and in adolescent subjects as well. Additionally, research needs to further explore how female biology and the menstrual cycle interact with not just DTG, but other HIV treatment drugs as well, especially since female biology and the menstrual cycle present challenges in keeping variables consistent for research (Curno et al. 2016). Women are already underrepresented in HIV research (Curno et al. 2016), and the safety of HIV treatments for women should not rely on test results from only men. In summary, pharmacokinetics is an incredibly important tool in research for HIV treatment, and along with treatment drugs like DTG, could expand knowledge around HIV treatment and save lives in the process.

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