Introduction

Marta Boffito & Samantha Abel¹

St Stephens Aids Trust, Crusaid Research Institute, St Stephen's Centre, London and ¹Pfizer Global R&D, Sandwich, UK

According to the 2006 UNAIDS/WHO AIDS epidemic update, an estimated 39.5 million people worldwide were infected with human immunodeficiency virus (HIV), and of these, 4.3 million represented new infections [1]. That same year, 2.9 million people died of AIDS-related illnesses. These statistics underscore the need for new and improved therapies to prevent and manage HIV infection.

The armamentarium of drugs now in use to treat HIV has changed the course of infection so that many more people are living longer with HIV/AIDS, making it more akin to a chronic disease. Highly active antiretroviral therapy (HAART), a combination of drugs targeting different viral replicative/entry mechanisms, has been largely responsible for the improved survival of HIV-infected individuals. The current antiretroviral drugs work against three targets: the viral reverse transcriptase (RT) enzyme, which is responsible for the conversion of viral RNA to DNA; the viral protease enzyme, which processes viral proteins required for virion assembly and budding; and gp41, which is involved in the fusion and entry of the viral core. HAART has been successful in suppressing viral replication and reducing viral load below the threshold of detection; however, it does not eliminate HIV completely, resulting in a chronic, low-level state of infection [2]. The persistence of virus over time is a causative factor for treatment failure and may be explained by several factors [3]. Drug failure can occur owing to factors intrinsic to the virus, whereby drug-resistant variants arise as a result of ongoing low-level viral replication, the high error rate of RT and the selective drug pressure. Patients who fail treatment because of mutational changes in the virus often develop resistance across an entire class of drugs, severely limiting future therapeutic options. Failure can also be caused by poor patient compliance due to inconvenient dosing regimens, adverse events, and heavy pill burden [4]. Scheduled treatment interruptions have been used to reduce short- and long-term adverse events, offset selective pressure of drugs, reduce drug cost, and prevent 'pill fatigue' [5]. However, this strategy remains controversial and has ironically been shown to increase adverse events (the SMART study) [6] and resistance (STACCATO study) [7]. New therapeutic options that target different steps in the virus life cycle are therefore critical for disease management.

Viral entry into the cell is an essential step in the replication cycle of HIV. The discovery that this process requires attachment of the virus to both the CD4 receptor and a chemokine receptor [8] has led to a treatment strategy that targets the earliest steps of the viral replication process. Blocking viral entry before infection of a cell has the advantage of protecting uninfected cells, reducing intracellular virus as well as collateral alterations in gene transcription resulting from the insertion of highly active viral regulatory sequences. HIV utilizes two different chemokine receptors for entry, CCR5 and CXCR4, with receptor usage determined by viral strain. CCR5 is used by most primary HIV isolates and is the predominant receptor at the time of infection, with CXCR4 usage occurring during later stages of the disease in approximately 30–50% of HIV-infected patients, generally associated with lower CD4 cell counts [9].

CCR5 is one of a large family of chemokine receptors and functions to activate leucocytes during inflammation [10]. CCR5 is an attractive target for therapy, because individuals with a naturally occurring mutation in CCR5 (CCR5 Δ 32), which results in loss of function, have essentially normal immune function, natural 'resistance' to HIV in the homozygous state or slower CD4 decline or progression to AIDS or death in individuals infected with HIV in the presence of a single copy of CCR5 Δ 32 heterozygous state [11–16].

Several small-molecule inhibitors and monoclonal antibodies targeted to disrupt the interaction between HIV and CCR5 are currently in development, with one, maraviroc, recently approved in the USA, European Union and Canada. Maraviroc is a potent, orally bioavailable CCR5 antagonist that has been shown to be safe and effective in treatment-experienced patients infected with CCR5-tropic HIV-1 [17, 18]. This supplement represents a compilation of studies that report the pharmacokinetics, pharmacodynamics and potential drug interactions of maraviroc, as well as modelling of the maraviroc–CCR5 interaction. The information provided herein should aid in the incorporation of maraviroc into existing treatment regimens to achieve maximum clinical benefit.

The first article in this supplement evaluates the pharmacokinetics and tolerability of single and multiple oral

doses of up to 1200 mg once daily of maraviroc in healthy subjects. Maraviroc was rapidly absorbed into systemic circulation, was efficiently cleared, and did not significantly influence the activity of major drug-metabolizing enzymes. Maraviroc was well tolerated at clinically relevant doses, with most adverse events being mild or moderate. The dose-limiting adverse event was postural hypotension, which was seen at incidences greater than those seen with placebo, at maraviroc doses of ≥ 600 mg.

The second article investigates the effect of maraviroc on the pharmacokinetics of midazolam, lamivudine/zidovudine, and oral contraceptives in healthy subjects. At clinically relevant doses, maraviroc had only a minor influence on the pharmacokinetics of midazolam, a drug commonly used as a probe for cytochrome P450 (CYP) 3A4 interactions, suggesting that maraviroc is unlikely to interfere with other drugs metabolized by CYP3A4. Maraviroc had no clinically relevant effects on the pharmacokinetics of lamivudine and zidovudine [two nucleoside RT inhibitors (NRTIs) used in HAART], or the oral contraceptive steroids ethinylloestradiol and levonorgestrel. Lamivudine and zidovudine are primarily cleared by the renal route and non-CYP metabolism, respectively; whereas ethinylloestradiol and levonorgestrel are metabolized by a number of different enzymes, including CYP, UDP-glucuronosyltransferases, and sulphotransferases. Because maraviroc had no clinically significant effect on any of these drugs, the likelihood that maraviroc would affect the pharmacokinetics of other drugs, cleared by this wide range of routes, is low.

Maraviroc is predominantly cleared by CYP3A4-mediated metabolism and is also a P-glycoprotein (Pgp) substrate. Hence, there is the potential for drugs that affect these enzymes/transporters to influence the pharmacokinetics of maraviroc. Given that maraviroc will be co-administered with other antiretroviral agents, many of which are CYP3A4/Pgp modulators, such as the protease inhibitors (PIs) and non-NRTIs, this is an important area to study. The third and fourth articles examine the effect of CYP3A4 inhibitors and inducers on the pharmacokinetics of maraviroc in healthy subjects. The CYP3A4 inhibitors ketoconazole, lopinavir/ritonavir, saquinavir with/without ritonavir, low-dose ritonavir, and atazanavir with/without ritonavir increased maraviroc exposure, albeit to different degrees of magnitude. Of the drugs studied, saquinavir/ritonavir caused the largest increase in maraviroc exposure, and low-dose ritonavir caused the smallest increase; in all cases the increase in peak concentration (C_{max}) was much lower than the increase in total exposure [area under the concentration–time curve (AUC)]. Downward adjustment of the maraviroc dose by 50% appears to be able to compensate for the interaction. Tipranavir/ritonavir did not appear to effect maraviroc exposure at steady state. CYP3A4 inducers with and without CYP3A4 inhibitors were also investigated. Maraviroc exposure was decreased by approximately 70% and 50% with concurrent administra-

tion of rifampicin and efavirenz, respectively. Doubling the maraviroc dose appeared to compensate for the induction. Co-administration of maraviroc with either lopinavir/ritonavir plus efavirenz or saquinavir/ritonavir plus efavirenz resulted in an increase in maraviroc exposure to approximately half the increase seen with these PIs alone.

The next article examines renal clearance; maraviroc is partially cleared by the kidneys and hence could be affected by drugs that rely on, or inhibit, renal elimination. Cotrimoxazole (sulfamethoxazole/trimethoprim) and tenofovir are commonly used in HIV-infected patients and are inhibitors or substrates of renal clearance. Data from these studies demonstrate that neither cotrimoxazole nor tenofovir causes a clinically relevant change in maraviroc pharmacokinetic parameters.

Another study examines the effects of selected drug combinations on the pharmacokinetics of maraviroc in HIV-1 positive patients on stable HAART regimens. Treatment regimens investigated included efavirenz/zidovudine/lamivudine, efavirenz/didanosine/tenofovir, nevirapine/lamivudine/tenofovir, and lopinavir/ritonavir/stavudine/lamivudine. The efavirenz-containing regimens resulted in an approximate 50% reduction in exposure (AUC_{12}) to maraviroc compared with historical controls. The lopinavir/ritonavir-containing regimen resulted in an approximate doubling of maraviroc exposure (AUC_{12}), whereas the nevirapine-containing regimen resulted in a small increase in C_{max} , but no effect on AUC_{12} . The results for efavirenz and lopinavir/ritonavir are consistent with previous data in healthy subjects.

Another study examines the effect of maraviroc on the QT/QTc interval in healthy subjects. At single doses up to and including 900 mg, maraviroc did not have any clinically relevant effect on QTcF (Fridericia's correction) or QTcI (individual correction factor based on each subject's QT:RR relationship). The mean difference from placebo in QTcF and QTcI was <4 ms for all doses of maraviroc vs. 14 ms for the active comparator, moxifloxacin.

In the next article, the absorption, metabolism and elimination pathways for maraviroc are explored, and the absolute bioavailability of an oral tablet dose is quantified. Data indicate that most of the orally administered 100-mg maraviroc dose was excreted in the faeces (76.4%), with 19.6% excreted in the urine. Unchanged maraviroc was the major circulating component in the plasma, accounting for 42% of circulating radioactivity. Profiling of urine and faeces showed extensive metabolism, although unchanged maraviroc was the major excreted component. Absolute bioavailability of the 100-mg oral tablet dose of maraviroc was found to be 23%.

Meta-analysis of maraviroc pharmacokinetics was conducted using data from 15 studies in healthy subjects and two studies in asymptomatic HIV-infected subjects. A two-compartment model parameterized to separate out absorption and clearance components on bioavailability was used. Absorption was described by a lagged first-order

process and a sigmoid maximum effect ($E_{\max}$) model described the effect of dose on absorption. The meta-analysis concluded that, for the typical non-Asian subject, fasted bioavailability increased asymptotically with dose from 24% at 100 mg to 33% at 600 mg. The typical Asian subject has a drug exposure (AUC) 26.5% higher than the typical non-Asian subject, a difference that is not considered to be clinically relevant. None of the other covariates tested had any clinically relevant effects on exposure.

The final two articles focus on interactions between the CCR5 receptor and maraviroc. One study determined that, at doses as low as 3 mg b.i.d., the majority of plasma maraviroc concentrations were associated with receptor occupancy $\geq 50\%$. A simple direct $E_{\max}$ model appeared to describe the pharmacokinetic receptor occupancy relationship, with an estimated dissociation constant (K_D) of $\sim 0.0894 \text{ ng ml}^{-1}$, which was far below the estimated operational *in vivo* concentration that results in 50% functional inhibition (IC_{50}) of $\sim 8 \text{ ng ml}^{-1}$. Accordingly, simulations using the estimated K_D in place of the operational IC_{50} led to a marked overprediction of the decrease in viral load–time profiles. It was concluded that CCR5 receptor occupancy by maraviroc as measured by this assay is not a direct measure of the operational inhibition of the infectivity rate of the virus and will probably not be valuable as a biomarker for predicting CCR5 antagonist efficacy. The other study developed a novel combined viral dynamic and operational model of (ant-) agonism that describes the pharmacodynamic effects of maraviroc on viral load. The anchor point of the operational model in the differential equations of the viral dynamic model is the infection rate constant, which is assumed to be dependent on the number of free activated receptors on each target cell. The new model offers an explanation for the apparent discrepancy between the *in vivo* binding of maraviroc to the CCR5 receptor ($K_D = 0.089 \text{ ng ml}^{-1}$) and the estimated *in vivo* inhibition of the infection rate ($IC_{50} \sim 8 \text{ ng ml}^{-1}$). The estimated concentration of activated receptor that gives half maximum infection rate (K_E) value of the operational model indicates that only 1.2% of the free activated receptors are utilized to elicit 50% of the maximum infection rate, suggesting that activated target cells express more receptors than needed for efficient infection. Consequently, the spare receptors require blocking before any decrease in the infection rate and, consequently, the viral load at equilibrium can be detected. The new model allows for simultaneous simulation of the binding of maraviroc to CCR5 and the predicted change in viral load after both short- and long-term treatment.

In summary, orally administered maraviroc was rapidly absorbed into the systemic circulation, was efficiently cleared, and did not yield adverse events or drug interactions that would preclude its use in HAART regimens. The papers presented here outline the pharmacokinetic, pharmacodynamic and safety data for maraviroc from studies in healthy subjects and HIV-1-infected patients (Phase 1/2a

studies) and should assist physicians in integrating maraviroc into appropriate treatment regimens for HIV patients.

Competing interests

M.B. received an honorarium from Pfizer Inc. for her work as co-editor of this supplement. S.A. was employed by Pfizer Ltd at the time of this research.

M.B. received an honorarium from Pfizer in connection with her role as guest editor of this supplement. Editorial assistance was provided by Susan DeRocco, PhD and Janet E. Matsuura, PhD at Complete Healthcare Communications, Inc., and was funded by Pfizer Inc, New York, NY, USA.

REFERENCES

- 1 Joint United Nations Programme on HIV/AIDS. AIDS Epidemic Update: Special Report on HIV/AIDS. Geneva, Switzerland: UNAIDS/WHO, 2006.
- 2 Dornadula G, Zhang H, VanUitert B, Stern J, Livornese L Jr, Ingerman MJ, Wilek J, Kedaris RJ, Natkin J, De Simone J, Pomerantz RJ. Residual HIV-1 RNA in blood plasma of patients taking suppressive highly active antiretroviral therapy. *JAMA* 1999; 282: 1627–32.
- 3 Department of Health and Human Services Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents: definitions and causes of antiretroviral treatment failure: 28–9. 10 October 2006.
- 4 Cohen OJ, Fauci AS. Current strategies in the treatment of HIV infection. *Adv Intern Med* 2001; 46: 207–46.
- 5 Gulick RM. Structured treatment interruption in patients infected with HIV: a new approach to therapy. *Drugs* 2002; 62: 245–53.
- 6 El-Sadr W, Neaton J. Episodic CD4-guided use of ART is inferior to continuous therapy: results of the SMART study. In: 13th Conference on Retroviruses and Opportunistic Infections; 2006 February 5–8; Denver, CO.
- 7 Ananworanich J, Gayet-Ageron A, Le Braz M, Prasithsirikul W, Chetchotisakd P, Kiertiburanakul S, Munsakul W, Raksakulkarn P, Tansuphasawasdikul S, Sirivichayakul S, Cavassini M, Karrer U, Genne D, Nuesch R, Vernazza P, Bernasconi E, Leduc D, Satchell C, Yerly S, Perrin L, Hill A, Perneger T, Phanuphak P, Furrer H, Cooper D, Ruxrungtham K, Hirschel B; Staccato Study Group; Swiss HIV Cohort Study. CD4-guided scheduled treatment interruptions compared with continuous therapy for patients infected with HIV-1: results of the Staccato randomised trial. *Lancet* 2006; 368: 459–65.
- 8 Cocchi F, DeVico AL, Garzino-Demo A, Arya SK, Gallo RC, Lusso P. Identification of RANTES, MIP-1 alpha, and MIP-1

- beta as the major HIV-suppressive factors produced by CD8+ T cells. *Science* 1995; 270: 1811–5.
- 9 Shaheen F, Collman RG. Co-receptor antagonists as HIV-1 entry inhibitors. *Curr Opin Infect Dis* 2004; 17: 7–16.
 - 10 Mueller A, Strange PG. The chemokine receptor, CCR5. *Int J Biochem Cell Biol* 2004; 36: 35–8.
 - 11 Dean M, Carrington M, Winkler C, Huttley GA, Smith MW, Allikmets R, Goedert JJ, Buchbinder SP, Vittinghoff E, Gomperts E, Donfield S, Vlahov D, Kaslow R, Saah A, Rinaldo C, Detels R, O'Brien SJ. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CCR5 structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. *Science* 1996; 273: 1856–62.
 - 12 Eugen-Olsen J, Iversen AK, Garred P, Koppelhus U, Pedersen C, Benfield TL, Sorensen AM, Katzenstein T, Dickmeiss E, Gerstoft J, Skinhøj P, Svejgaard A, Nielsen JO, Hofmann B. Heterozygosity for a deletion in the CCR-5 gene leads to prolonged AIDS-free survival and slower CD4 T-cell decline in a cohort of HIV-seropositive individuals. *Aids* 1997; 11: 305–10.
 - 13 Huang Y, Paxton WA, Wolinsky SM, Neumann AU, Zhang L, He T, Kang S, Ceradini D, Jin Z, Yazdanbakhsh K, Kunstman K, Erickson D, Dragon E, Landau NR, Phair J, Ho DD, Koup RA. The role of a mutant CCR5 allele in HIV-1 transmission and disease progression. *Nat Med* 1996; 2: 1240–3.
 - 14 Liu R, Paxton WA, Choe S, Ceradini D, Martin SR, Horuk R, MacDonald ME, Stuhlmann H, Koup RA, Landau NR. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. *Cell* 1996; 86: 367–77.
 - 15 Michael NL, Louie LG, Rohrbaugh AL, Schultz KA, Dayhoff DE, Wang CE, Sheppard HW. The role of CCR5 and CCR2 polymorphisms in HIV-1 transmission and disease progression. *Nat Med* 1997; 3: 1160–2.
 - 16 Samson M, Libert F, Doranz BJ, Rucker J, Liesnard C, Farber CM, Saragosti S, Lapoumeroulie C, Cogniaux J, Forceille C, Muyldermans G, Verhofstede C, Burtonboy G, Georges M, Imai T, Rana S, Yi Y, Smyth RJ, Collman RG, Doms RW, Vassart G, Parmentier M. Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. *Nature* 1996; 382: 722–5.
 - 17 Lalezari J, Goodrich J, DeJesus E, Lampiris H, Gulick R, Saag M, Ridgway C, McHale M, van der Ryst E, Mayer H. Efficacy and safety of maraviroc (MVC) plus optimized background therapy (OBT) in viremic antiretroviral treatment experienced patients infected with CCR5-tropic HIV-1: 24-week results of a phase 2b/3 study in the USA and Canada. In: 14th Conference on Retroviruses and Opportunistic Infections; 2007 February 25–28; Los Angeles, CA.
 - 18 Nelson M, Fätkenheuer G, Konourina I, Lazzarin A, Clumeck N, Horban A, Tawadrous M, Sullivan J, Mayer H, van der Ryst E. Efficacy and safety of maraviroc (MVC) plus optimized background therapy (OBT) in viremic, antiretroviral treatment experienced patients infected with CCR5-tropic (R5) HIV-1 in Europe, Australia and North America: 24-week results. In: 14th Conference on Retroviruses and Opportunistic Infections; 2007 February 25–28; Los Angeles, CA.

RECEIVED

5 November 2007

ACCEPTED

11 January 2008

CORRESPONDENCE

Dr Marta Boffito, PhD.

Tel: +44 2088 466507

Fax: +44 2087 465628

E-mail: marta.boffito@chelwest.nhs.uk