Eur J Med Res (2007) 12: 409-417

CCR5 Antagonists: Comparison of Efficacy, Side Effects, Pharmacokinetics and Interactions – Review of the Literature

J. M. Emmelkamp, J. K. Rockstroh

Department of Medicine I, University Clinic Bonn, Germany

Abstract

In the context of emerging resistance to antiretroviral agents in HIV medicine, the development of new drugs classes with a novel mechanism of action remains essential. The CCR5 co-receptor antagonists inhibit fusion of HIV with the host cell by blocking the interaction between the gp-120 viral glycoprotein and the CCR5 chemokine receptor. So far, four CCR5 antagonists have entered clinical evaluation, of which three are currently still in different stages of clinical assessment. In this review we compare the clinical efficacy in phase I and II as well as the long-term tolerability, pharmacokinetics and interactions of these new antiretroviral drugs entering HIV practice.

Being the first CCR5 antagonist to be investigated in clinical trials, aplaviroc showed initial potent antiviral activity. However, after the occurrence of severe hepatotoxicity in several patients, its development had to be stopped in October 2005. The second CCR5 antagonist, maraviroc, has displayed promising results in phase I, II and III studies, showing a significantly greater decline in HIV RNA and CD4 cell increase compared to placebo, with no clinically relevant differences in safety profile and tolerability. The expanded access program for maraviroc was opened in June 2007 in several European countries. The FDA approved the use of maraviroc for antiretroviral therapy of HIV on the 7th of august, 2007. Finally, the third CCR5 antagonist vicriviroc also showed long-term potent viral activity in phase II studies as long as it was boosted with low-dose ritonavir, with no significant differences in grade 3 and grade 4 adverse effects compared to placebo. The phase II clinical trial amongst ART experienced individuals who received Ritonavir-boosted vicriviroc 10-15 mg qd was unblinded early because of the unexpected occurrence of malignant lymphoma and adenoma. However, no further malignancies occurred in the extended follow-up evaluation of this drug until today. Vicriviroc is currently entering phase III evaluation. Pharmacokinetics of maraviroc and vicriviroc may be influenced by coadministration of CYP3A4-inhibitors and –inducers, since both substances are metabolised primarily by the CYP3A4 system. This requires dose adjustments when combined with for instance protease inhibitors (with the exception of tipranavir/r), efavirenz, ketoconazole or rifampin.

Concerns have risen about possible class-specific long-term adverse effects of CCR5 antagonists, particularly with regard to hepatotoxicity or malignancy. The pooled data from phase II and III however, so far show no new or added toxicity risk for maraviroc or vicriviroc compared to the respective placebo arms of the trials. Extended follow-up of the vicriviroc trials showed no further case of malignancy, reassuring the overall good tolerability profile of the drug so far.

Introduction

In order for HIV to complete replication and infect further cells, binding to the CD4 receptor is essential for HIV entry into human cells. After binding to CD4, HIV gp120 binds to either the CCR5- or the CXCR4 co-receptors in order to fuse cells membranes and enter CD4-positive T-cells of the host. Interestingly, 1% of Caucasians have a homozygous 32-base pair deletion in the CCR5 gene (CCR5-Δ32). In these individuals, CCR5 expression on the CD4 cell-surface is absent. This has been shown to be protective against acquiring HIV-infection [1]. HIV-infected patients who are heterozygous for CCR5-Δ32 have been demonstrated to have delayed disease progression [2, 3]. Taking into account the importance of chemokine receptors for HIV to enter the cell and the marked influence on infectibility and disease progression, blockade of chemokine receptors emerges as an new exciting extracellular target in HIV drug development. Subsequently, first CCR5 co-receptor antagonists have been developed which inhibit entry of HIV into the host cell by blocking the CCR5 chemokine receptor. So far four CCR5 antagonists, aplaviroc (manufactured by GSK), maraviroc (manufactured by Pfizer) vicriviroc (manufactured by Schering Plough) and INCB-9471 (Incyte) have entered clinical development and have proved to reduce plasma HIV-RNA in HIV-infected adults. In the following review, efficacy, side effects, interactions and pharmacokinetics of the three CCR5 co-receptor antagonists from which more extensive public data are currently available (aplaviroc, vicriviroc, and maraviroc) will be introduced, compared and critically discussed.

Stage of Development

The development of the first CCR5 co-receptor antagonist aplaviroc had to be stopped in October 2005 after the occurrence of severe hepatotoxicity in several patients [4, 5]. Therefore currently three CCR5 co-

receptor antagonists, remain in clinical development. Most recently maraviroc (Celsentri) became the first FDA approved CCR5-antagonist, whereas vicriviroc has completed its phase II development and is currently starting to enrol in phase III studies.

After initial reports of significant reductions in viral load in a phase IIa placebo-controlled trial of INCB-9471 [6], phase IIb clinical studies are expected to enrol in late 2007 and early 2008. Finally, two CCR5 antagonists developed by Takeda are currently in early evaluation. TAK-652 has shown potent selective inhibition of R5 HIV-1 replication in preclinical and in phase I pharmacokinetic assessment [7]. TAK-220 has also shown promising findings in preclinical evaluation [8]. Since no extended clinical data on INCB9471 and the Takeda-drugs are available yet, these agents will not be discussed here in further detail.

Methods

Literature was searched in Medline and the PubMed database using the MESH-keywords CCR5 receptor, antiretroviral agents and treatment outcome. Articles that seemed suitable based on title and abstract were included. Additionally, a personal collection of literature on the subject (congress-papers, posters, slide sets) was consulted.

Efficacy of CCR5-antagonists

All three CCR5 antagonists showed high antiretroviral efficacy in phase I studies with an average decline in HIV viral load after 10-14 days of monotherapy of 1.45-1.66 $\log_{10}$ c/mL (Fig. 1), hereby confirming in a proof of concept study that extracellular blockade of CCR5 is a promising new strategy in inhibiting HIV replication. In the following we will discuss the outcome of phase I and II trials for the three drugs, respectively. The results of the most relevant studies are summarized in Table 1.

Efficacy of Maraviroc in Phase I and II

Maraviroc is active against CCR5 receptor-tropic HIV-1 but not against CXCR4 or dual-tropic virus. The antiretroviral potency of maraviroc was studied in a phase I 10-day monotherapy study in 63 asymptomatic, HIV positive patients who were pre-screened for R5-tropism. Patients were randomized to treatment with 25 mg, 100 mg, 300 mg maraviroc once daily (qd) or 50 mg, 100 mg, 150 mg maraviroc twice daily (bid) or placebo for a period of 10 days. Mean decline of viral load was greater in all maraviroc treatment arms compared to placebo on day 11, with an exemplary -1,45 $\log_{10}$ c/mL in the 150 mg bid arm versus 0,02 $\log_{10}$ c/mL in the placebo treated patients (Fig. 1). No difference in viral load reduction under maraviroc was observed between doses of 200 mg and above, and all patients that received 200 mg or more of maraviroc achieved a HIV-RNA decline of > 1 $\log_{10}$ c/mL. Furthermore, there was no difference in reduction of viral load in patients who were fed versus in fasted individuals [9]. In a comparison of 150 mg maraviroc bid versus 300 mg once daily dosing, no differences in reduction of HIV-RNA were seen at day 11. Thus, a once daily administration of maraviroc appeared feasible.

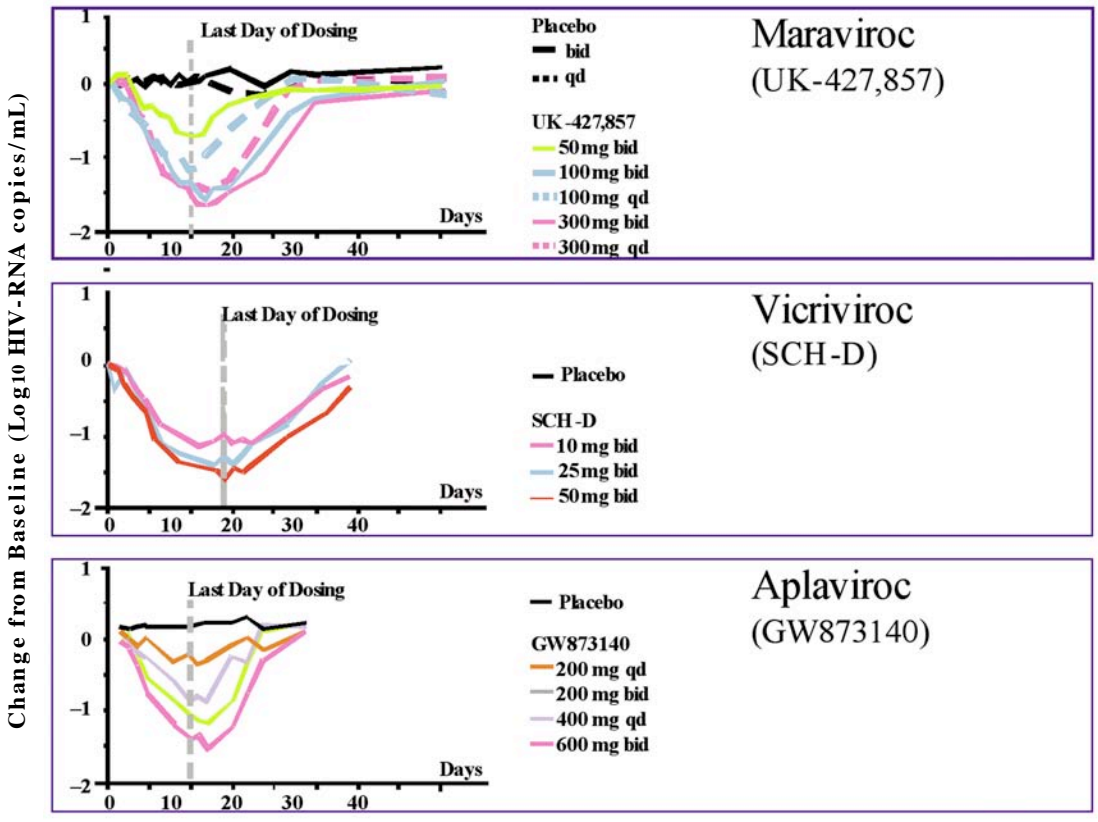

Fig. 1. antiviral activity of CCR5-antagonists in phase I studies.

In a phase IIb exploratory trial, efficacy of maraviroc was also assessed as an add-on to an optimized background therapy (OBT) in pre-treated patients with mixed X4/R5-tropic virus. The mean decrease in HIV-RNA obtained was -0,91 $\log_{10}$ c/mL in the 150 mg maraviroc qd + OBT arm, -1.20 $\log_{10}$ c/mL in the maraviroc 150 mg bid + OBT arm and -0.97 $\log_{10}$ c/mL in patients receiving placebo. These findings showed no significant decline in viral load reduction in patients with dual or mixed tropic infection in maraviroc treated patients compared to placebo. However, a greater increase in CD4 cell count was seen in the maraviroc study arms, with a change of CD4 cells/mm^3 from baseline of +60, +62 and +36 in the 150 mg maraviroc qd arm, 150 mg maraviroc bid arm and placebo group, respectively [10].

Maraviroc is currently being evaluated in heavily pre-treated patients in the phase III studies MOTIVATE 1 (USA and Canada) and MOTIVATE 2 (Europe, Australia, USA), as well as in ART-naive patients in the Pfizer 1026 (MERIT) study, where maraviroc is compared with efavirenz against an NRTI-Background with AZT+3TC. The findings of these studies will be discussed in further detail in the following articles in this edition by Prof. Plettenberg and Dr. Bredeek, respectively.

Efficacy of Vicriviroc in Phase I and II

Vicriviroc also caused a significant decline in viral load in phase I studies (Fig. 1). In a sequential rising dose study 48 treatment naïve R5 HIV-infected subjects were enrolled and treated with 10 mg, 25mg, or 50mg vicriviroc bid or placebo for 14 days in a randomized blinded design. Decline of viral load in this study was dose related with a mean $\log_{10}$ c/mL drop of -1.08, -1.56 and -1.62 in the different active treatment arms, respectively [11, 12].

However, subsequently a phase II randomized, placebo-controlled trial in 92 treatment-naïve subjects with R5-tropic HIV had to be terminated because of early virological breakthrough in the vicriviroc arms [13]. In this study, individuals were randomized to receive either vicriviroc at doses of 25mg, 50mg and 75mg once daily or placebo for 14 days against an AZT/3TC background. In the placebo group, efavirenz was added. After 2 weeks of treatment a promising early viral response was seen with a mean viral load decline of 0.93 $\log_{10}$ c/mL in the group treated with 25 mg, 1.19 $\log_{10}$ c/mL in the group receiving 50 mg, 1,34 $\log_{10}$ c/mL in those receiving 75 mg in the vicriviroc arms and 0,07 $\log_{10}$ c/mL in the placebo arm with $p<0.001$. Mean increase of CD4-cell count was 25, 85 and 90 in the vicriviroc arms and 3 in the placebo group. Planned duration of this study was 48 weeks. However, at 32 weeks the study was terminated early after an increased rate of viral breakthrough was seen in the vircriviroc arms relative to the efavirenz arm (57% of patients in the 25 mg vicriviroc arm, 45% in the 50 mg vicriviroc arm and 22% in the 75 mg vicriviroc arm versus 8% in the placebo arm, $p<0.001$). M184V mutations were detected in all patients failing on vicriviroc and who had obtainable genotypes [13].

In a parallel double-blind randomized phase II study (ACTG 5211) in 118 subjects who experienced virologic failure while receiving ≥1 antiretroviral regimen containing ≥3 drugs before their current regimen and who were screened for CCR5 utilizing HIV however, vicriviroc showed a significant greater decline in HIV-RNA compared to placebo after 24 weeks of treatment when boosted with low-dose ritonavir (Fig. 2). Patients in this study received 5 mg, 10 mg or 15 mg vicriviroc as add-on to a failing ritonavir-containing HAART. After 14 days of treatment, optimisation of the background regimen was performed. Similar to the results in the treatment-naive study, the 5 mg vicriviroc arm was discontinued due to a high virologic failure rate and patients in this treatment-arm were allowed to increase the vicriviroc dose. The use of the HIV fusion inhibitor enfuvirtide in OBT was associated with better viral suppression in both the vicriviroc and placebo groups in this study [14, 15, 16].

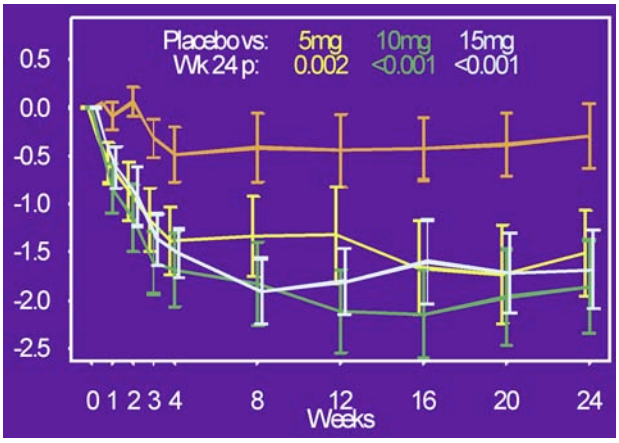

Fig. 2 (modified from Gulick et al. 2007). 24-week mean change in viral load in $\log_{10}$ c/mL induced by vicriviroc or placebo in ART-experienced patients (bars represent the 95% CI).

Recently however, more promising results from the extended follow-up study for the higher dosage arms of this phase II became available. Long term antiretroviral activity was described with a median HIV-RNA change at 48 weeks of treatment of -1.92 $\log_{10}$ c/mL in the group treated with 10 mg vicriviroc qd and -1.44 $\log_{10}$ c/mL copies/ml in the group receiving 15 mg vicriviroc qd. Seventy percent of patients with suppression of viral load of <50 copies/ml at week 24 continued to have <50 copies/ml at 48 weeks. A co-receptor shift was documented in 35 % of patients on vicriviroc who developed virologic failure. Median CD4 cell count gain was +130 in the 10 mg group and +96 in the 15 mg group [17].

Efficacy of Aplaviroc in Phase I and II

In a phase I and IIa evaluation, the CCR5-receptor antagonist aplaviroc showed initial potent antiviral activity (Fig. 1). A decline of HIV-RNA of >1 $\log_{10}$ was seen in 0% of the placebo group compared to 17% of

Table 1. efficacy of CCR5 receptor-antagonists in primary analysis.

CCR5 antagonist	Dose	Mean decline VL $\log_{10}$ c/mL	Reference
Maraviroc mono	25 mg qd	-0.43	
	100 mg qd	-1.13	
	300 mg qd	-1.35	
	50 mg bid	-0.66	
	100 mg bid	-1.42	
	150 mg bid (fasting)	-1.45	
	150 mg bid (fed)	-1.34 at day 11	Fätkenheuer 2005
Vicriviroc mono	10 mg qd	-1.08	
	25 mg qd	-1.56	
	50 mg qd	-1.62 at day 15	Schürmann 2004
Aplaviroc mono	200 mg qd	-0.46	
	200 mg bid	-1.23	
	400 mg qd	-1.03	
	600 mg bid	-1.66 at day 11	Lalezari 2005

patients receiving 200mg aplaviroc qd, 75% of patients receiving 200 mg aplaviroc bid, 63% of those treated with 400 mg aplaviroc qd and 100% of patients receiving 600 mg aplaviroc bid after 10 days of treatment. Viral load reduction was dose dependent with a mean decline of 0,12 $\log_{10}$ c/mL for placebo and 0,46 $\log_{10}$ c/mL, 1.23 $\log_{10}$ c/mL, 1.03 $\log_{10}$ c/mL and 1.66 $\log_{10}$ c/mL in the aplaviroc arms [18] (Table 1). However, the following phase IIb and III trials of aplaviroc were halted in October 2005 due to concerns about liver toxicity after four out of approximately 300 patients presented with grade 3-4 elevated liver enzymes and total bilirubin [4, 5, 19].

Tolerability and Side Effects

Adverse Events of Maraviroc and Vicriviroc

In healthy volunteers, maraviroc was well tolerated in single and multiple oral doses up to 900mg and 600mg once daily [20]. Maraviroc was also well tolerated in all doses tested in phase I and II studies. From the 195 individuals treated in phase I and II trials with maraviroc at doses up to and including 300mg bid, there were no significant differences seen in the occurrence of adverse events as compared to the patients receiving placebo [21]. Most frequently reported adverse effects included headache, asthenia, dizziness, gingivitis and nausea [9, 10]. Orthostatic hypotension occurred slightly more frequent in the maraviroc group, but only at doses of 600 mg and above [21]. In both MOTIVATE studies where pre-treated patients with R5-tropic HIV received an optimised background therapy with either 150 mg maraviroc qd, 150 mg maraviroc bid or placebo, there were no clinically relevant differences in safety profile between maraviroc and placebo treatment groups, with diarrhoea, nausea, headache and fatigue being most frequent in all groups (Table 2). A slightly higher incidence of respiratory infections and drowsiness was reported in the maraviroc arms [22, 23].

The 48 weeks-results of vicriviroc in phase II evaluation also showed good overall tolerability. No significant differences for grade 3 and 4 adverse effects were seen among the different treatment arms with placebo, 5mg, 10mg or 15mg vicriviroc. There were no seizures reported, neither did prolongation of QT interval to 1500 ms or 160 ms above baseline occur, an adverse event that had been attributed to prior investigational CCR5 antagonists [15].

Malignancies:

The ACTG 5211 trial amongst ART experienced adults with R5 tropic HIV who received ritonavir-boosted vicriviroc 10-15 mg qd was unblinded in early stages because of the unexpected occurrence of malignant lymphomas [24]. Malignancies occurred in 6 subjects randomized to vicriviroc and in 2 to placebo, from which one had been exposed to vicriviroc for a period of three months. From the 6 patients in the vicriviroc group 1 was diagnosed with gastric adenoma, 1 patient developed HPV-related squamous cell carcinoma, 2 patients developed m. Hodgkin (one of which had a history of treated Hodgkin disease) and 2 patients developed non Hodgkins lymphoma (one of which also with a history of history of Hodgkin disease) [15], which is remarkable as prevalence of non-Hodgkin lymphoma is usually lower in individuals heterozygous for CCR5-Δ32 than in the population without this genetic mutation [25]. The association of vicriviroc treatment and the occurrence of malignancies remains uncertain but appears to be not drug related. Indeed, recently published data of the ACTG 5211 study showed no further development of malignancies and a sustained antiretroviral activity of vicriviroc over 48 weeks when added to OBT [17]. Further follow up on this possible association of vicriviroc use and malignant development is needed. In the pooled data of MOTIVATE 1 and MOTIVATE 2 there was no significant difference in the occurrence of malignant disease between maraviroc-treated individuals and the placebo group [21].

Laboratory Abnormalities of Maraviroc and Vicriviroc

No higher incidence of clinically significant laboratory

alterations of maraviroc compared to placebo could be detected in different clinical trials. No clear effect on hematology parameters was observed in short term dosing studies. In phase I and II an elevation of liver function tests occurred in 7 of 195 patients receiving varying doses of maraviroc and were not dose-dependent, nor combined with hyperbilirubinemia (4 subjects had >3x ULN transaminases and 3 subjects had >1.25 to <2x ULN bilirubin) [21]. In the MOTIVATE studies in pre-treated subjects in phase III, there were no differences between the maraviroc and placebo arms regarding significant abnormalities of liver enzymes (Table 2). Alterations in amylase, lipase and neutrophil count were not described with a significantly higher frequency in the maraviroc arm than in the placebo arms. In the MERIT study which compared maraviroc with efavirenz, both in combination with combivir in ARV-naïve subjects, median maximum change in fasting lipid levels from baseline (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides) were greater in the EFV arm [26].

Under vicriviroc there was no significant difference in the incidence of grade 3 and grade 4 adverse events and placebo in phase I and II studies [11, 15]. In the ACTG 5211 study including 118 HIV-infected treatment experienced patients, grade 3 toxicity occurred in 12 of 30 patients receiving 5 mg vicriviroc, in 12 of 30 patients receiving 10 mg vicriviroc, in 15 of 30 patients treated with 15 mg vicriviroc and in 10 of the 28 patients enrolled in the placebo arm. Grade 4 toxicity occurred in 2 of 30 patients in the 5 mg vicriviroc arm, 5 of 30 patients in the 10 mg vicriviroc arm, 2 of 30 patients in the 15 mg vicriviroc arm and in 3 of 28 patients treated with placebo [15]. In a double blind dose finding study enrolling 116 antiretroviral-experienced patients, no hepatotoxicity was seen after a mean treatment duration of 14 weeks (12-28) with vicriviroc 20 mg and 30 mg qd [27].

Table 2. Maraviroc, adverse events & toxicity in phase III (MOTIVATE pooled data).

Adverse Events	**MVC bid + OBT (n 426)**	**OBT alone (n 209)**
Diarrhoea	89 (20.9 %)	45 (21.5 %)
Nausea	73 (17.1 %)	39 (18.7 %)
Headache	54 (12.7 %)	32 (15.3 %)
Fatigue	54 (12. 7%)	31 (14.8 %)
Fever	51 (12.0 %)	17 (8.1 %)
Cough	48 (11.3 %)	10 (4.8 %)
Total AE	383 (89.9 %)	175 (83.7 %)
Grade 3 AE	92 (21.6 %)	43 (20.6 %)
Grade 4 AE	42 (9.9 %)	13 (6.2 %)
Toxicities (%)	**MVC bid + OBT (n 421)**	**OBT alone (n 207)**
Discontinuations due to hepatic adverse events	1.2	1
Aspartate aminotransferase: Grade 3 >5.0 to 10.0 x ULN	3.1	2.9
Grade 4 >10.0 x ULN	1.4	0
Alanine aminotransferase: Grade 3 >5.0 to 10.0 x ULN	1.4	2.9
Grade 4 >10.0 x ULN	1.0	0.5
Total bilirubin: Grade 3 >2.5 to 5.0 x ULN	5.0	3.9
Grade 4 >5.0 x ULN	0.7	1.5

The adverse events and toxicities reported in this new class of antiretroviral agents, especially the cases of hepatic toxicity under aplaviroc and the occurrence of malignancies in individuals treated with vicriviroc, have risen concern amongst practitioners in HIV-medicine about the possibility of class-specific long term adverse effects of CCR5 antagonists. Given the early occurrence of toxicities in clinical evaluation of aplaviroc and as a higher frequency of elevated liver enzymes could not be detected in individuals treated with the other two CCR5 receptor antagonists compared to those receiving placebo even after 48 weeks of treatment, the possibility of a class specific hepatotoxic effect is highly unlikely. As for the concerns about an increased risk for development of malignancies under CCR5-antagonist containing HAART, the not forthcoming appearance of malignancies in 48 weeks of follow-up in the vicriviroc trials as well as no corresponding signal from the maraviroc trials, lessens the suspicion of a direct association between the two. Therefore, although these results are to be interpretated with caution until longer follow-up has been performed, at present the reported adverse events and toxicities of CCR5 antagonists are not to be interpreted as class-specific and related concerns should not hamper further development in this new promising class of antiretroviral drugs.

PHARMACOKINETICS

Pharmacokinetic (PK) assessment in HIV-infected subjects revealed that maraviroc is rapidly absorbed, with a time to maximum concentration (Tmax) occurring between 1 and 4 hours postdose. The plasma terminal half-life ranges from 16 to 23 hours and is dose dependent (50-100 mg bid or 300 mg bid) [9, 20]. Vicriviroc is also rapidly absorbed in the presence of food and is characterised by a Tmax of approximately 2 to 3 hours and a plasma terminal half-life of 28-32 hours, thereby supporting once daily dosing [12, 28].

A phase 1 study performed in 24 HIV-positive patients with R5 virus showed that steady-state drug concentrations of maraviroc were reached within 7 days and that approximately 50% lower plasma concentrations were observed in the fasted state. However, the antiviral effect of 150 mg bid dosing of maraviroc appeared to be independent of food intake, with

viral load reductions of 1.34 $\log_{10}$ copies/mL and 1.45 $\log_{10}$ copies/mL for the fed and fasted groups, respectively. Studies investigating the food effect for vicriviroc also demonstrated no clinically relevant food interaction. Despite a decrease in the rate of absorption and decrease in C_{max} of 58%, AUC of vicriviroc was not significantly affected by a high fat meal. Therefore, vicriviroc, as maraviroc, can be administered with or without food [29].

Drug–drug Interactions:

Both maraviroc and vicriviroc are primarily metabolized by CYP3A4, an enzyme that is part of the cytochrome p450 (CYP450) system. As a CYP3A4 substrate their drug levels may decrease when coadministered with strong CYP3A4 inducers and increase when coadministered with CYP3A4 inhibitors. Therefore, drug-drug interactions can be expected particularly with HIV protease-inhibitors. A reduction of maraviroc dose by 50% (to 150 mg bid) in the presence of protease inhibitors/potent CYP3A4 inhibitors is therefore recommended. An exception is made for the protease inhibitor tipranavir, which in healthy subjects did not lead to any significant changes in maraviroc exposure [30]. On the contrary, when administering maraviroc with efavirenz (EFV) or rifampin (in the absence of protease inhibitors), maraviroc dose should be doubled (to 600 mg bid) [31]. Table 3 summarizes the clinically relevant drug-drug interactions and possible dose adaptations for maraviroc (further in development). Maraviroc and vicriviroc have no significant inhibitory effect on any major CYP450 enzyme thereby making it unlikely that they can alter the metabolism of co-administered drugs that are metabolized by CYP450 enzymes [31, 32].

Data obtained from healthy volunteer pharmacokinetic studies indicate that maraviroc does not affect the PK of the N(t)RTIs Zidovudin (AZT), Lamivudin (3TC), or Tenofovir (TDF). Data from clinical studies further confirmed that maraviroc had no effect on components of the oral contraceptive pill (ethinylestradiol and levonorgestrel) or the renal clearance of AZT and 3TC, and only a clinically insignificant effect on midazolam (probe CYP3A4 substrate) [31, 33, 34].

CYP3A4 inducers decrease maraviroc exposure, with reductions in AUC and C_{max} of 50–70% seen in studies with efavirenz and rifampin [35, 36]. Significant decreases in systemic exposure with CYP3A4 inducers can be corrected by increasing the maraviroc dosage (see also Table 3).

CYP3A4 inhibitors increase maraviroc exposure; ketoconazole, the protease inhibitors (with the exception of tipranavir/r) and delavirdine are associated with increases in AUC (↑3–10x) and C_{max} (↑2–5x) [34, 37]. Significant increases in systemic exposure with CYP3A4 inhibitors can be corrected by reductions in the maraviroc dose (see also Table 3).

Vicriviroc shows similar metabolism characteristics to maraviroc. The pharmacokinetics of vicriviroc and AZT/3TC or TDF when co-administered to healthy volunteers showed no clinically relevant effect on the plasma exposure of vicriviroc, AZT, 3TC or TDF [38, 39]. Co-administration of EFV 600 mg qd and vicriviroc 10 mg qd resulted in an 81% decrease in vicriviroc AUC. The decrease in vicriviroc concentration, resulting from EFV induction, was more than compensated by the co-administration of 100 mg ritonavir qd, which led to an increase (384%) in vicriviroc AUC compared with vicriviroc alone [40, 41]. This is in accordance with the results of a study investigating the PK of vicriviroc in healthy volunteers during co-administration with different doses of ritonavir (100 mg qd, 100 to 400 mg bid) [42]. The latter showed an increase in vicriviroc AUC of approximately 500%, regardless of the dose of ritonavir administered. Similarly, vicriviroc AUC increased by 4.2-fold during co-administration with LPV/r. The currently investigated dose of 15 mg vicriviroc + 100 mg ritonavir bid leads to comparable vicriviroc levels as when vicriviroc 15 mg is added to a ritonavir-boosted PI. Therefore in the future vicriviroc will be able to be added to ritonavir-boosted PI regimens without any need for dose adaptation [43].

Discussion

In the light of increasing viral resistance against current antiretroviral agents, the recent development of

Table 3. Summary of important drug–drug interactions with maraviroc.

Drug name	Effect on maraviroc levels	Recommended dose adjustments
Atazanavir/r	Increased maraviroc exposure (5-fold)	Reduce maraviroc dose by 50%
Darunavir/r	Increased maraviroc exposure (4-fold)	Reduce maraviroc dose by 50%
Efavirenz	Reduced maraviroc exposure by half	Double maraviroc dose (in the absence of PIs) Reduce maraviroc dose by 50% in the presence of a boosting dose of ritonavir
Ketoconazole	Increased maraviroc exposure (5-fold)	Reduce maraviroc dose by 50%
Lopinavir/r	Increased maraviroc exposure (4-fold)	Reduce maraviroc dose by 50%
Rifampin	Reduced maraviroc exposure by one third	Double maraviroc dose (in the absence of PIs)
Ritonavir (full dose)	Increased maraviroc exposure (2.6-fold)	Reduce maraviroc dose by 50%
Tipranavir/r	No change in maraviroc exposure	No dose modification required

this new class of ARV-drug with a completely novel mode of action is hopeful. The CCR5-antagonists maraviroc and vicriviroc are active against current 3 drug-class-resistant R5-tropic HIV-1. Both substances have shown potent antiretroviral activity in pre-treated patients with advanced HIV-infection. The phase I, II and III study results of maraviroc are promising. Together with an optimised background therapy maraviroc displayed significant greater decline in HIV RNA and CD4 cell increase compared to placebo, with no clinically relevant differences in safety profile and tolerability. Vicriviroc was confronted with more obstacles on its way through clinical evaluation. Still, after initial concerns related to virologic breakthrough in low-dose treatment arms, sustained antiviral activity of vicriviroc could also be reported as long as it was boosted with ritonavir. Grade 3 and 4 adverse effects occurred equally in vicriviroc and placebo groups. Concerns about the appearance of malignancies in patients treated with vicriviroc could not be confirmed in further follow-up evaluation of this drug. The CCR5-antagonists are metabolised primarily by the CYP3A4 system. They do not inhibit or induce CYP450 at clinically relevant concentrations, but pharmacokinetics of maraviroc and vicriviroc can be influenced by coadministration of CYP3A4-inhibitors and –inductors. Hence, dose adjustments may be necessary when CCR5 antagonists are combined with other (ARV) drugs. Herewith two powerful new antiretroviral tools are presented in HIV practice, opening new treatment opportunities for patients with multiresistant strains of HIV.

REFERENCES

1. Samson M, Libert F, Doranz BJ et al.: Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. Nature 1996, 382(6593):722-725
2. Westby M, van der Ryst E. CCR5 antagonists: host- targeted antivirals fort he treatment of HIV infection. Antiviral Chemistry and Chemotherapy 2005, 16:339-354
3. Lederman M, Penn-Nicholson A, Cho M, Mosier D. Biology of CCR5 and its role on HIV infection and treatment. JAMA 2006, 296:815-826
4. Steel HM. Special presentation on aplaviroc-related hepatotoxicity. 10th EACS 2005, Dublin
5. GlaxoSmithKline terminates patient enrolment for phase III studies of investigational HIV entry inhibitor Aplaviroc (press release). GlaxoSmithKline; October 25, 2005
6. Cohen C et al. Potent antiretroviral activity of the once-daily CCR5 antagonist INCB009471 over 14 days of monotherapy. Fourth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, abstract TUAB106, Sydney, 2007
7. Masanori Baba, Katsunori Takashima, Hiroshi Miyake et al. TAK-652 inhibits CCR5-mediated human immunodeficiency virus type 1 infection in vitro and has favorable pharmacokinetics in humans. Antimicrob. Agents Chemother. 2005 49: 4584-4591
8. Masao Nishikawa, Katsunori Takashima, Toshiya Nishi et al. Analysis of binding sites for the new small-molecule CCR5 antagonist TAK-220 on human CCR5. Antimicrob. Agents Chemother. 2005 49: 4708-4715
9. Fatkenheuer G, Pozniak AL, Johnson MA, et al. Efficacy of short-term monotherapy with maraviroc, a new CCR5 antagonist, in patients infected with HIV-1. Nat Med 2005, 11:1170-2
10. Mayer H, van der Ryst E, Saag M, et al. Safety and efficacy of maraviroc, a novel CCR5 antagonist, when used in combination with optimized background therapy for the treatment of antiretroviral-experienced subjects infected with dual/mixed-tropic HIV-1: 24-week results of a phase 2b exploratory trial. Abstract ThLB0215, XVI IAC 2006, Toronto
11. Schürmann D, Rouzier R, Nourgarede R. SCH D: Antiviral activity of a CCR5 receptor antagonist. Abstract 140LB, 11th CROI 2004, San Francisco
12. Schürmann D, Pechardscheck C, Rouzier R, et al. SCH 417690: antiviral activity of a potent new CCR5 receptor antagonist. 3rd IAS Conference on HIV Pathogenesis and Treatment; 2005 July 24–27; Rio de Janeiro, Brazil; (abstr TuOa0205).
13. Greaves W, Landovitz R, Fätkenheuer G et al. Late virologic breakthrough in treatment-naïve patients on a regimen of combivir plus vicriviroc. XIII CROI; Denver 2006, Abstract 161LB
14. Gulick R, Su Z, Flexner C, et al. ACTG 5211: phase 2 study of the safety and efficacy of vicriviroc in HIV-infected treatment-experienced subjects. Abstract ThLB0217, XVI IAC 2006, Toronto
15. Gulick R, Su Z, Flexner C et al. Phase 2 Study of the Safety and Efficacy of Vicriviroc, a CCR5 Inhibitor, in HIV-1–Infected, Treatment-Experienced Patients: AIDS Clinical Trials Group 5211. J Infect Dis 2007 Jul 15 196 (2): 304-12
16. Tremblay CL, Giguel F, Kollmann C, et al. Anti-human immunodeficiency virus interactions of SCH-C (SCH 351125), a CCR5 antagonist, with other antiretroviral agents in vitro. Antimicrob Agents Chemother 2002; 46:1336–9.
17. Gulick R, Su Z, Flexner C et al. ACTG 5211: phase II study of the safety and efficacy of vicriviroc (VCV) in HIV-infected treatment-experienced subjects: 48 week results. 4th IAS Conference 2007. Abstract TUAB102
18. Lalezari J, Thompson M, Kumar P, et al. Antiviral activity and safety of 873140, a novel CCR5 antagonist, during short-term monotherapy in HIV-infected adults. AIDS 2005; 19: 1443–48
19. Crabb C. GlaxoSmithKline ends aplaviroc trials. AIDS 2006; 20: 641
20. Abel S, E. Van der Ryst, G. J. Muirhead, M. Rosario, A. Edgington, G. Weissgerber. Pharmacokinetics of Single and Multiple Oral Doses of UK-427,857-A Novel CCR5 Antagonist in Healthy Volunteers. 10th CROI, Boston, USA. February 2003. Abstract 547
21. McHale M., et al. Overview of phase 1 and 2a safety and efficacy data of maraviroc (UK-427,857). Oral Abstract Sessions: The 3rd IAS Conference on HIV Pathogenesis and Treatment 2005: Abstract no. TuOa0204
22. Lalezari J, Goodrich J, DeJesus E et al. Efficacy and Safety of Maraviroc plus Optimized Background Therapy in Viremic ART-experienced Patients Infected with CCR5-tropic HIV-1: 24-Week Results of a Phase 2b/3 Study in the US and Canada 14th CROI, Los Angeles 2007: Abstract 104bLB
23. Nelson M, Fätkenheuer G, Kounourina I et al. Efficacy and Safety of Maraviroc plus Optimized Background Therapy in Viremic, ART-experienced Patients Infected with CCR5-tropic HIV-1 in Europe, Australia, and North America: 24-Week Results. 14th CROI, Los Angeles 2007: Abstract 104aLB
24. Schering-Plough provides update on phase II study of vicriviroc: study continues in HIV treatment experienced patients (press release). Schering-Plough Corp, March 3, 2006
25. Dean M, Jacobson LP, McFarlane G et al. Reduced risk of AIDS lymphoma in individuals heterozygous for the

CCR5-Δ32 mutation. Cancer Res. 1999; 59:3561-3564
26. Saag m et al. A Multicenter, Randomized, Double-Blind, Comparative Trial of a Novel CCR5 Antagonist, Maraviroc Versus Efavirenz, both in Combination with Combivir (Zidovudine/Lamivudine), for the Treatment of Antiretroviral-Naive Subjects Infected with R5 HIV 1: Week 48 Results of the MERIT Study. 4th IAS, Sydney, July 2007. Abstract Number WESS104
27. Slim J, Sobhie DR, DeJesus e, et al. Safety of vicriviroc in antiretroviral-experienced patients: 12-week VICTOR-E1 results. Poster exhibition: 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention: Abstract No. WEPEA108
28. Strizki JM, Tremblay C, Xu S, et al. Discovery and characterization of vicriviroc (SCH 417690), a R5 antagonist with potent activity against human immunodeficiency virus type 1. Antimicrob Agents Chemother 2005; 49: 4911-9.
29. Keung A, Sansone A, Caceres M, Kraan M, Gaillac B. Effect of Food on Bioavailability of SCH 417690 in Healthy Volunteers [abstract A-1200]. 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC. December 16-19, 2005.
30. Abel S, al. E. Effect of boosted tipranavir on the pharmacokinetics of maraviroc (UK 427,857) in healthy volunteers [abstract LBPE4.3/15]. 10th European AIDS Conference, Dublin. November 17-20, 2005
31. Abel S, Russell D, Ridgway C, Muirhead G. Overview of the drug-drug interaction data for maraviroc (UK-427,857). 6th International Workshop on Clinical Pharmacology of HIV Therapy, April 28-30, 2005;Quebec City, Quebec, Canada. Abstract 76
32. Muirhead G, Pozniak A, Gazzard B, Nelson M, Moyle G, Ridgway C, Taylor-Worth R, Russell D. A Novel Probe Drug Interaction Study to Investigate the Effect of Selected ARV Combinations on the Pharmacokinetics of a Single Oral Dose of UK-427,857 in HIV + ve Subjects. 12th Retroconference on Retroviruses and Opportunistic Infections, February 22-25, 2005; Boston, MA, USA. Abstract 663.
33. Abel S, et al. 5th International Workshop on Clinical Pharmacology of HIV Therapy. Rome, Italy, 1-3 April 2004; Abstract 5.7
34. Abel S, et al. 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, Illinois, USA, 14-17 September 2003; Abstract A-1619
35. Pfizer. Data on file. Presented as part of the FDA Antiviral Drugs Advisory Committee (AVDAC) meeting, held 24 April 2007. Available at: http://www.fda.gov/ohrms/dockets/ac/cder07.htm#AntiviralDrugs. 2007.
36. Jenkins T, et al. 5th International Workshop on Clinical Pharmacology of HIV Therapy. Rome, Italy, 1-3 April 2004; Abstract 5.4.
37. Abel S, et al. 5th International Workshop on Clinical Pharmacology of HIV Therapy. Rome, Italy, 1-3 April 2004; Abstract 5.8
38. Sansone A, Guillaume M, Kraan M, Keung A, Caceres M, Boutros T. The pharmacokinetics of SCH 417690 when administered alone and in combination with lamivudine/zidovudine. 6th International Workshop on Clinical Pharmacology of HIV Therapy, April 28-30, 2005; Quebec City, Quebec, Canada. Abstract 84.
39. Sansone A, Guillaume M, Kraan M, Soni P, Keung A, Boutros T. Pharmacokinetics of SCH 417690 administered alone and in combination with tenofovir. 6th International Workshop on Clinical Pharmacology of HIV Therapy, April 28-30, 2005; Quebec City, Quebec, Canada. Abstract 85.
40. Saltzman M, Rosenberg M, Kraan M, Keung A, Boutros T, Soni P, Sansone A. Pharmacokinetics of SCH417690 administered alone or in combination with ritonavir and efavirenz in healthy volunteers. 3rd IAS Conference on HIV Pathogenesis and Treatment, July 24-27, 2005; Rio de Janeiro, Brazil. Abstract TuPe3.1.B08.
41. Sansone A, Saltzman M, Rosenberg M, et al. Pharmacokinetics of SCH 417690 administered alone or in combination with ritonavir and efavirenz in healthy volunteers 6th International Workshop on Clinical Pharmacology of HIV Therapy, April 28-30, 2005; Quebec City, Quebec, Canada. Abstract 79.
42. Sansone A, Seiberling M, Kraan M, Keung A, Martinho M. Similar increase in SCH 417690 plasma exposure with coadministration of varying doses of ritonavir in healthy volunteers. 6th International Workshop on Clinical Pharmacology of HIV Therapy, April 28-30, 2005; Quebec City, Quebec, Canada. Abstract 78.
43. Sansone A, Keung A, Tetteh E, Weisbrot H, Martinho M, Lang S, et al.Pharmacokinetics of vicriviroc are not affected in combination with five different protease inhibitors boosted by ritonavir [abstract 582]. 13th Conference on Retroviruses and Opportunistic Infections, Denver, CO. February 5-8, 2006

Received: August 27, 2007 / Accepted: August 28, 2007

Address for correspondence:
Professor Dr. med. Jürgen Rockstroh
Department of Medicine I
University Clinic Bonn
Sigmund-Freud-Str. 25
53105 Bonn

Curriculum Vitae

Jetske Emmelkamp
Jetske Emmelkamp obtained the medical degree in 2005 at the university of Amsterdam in the Netherlands. She is currently continuing medical education as a resident in the immunological outpatient clinic of the Friedrich-Wilhelms-University in Bonn, Germany.

Curriculum Vitae

Professor Dr. med. Jürgen Rockstroh
Professor Dr. med. Jürgen K. Rockstroh is a well known physician in HIV medicine, leading the immunological outpatient department of the Friedrich-Wilhelms-University in Bonn, Germany. He is chairman of DAIG (German AIDS Society), and has published over 200 papers in leading medical journals. His main interests lie in the field of HIV/HCV-coinfection as well as in the development and improvement of antiretroviral therapy strategies In 2002 he received the Clinical Infectious Diseases Prize and in 2005 the AIDS-Prize from the German Society for Infectious Diseases.