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CCR5 Antagonists in the Treatment of Treatment-naïve Patients Infected with CCR5 Tropic HIV-1

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Abstract
A new class of antiretroviral drugs is now available to the HIV provider: The CCR5 Antagonists belong to a group of entry inhibitors with a novel mechanism of action. While these antagonists do not directly interfere with any of the steps of HIV replication, they block the CCR5 receptor, one of the co-receptors HIV uses to enter its target cell. Thus CCR5 antagonists are able to prevent infection of the cell and represent a new and unique mechanism for the treatment of HIV. There is great interest in utilizing this new drug class in early treatment of HIV to prevent infection of large cell pools; CCR5 antagonists even may be useful tools in the various settings of exposure prophylaxis. Maraviroc is now approved in both the European Union and the United States for the treatment of HIV infection. This is the first medication belonging to the new class of CCR5 antagonists, and the first approval of an orally available drug in a new class since 1996.

Aplaviroc, maraviroc, and vicriviroc are small molecule inhibitors of CCR5 that block HIV-1 infection in vitro and reduce plasma HIV-1 RNA in HIV infected subjects by approximately 1.5 $\log_{10}$ copies/mL over 10-14 days when given as single agents. Very limited data is available on the use of CCR5 antagonists in treatment naïve patients due to early termination of many trials because of inferior performance or toxicity and at the time of this writing in August 2007 there is only one ongoing non-inferiority trial in the naïve patient population. The 48 week interim results of this trial using twice daily maraviroc were reported at the International AIDS Society meeting in July 2007. Maraviroc compared to efavirenz was non-inferior in regards to percentage of subjects reaching viral loads below 400 copies/mL, but not so for the analysis of subjects reaching viral loads below 50 copies/mL. On the other hand maraviroc had a superior side-effect profile, fewer adverse events and a greater increase of CD4 cell count than efavirenz. These data will revitalize the interest in CCR5 antagonists as a treatment option for the treatment-naïve patients.

In order to be used as first line drugs, CCR5 antagonists face a number of challenges: They will have to be proven to be as potent, durable, safe, and convenient as current available options. Important questions unique to this new class will have to be answered: What are the mechanisms and risks of tropism change? What is the role and needed frequency of tropism testing, and what efficacy is seen in patients with dual-tropic/mixed infection in the long term? Clearly until we have answers to these questions CCR5 antagonists should be reserved for the treatment-experienced patient population with limited treatment options.

Introduction

Maraviroc is now approved in both the European Union and the United States for the treatment of HIV infection. This is the first medication belonging to the new class of CCR5 antagonists, and the first approval of an oraly available drug in a new class since 1996. Yet another new class, the integrase inhibitors, are available in expanded access programs and are likely to become approved in 2007. The opportunity of providing two new drug classes revolutionizes the care of the treatment experienced patient in a manner not seen since the mid-1990's. With other drugs available in the salvage setting, like the third generation protease inhibitors darunavir or tipranavir, it is now possible for many patients to receive a fully suppressive antiretroviral regimen.

Past experience in the HIV field has taught us that drugs initially approved for the treatment-experienced often become treatment options for naïve patients over time. This is true for commonly used drugs like Lopinavir/ritonavir, Fosamprenavir, Atazanavir and Tenofovir; it follows to ask what is the efficacy of CCR5 antagonists in the treatment-naïve population. Most of the clinical trials involving CCR5 antagonists were conducted in groups of highly treatment experienced patients, for whom there is the greatest need for new medications. Designs of these trials often use the CCR5 antagonist as an add-on drug to an optimized background regimen (OBR) based on individual resistance test results compared to OBR. Data from these trials have very little value for the evaluation of CCR5 antagonist use in treatment-naïve patients. Since the early proof-of-concept studies demonstrated prompt reductions in plasma HIV-1 RNA, averaging approximately 1.5-1.7 $\log_{10}$ copies/mL over 10-14 days when CCR5 antagonists were administered as single agents (Schurmann D et al. 2007, Fatkenheuer G et al. 2005)

it is clear that these potent agents have a larger role beyond just as add-on drugs. Three CCR5 inhibitors, aplaviroc, vicriviroc and maraviroc entered into Phase 2b and Phase 3 clinical development studies. All of them have also been studied for the treatment of naïve patients. Unfortunately a number of challenges have hindered the development in regards to the treatment naïve population: Vicriviroc's treatment-naive study was terminated due to non-inferior performance of vicriviroc compared to efavirenz. Similarly, once daily maraviroc performed not non-inferior compared to efavirenz. Safety of the drug class has been a major concern; aplaviroc's development was halted due to hepatotoxicity seen in trials. Several subjects receiving vicriviroc developed malignancies. It remains unclear whether these cases are drug associated adverse events or unfortunate coincidences.

Aplaviroc

Aplaviroc in a 10-day monotherapy trial showed impressive results with a mean change in HIV RNA between 1.03 and 1.66 $\log_{10}$ for the 400mg and 600mg twice daily dosing arm (Lalezari J et al. 2005). In the subsequent development steps two trials using aplaviroc in treatment-naïve patients were initiated. Both trials were planned as 96-week studies but were prematurely terminated due to idiosyncratic hepatotoxicity on September 15th, 2005 (Nichols WG et al. 2005; Ryan CT, 2005).

In the ASCENT trial, fixed-dose combination zidovudine/lamivudine (COM) was used as backbone (Currier J. et al. 2006), and in the EPIC trial fixed-dose lopinavir/ritonavir (LPV/r) was used as backbone (Yeni P et al. 2006). Both of these trials were dose-finding trials using different doses of aplaviroc and were sponsored by the manufacturer of aplaviroc, GlaxoSmithKline. Both trials had similar designs as randomized, partially double-blinded, multicenter, parallel-group studies with primary endpoints defined as the proportion of responders with vRNA <400 copies/mL at week 12, as well as the short-term safety and tolerability of different oral doses of aplaviroc (APL). The secondary endpoints were to determine HIV-1 RNA decay rate over the initial weeks of treatment and long-term safety and antiviral activity of APL. Virologic failures were defined in three different ways as follows: 1. A viral load decrease of less than 1 $\log_{10}$ copies/ml from baseline by week 4; or 2. a confirmed increase of viral load ≥400 copies/mL after reaching undetectable levels (<400 copies/mL); or 3. a confirmed increase of more than 0.5 $\log_{10}$ copies/mL from the lowest HIV-RNA value.

ASCENT

Methods:
Therapy-naïve, HIV-1 infected subjects aged 18 years or older with screening vRNA ≥10,000 copies/mL, CD4+ cell count ≥100 cells/mL, R5-tropic virus based on viral tropism assessment, and no reverse transcriptase (RT) drug resistance mutations were randomized 2:2:1 to APL 600mg twice daily, APL 800mg twice daily or efavirenz (EFV) once daily each in combination with COM twice daily. Plasma from baseline and virologic failures were assessed for co-receptor tropism and APL susceptibility. Efficacy data were presented in the Intent-to-Treat (ITT) format which included all subjects who received at least one dose of randomized treatment. The primary efficacy analysis was based on the ITT population, which was the proportion of responders at week 12 as defined by the "time-to-loss-of-virologic-response" (TLOVR) algorithm. The study population included 147 subjects with R5-tropic virus who were enrolled from sites in Europe, the United States and Canada, of which 145 subjects received study medication ("ITT population"). The demographics were similar across the treatment groups, including a mean age of 39 years, 75% Caucasian and 83% male. Baseline characteristics were similar across treatment groups with regards to HIV viral load, CDC classification, HIV risk factor and co-infection status with Hepatitis B or C Virus. The majority of patients had stable tropism readouts with 140 of 145 subjects testing R5-tropic at screening and remaining R5-tropic at baseline

Results:
Because of early termination of the study, data were presented on only 142/145 (98%) of the subjects randomized at least 12 weeks prior to study termination. Similar CD4+ cell increases were seen across treatment groups. The proportion of subjects with vRNA<400copies/mL at week 12 (ITT) was 53% (95%CI: 40%, 67%) for the group taking APL 600mg twice daily, 50% (37%, 63%) for the group taking APL 800mg twice daily and 66% (46%, 82%) for those on COM+EFV. Plasma HIV-1 RNA change from baseline was seen with a mean of 3 $\log_{10}$ copies/mL decline across all treatment groups at the 12 week time point. However, there was a greater variability in response seen in the two APL treatment arms compared to the control. Eight subjects met the criteria for virologic failure, in 6/8 subjects the mutation M184V was detected confirming resistance to lamivudine. Grade 2-4 increases of ALT, AST and bilirubin were seen in more than 10% of patients on aplaviroc. One subject withdrew due to hepatic cytolysis. This case led subsequently to the premature termination of the study and to the termination of the APL program by GSK.

Discussion:
In general for the primary endpoint analysis, antiretroviral response rates were similar between the APL dosage regimens. However, a moderately diminished response relative to COM+EFV was noted overall, especially in the higher viral load stratum. Protocol defined virologic failure was infrequent in the study (6%) and was not associated with the development of resistance to APL or a change in tropism readout. Primary resistance to lamivudine may have been a component to virologic failure for subjects receiving an APL- containing regimen (Kitrinos KM et al. 2006). Substantially more subjects treated with both APL regimens experienced gastrointestinal adverse events than did subjects with COM+EFV. Specifically, diarrhea, nausea and vomiting were more than twice as likely to be observed in the APL treatment arms. One subject died

due to Burkitt's lymphoma in the APL arms. At the time of termination of the study this was not considered to be related to the study drug.

EPIC

Methods:
Therapy-naïve, HIV-1 infected subjects aged 18 years or older with screening vRNA ≥50,000 copies/mL, CD4+ cell count ≥100 cells/mL, and R5-tropic or dual-tropic/mixed virus based on viral tropism assessment were randomized 2:2:2:1 to APL 200mg twice daily, APL 400mg twice daily, APL 800mg once daily or COM each in combination with LPV/r twice daily. Plasma from baseline and virologic failures were assessed for co-receptor tropism and APL susceptibility. Subjects were analyzed according to the actual treatments received. Efficacy data were presented in a Modified-Intent-To-Treat (M-ITT) analysis to eliminate subjects who did not complete 12 weeks of treatment, and the ITT format which included all subjects. The primary efficacy analysis was based on the M-ITT population using the proportion of responders at week 12 as defined by the TLOVR algorithm. Study population: 193 subjects with R5-tropic or dual-tropic/mixed virus were enrolled from 79 centers in the US, Canada and the EU. 191 of 193 subjects received at least one dose of study medication, 133 subjects completed the 12-week treatment phase and were analysed in the M-ITT population. Demographic characteristics for the entire study cohort were well balanced across treatment groups. The mean age was 38 years, with the majority of patients being Caucasian (81%) and male (85%). More subjects in the R5-tropic group had baseline plasma HIV-1 RNA ≥100,000 copies/mL compared to the mixed/dual-tropic group (62% versus 28%). Most subjects were CDC Class A (85%), had homosexual contact as their primary HIV risk factor (73%), and were negative for Hepatitis B and C (95% and 88%, respectively).

Results:
The proportion of subjects with vRNA <400 copies/mL at week 12 (M-ITT R5 only) was similar in all study arms with a trend towards diminished response in the APL arms. 9 subjects met the criteria of virologic failure. No subject developed reduced susceptibility to LPV/r or APL and no treatment emergent mutations or change in tropism readout was seen (Kitrinos KM et al. 2006). In the small number of subjects with mixed/dual-tropic virus a trend towards better treatment response in the control arm was seen. Similar increases in CD4+ cell counts were observed across all treatment groups. Safety: More subjects treated with APL experienced treatment emergent gastrointestinal adverse events, at all grades, than subjects in the control arm. Another subject died approximately four months after discontinuing APL as a result of end-stage liver failure (alcoholic cirrhosis, hepatitis C and portal hypertension with ascites, all of which predated treatment with APL). This event was not considered APL-related. Laboratory parameters: The majority of subjects had no treatment emergent clinical chemistry abnormalities. The combination of increases in ALT (>5x the upper limits of normal (ULN)) and total bilirubin (>2.5 x ULN) occurred in one subject (Nichols WG et al. 2005).

Discussion:
Antiviral response rates were similar between the APL dosage regimens; however, a moderately diminished response relative to COM + LPV/r was noted overall. Protocol-defined virologic failure was infrequent in this study (6%) and was not associated with the development of resistance to APL or a change in tropism (Kitrinos KM et al. 2006). Short-term immunologic responses, measured by increase in CD4+ cell count were similar in all treatment groups.

VICRIVIROC

Vicriviroc is a small molecule CCR5 receptor antagonist, which in phase I trials showed potent antiviral activity of about a 1.6 $\log_{10}$ viral load reduction (Schurmann D et al. 2007). The drug is primarily metabolized by the CYP3A4 pathway with a long half life of about 27 hours and therefore can be dosed once daily. To date there has only been one Phase 2 study evaluating its use in treatment-naïve subjects. The trial was halted early due to higher virologic failure rates in the vicriviroc arms. The study of this drug continues in treatment-experienced patients in an ongoing ACTG study (Gulick RM et al. 2007).

Methods:
Therapy-naïve, HIV-1 infected subjects with screening vRNA ≥5,000 copies/mL, CD4+ cell count ≥150 cells/mL, R5-tropic virus based on viral tropism assessment, and without resistance to all study drugs by genotype at baseline were randomized 1:1:1:1 to vicriviroc 25mg once daily, 50mg once daily, 75mg once daily or placebo for a 14 day monotherapy phase. Monotherapy was followed by a 46 week combination-therapy phase in which fixed-dose zidovudine/lamivudine (COM) was added, and the control arm received efavirenz and COM instead of placebo. Primary endpoints were safety, tolerability, and antiviral activity of vicriviroc with plasma vRNA measured at screening, baseline, day 4, day 7, day 14, monthly to 6 months, then bimonthly. Tropism testing was done at screening, baseline, day-14, week-24, and at virologic failure or week 48. The primary analysis was conducted when all study subjects had completed two weeks of dosing. The study endpoints were mean change in vRNA from baseline, proportion with >1 $\log_{10}$ vRNA decrease, proportion with <50 and <400 copies/mL and mean change in CD4 cell count from baseline. Study Population: Baseline characteristics included a median CD4 cell count of 290 (range: 103-687) and a median vRNA of 4.79 $\log_{10}$ (range: 3.55-6.02). The median age was 37 years (range: 18-72); 80% were men, 14% non-Caucasian; 28% of the subjects carried non-subtype B virus. All these characteristics were balanced across the study arms.

Results:
For the monotherapy phase with vicriviroc 25mg, 50mg and 75mg at day 14 the median change in plas-

Table 1. Response at day 14 monotherapy with vicriviroc predicts response to combination therapy (Greaves W et al. 2006).

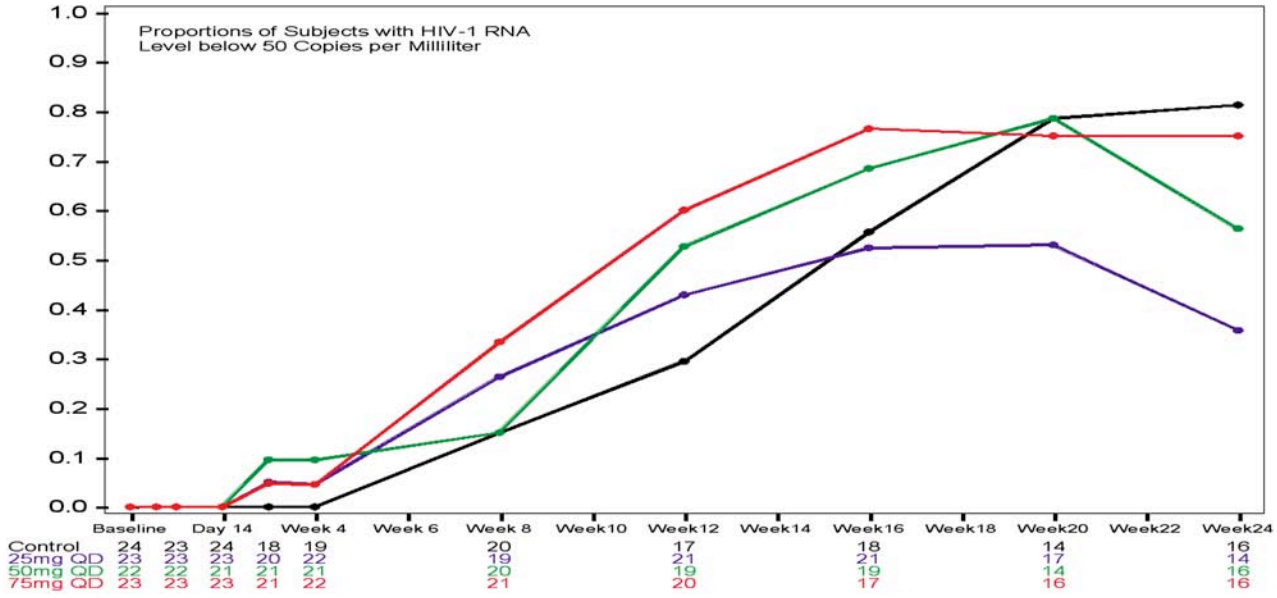
Day 14 HIV-1 RNA Response as Predictor of Sustained Suppression	Odds Ratio	P Value
≥ 1 versus < 1 $\log_{10}$ copies/mL decrease	3.67	0.017
Adjusted for baseline viral load	3.22	0.036
≥ 1.5 versus < 1.5 $\log_{10}$ copies/mL decrease	5.21	0.017
Adjusted for baseline viral load	6.50	0.010

ma vRNA was -0.83 $\log_{10}$, -1.18 $\log_{10}$ and - 1.34 $\log_{10}$ copies/mL respectively, compared to placebo with -0.07 $\log_{10}$ copies/mL. The decrease of viral load for all doses of vicriviroc versus placebo was statistically significant $P < 0.001$, as was the comparison between the vicriviroc 25mg and 75mg arm with $P = 0.0008$. During the following combination-therapy phase, significantly higher rates of virologic breakthrough (HIV-1 RNA > 50 copies/mL) in the vicriviroc arms versus control were observed. Highest rates of failure were observed at the lowest doses of vicriviroc. 56% (13/23) of the patients in the 25mg dose arm experienced viral breakthrough (versus control, $p<0.001$), 41% (9/22) in the 50mg arm (versus control, $p=0.003$), and 17% (4/23) in the 75mg arm (versus control, $p=0.188$) experienced viral breakthrough. This compared with only 4% of subjects (1/24) on COM+EFV who experienced virologic failure. At the time of study termination, there was no significant difference in virologic breakthrough between the 75mg arm & the EFV/COM arm. Interestingly, the virologic response to monotherapy during the first 14 days predicted sustained response to the combination therapy (Table 1).

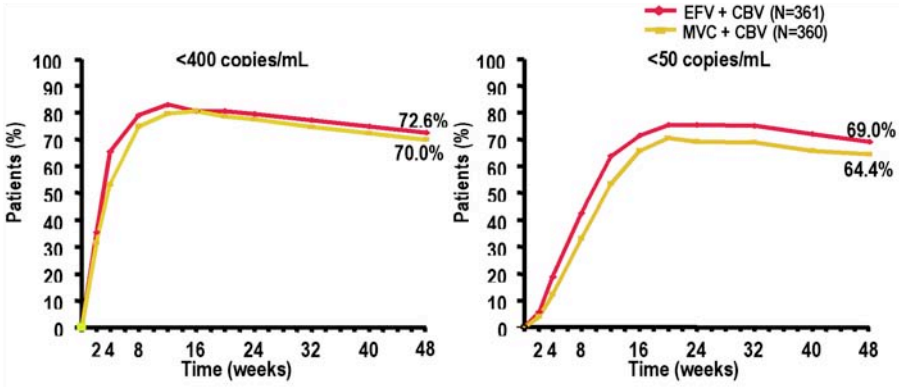
All patients on vicriviroc with virologic breakthrough and genotype results (22 of 26) tested positive for the M184V/I mutation. One subject also had a M41L mutation. Eight tropism shifts were seen during the course of the study in both the placebo and the vicriviroc arms (three in the placebo arm, one in the 25mg arm, and four in the 75mg arm) and there was no correlation between increases in HIV-1 RNA and shifts in viral tropism. Vicriviroc was determined to be safe and well tolerated and no evidence of hepatocellular injury was seen. There were four grade 3-4 adverse events, one in each of the four study arms. These adverse events were not further specified. A total of nine treatment-emergent severe adverse events were seen, all considered unrelated to vicriviroc. The results of this study were presented by W Greaves et al. at the Conference on Retroviruses and Opportunistic Infections, 2006 in Denver, Colorado, but no other publication has been released yet by Schering-Plough, the sponsor of the study.

Maraviroc

Maraviroc (Celsentri®) received scientific approval first from the European Union's drug regulatory body, the EMEA, on July 19th and by the Food and Drug Administration (FDA) in the US on August 6th, 2007. Both regulatory bodies approved maraviroc for the



Graph 1. Proportion of subjects with HIV-1 RNA< 50 copies/mL receiving various doses of vicriviroc + COM or efavirenz + COM, week 24 (Greaves W et al. 2006).



Graph 2. Proportion of subjects with HIV-1 RNA< 50 copies/ml in patients receiving maraviroc + COM or efavirenz + COM, week 48 (Saag M et al. 2007).

treatment of treatment experienced adults with CCR5-tropic HIV-1 for use in combination with other antiretroviral drugs. This approval comes on the basis of two studies in highly treatment-experienced patients with R5-tropic virus, the MOTIVATE 1 and 2 trials. More than half of the patients who received maraviroc with an optimized background regimen by resistance testing achieved a viral load below 400 copies after 24 weeks. A trial evaluating the use of maraviroc in treatment naïve patients (MERIT study) was recently presented at the International AIDS Society meeting in Sydney (Saag M et al. 2007).

Methods:
A worldwide study on therapy-naïve, HIV-1 infected subjects with screening vRNA ≥2,000 copies/mL, no CD4+ cell count requirements, R5-tropic virus based on viral tropism assessment, and without resistance to all study drugs by genotype at baseline were randomized 1:1 to maraviroc 300mg twice daily or efavirenz both in combination with fixed-dose zidovudine/ lamivudine (COM) twice daily. The two groups were further stratified by vRNA less than or greater than 100.000 copies/mL and by subject origin from the Northern or Southern hemisphere. Data were evaluated through an on-treatment noninferiority analysis of all patients who received ≥ 1 dose of study drug, with a noninferiority margin at -10% (lower bound of 97.5% confidence interval). A third arm of the study using maraviroc 300 mg once daily was halted after the interim analysis at week 16 was unable to demonstrate non-inferiority to efavirenz. The data from this third arm are not included in the analysis. The study is ongoing to continue for 96 weeks, the primary analysis was presented with 48 week data. Primary endpoints were proportion of patients with vRNA < 400 copies/mL and < 50 copies/mL at Week 48. Study Population: 721 treatment naïve patients with the following baseline characteristics: Mean age of 37 years, 72% men, 44% non-Caucasian; median CD4 cell count of 254 cells/mL (range: 8-1053) in the efavirenz arm and 241 cells (range: 5-1422) in the maraviroc arm, mean vRNA of 4.88 $\log_{10}$ (EFV) and 4.86 $\log_{10}$ (MVC). Baseline characteristics were well balanced between the arms.

Results:
At week 48, twice daily maraviroc was non-inferior to efavirenz in the proportion of patients with vRNA < 400 copies/mL (70.6% versus 73.1%) but not non-inferior in the < 50 copies/mL analysis (65.3% versus 69.3%). Further stratification for subjects with high viral loads (vRNA ≥ 100.000 copies/mL) revealed an even more pronounced difference favoring efavirenz: Proportion of subjects with <50 copies/mL on efavirenz 66.6% and on maraviroc 59.6%. A significantly larger mean increase in CD4+ cell count was seen in the maraviroc arm (+170 versus +144 cells/mL). Overall, the discontinuation rate was high in both arms. Reasons for discontinuations were different in the arms: Efavirenz discontinuations (total 25.2%) were more likely due to an adverse event (13.2%) followed by lack of efficacy (4.2%) and other factors (7.5%), maraviroc discontinuation (26.9%) were more likely to be due to lack of efficacy (11.9%), and only second, due to an adverse event (4.2%) or other factors (10.8%). There were fewer grade 3 and grade 4 adverse events and fewer category C AIDS-defining events, including fewer malignancies in the maraviroc arm and overall rates of adverse events and serious adverse events were similar in both arms. An overall low incidence of increase of liver function tests to grade 3 or 4 was observed and was equally distributed in both treatment arms. A greater increase in fasting lipids was seen in the efavirenz arm.

Discussion

The approval of maraviroc in the European Union and the United States has brought CCR5 antagonists onto the main stage for treatment of HIV infection. Because people infected with multidrug-resistant virus urgently need new antiretrovirals, CCR5 antagonists will clearly fill a niche in salvage therapy. Yet, several questions remain to be answered regarding the use of this novel class of agents. These questions fall mainly into three categories: The use in dual tropic/mixed HIV-infected patients, possible long-term side effects and optimal time of use in the course of HIV infection.

This article reviews the currently available data on the use of maraviroc, aplaviroc and vicriviroc in treatment-naïve patients. The idea of using these agents early in therapy is essentially tied to the changing tropism of the virus over the course of HIV infection. While exclusive X4 tropic virus is rare in patients, dual-tropic/mixed-tropic isolates usually emerge later

in infection and are not uncommon and are seen more frequently in patients with lower CD4 cell counts and higher viral loads (Moyle et al 2005). There is some controversy if treatment experience has an impact on the tropism shift over time. Moyle et al. 2005, did not find a difference beteen treatment-naïve and experienced patients. Hunt PW et al. 2006 describes a four times higher frequency of dual-tropic/mixed tropic virus in treatment experienced versus naïve subjects, but this observation was almost entirely tied to differences of nadir CD4 count. When adjusted for CD4 count there was almost no association with treatment experience and tropism determination. This is an important observations and likely means that once X4-tropic variants have emerged they persist despite treatment mediated restoration of peripheral CD4 cell counts.

How does this information on HIV tropism impact our decision when to use a CCR5 antagonist? Of importance is the fact that CCR5 antagonists have no activity on purely X4-tropic virus and the use of CCR5 antagonists in patients with dual-tropic/mixed virus has been associated with little or no reduction of viral load (Mayer H et al. 2006). Thus, if CCR5 antagonists are to be used in the treatment, this should precede the emergence of X4-tropic virus. Interestingly the use of CCR5 antagonists has not caused any harm with respect to tropism shift or decreasing CD4 counts in patients harboring dual-tropic/mixed virus (Mayer et al. 2006; Greaves W et al. 2006). Since CCR5 tropic virus dominates in the early years of infection and X4 tropic virus usually in later infection, CCR5 antagonists were thought to be drugs used in early therapy. In fact, all of the drugs in Phase 2 and 3 development have been evaluated for the use in the treatment naïve population. So, while the use of CCR5 antagonists theoretically may make more sense in early infections, most of the trials have been conducted in patients with later stages of HIV-infection. In most trials comparing CCR5 antagonists with current standard of care in naïve patients, the CCR5 antagonists arms underperformed. In the randomized trial comparing various doses of vicriviroc with a backbone of zidovudine/lamivudine, a higher percentage of virologic failures was observed than in the standard of care arm efavirenz + zidovudine/lamivudine (Greaves W et al. 2006). In fact, the higher failure rate led to early termination of the study. The number of virologic breakthroughs in the trial might have been influenced by two facts, the controversial trial design with a 14-day vicriviroc monotherapy induction phase, (which could have preselected for CCR5 resistant strains); and second, the apparently too low doses of vicriviroc studied: More virologic breakthroughs were observed on the lower vicriviroc doses. Interestingly, there was no statistically significant difference in time to loss of viral suppression between the highest vicriviroc dose and the control arm. The premature closure of the trial and the overall small size of the study with 22 to 24 subjects per arm limits the ability to interpret the true performance of vicriviroc. Similarly, the data on aplaviroc are limited because of early closures of the trials secondary to hepatotoxicity. Nevertheless, when aplaviroc + LPV/r was compared with standard of care COM + LPV/r, a trend toward better performance of COM+LPV/r was seen, even in the highest doses of aplaviroc. This effect was more pronounced for subjects with viral loads above 100.000 copies/mL. A lower percentage of study participants reached the endpoint of <400 copies/mL in the aplaviroc+ COM arms at week 12 compared to standard of care EFV+COM. None of the data reached statistical significance because of the early closure of the trials.

The most recent reported data on the use of a CCR5 antagonist in treatment-naïve subjects data was from the MERIT trial, presented at the International AIDS Society meeting in Sydney in July 2007. The comparison of twice daily maraviroc and efavirenz both with a backbone of a fixed-dose combination of zidovudine/lamivudine did not meet strict non-inferiority criteria regarding one of the two primary endpoint criteria: The percentage of subjects reaching viral load below 50 copies/mL at week 48. 65.3% of subjects on maraviroc versus 69.3% on efavirenz reached a viral load < 50copies/mL after 48 weeks. This was even more pronounced for a subanalysis of subjects with viral loads >100.000 copies/mL. Further analysis is needed to explain why subjects in the Northern hemisphere significantly performed better than those from the Southern hemisphere. In fact maraviroc performed equally well to efavirenz among patients in the Northern hemisphere. Maraviroc had a superior safety profile and a more benign lipid profile than efavirenz and an overall higher CD4 cell count increase. There were also fewer malignancies reported in the maraviroc-treated group, only one case, compared with the efavirenz group with four cases. This is an important observation, because in a study of vicriviroc in treatment-experienced subjects, eight cases of malignancies in patients receiving the drug were found (Gulick R et al. 2007). A once-daily dosing arm of this maraviroc study in treatment-naive subjects was terminated due to inferior performance relative to the efavirenz-based control arm.

CCR5 antagonists with their unique mechanism of interfering with a cellular instead of a viral target like antiretrovirals pose challenging questions: How does the paradigm of using three antiretrovirals in combination therapy for naïve patients apply to these new agents? Are they to replace one antiretroviral drug or should they be added as a supplement to triple therapy to reduce the number of cells that can be infected?. So far most trials using a CCR5 antagonist and 2 antiretrovirals in treatment naïve patients show less virologic potency than the available standard of care with three antiretrovirals. The one question remaining at the very end is a very simple one – is this exciting new class really to be counted as a true antiretroviral – and only time will tell.

Conclusion

Whether CCR5 antagonists in the future will make the grade to be first line HIV treatment options depends on both their potency and safety in the long run. Today's favored first-line combination therapies have enviable potency and safety records, displacing agents from these regimens will take some doing.

REFERENCES

Currier J, Lazzarin A, Kleim J-P, Steel H, Millard J, Bonny T, et al. 2006. Safety and antiviral activity of the novel CCR5 Antagonist Aplaviroc in combination with Zidovudin + Lamivudine in HIV-Infected Therapy-naïve Subjects, 8th International Congress on Drug Therapy in HIV; November 12-16, 2006; Glasgow, United Kingdom. Abstract P392.

Deeks SG. Challenges of developing R5 inhibitors in antiretroviral naive HIV-infected patients. Lancet 2006;367: 711-713.

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;11:1170-1172.

Greaves W, Landovitz R, Fatkenheuer G, et al. Late virologic breakthrough in treatment-naïve patients on a regimen of Combivir + vicriviroc. Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colorado. Abstract 161LB.

Gulick R et al. ACTG 5211: phase II study of the safety and efficacy of vicriviroc (VCV) in HIV+ treatment-experienced subjects: 48-week results. Program and abstracts of the 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; July 22-25, 2007; Sydney, Australia. Abstract TUAB102

Gulick RM, Su Z, Flexner C et al. and others (for the AIDS Clinical Trials Group 5211 Team). 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. Journal of Infectious Diseases 196(2): 304-312. July 15, 2007.

Hunt PW, Harrigan PR, Huang W, et al. Prevalence of CXCR4 tropism among antiretroviral-treated HIV-1-infected patients with detectable viremia. J Infect Dis 2006; 194:926-930.

Kitrinos, KM, Irlbeck, DM, LaBranche, CC, Madsen, HA, and Demarest, JF. 2006. Virologic characterization of treatment naive subjects failing an aplaviroc-based regimen with either lamivudine/zidovudine or lopinavir/ritonavir. XV International Drug Resistance Workshop; June 13-17, 2006; Sitges, Spain. Abstract 21

Lalezari J, Thomson 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; 19:1443-8

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-experiences subjects infected with dual/mixed-tropic HIV-1: 24-week results of a phase 2b exploratory trial. XVI International AIDS Conference. August 13-18, 2006. Toronto. Abstract THLB0215

Moyle G, Wildfire A, Mandalia S, Mayer H, Goodrich J, Whitcomb J, Gazzard BG: Epidemiology and Predictive Factors for Chemokine Receptor Use in HIV-1 Infection, The Journal of Infectious Diseases, volume 191 (2005), pages 866–872

Nichols WG, Steel HM, Bonny TM, Min SS, Curtis L, Kabeya K, Clumeck N. Hepatotoxicity observed in clinical trials of aplaviroc (APL, 873140). Special Oral Communication, 2005 EACS, Dublin, Ireland.

Pfizer, Selzenrty, Full Prescribing Information, August 2007. Http://media.pfizer.com/files/products/uspi_maraviroc.pdf

Ryan CT. Trials of aplaviroc halted in treatment-naive patients. AIDS Clin Care. November 2005;17(11):107-108.

Saag M, Ive P, Heera J, et al. A multicenter, randomized, double-blind, comparative trial of a novel CCR5 antagonist, maraviroc vs efavirenz, both in combination with Combivir for the treatment of antiretroviral naive patients infected with R5 HIV 1: week 48 results of the MERIT study. 4th International AIDS Society conference; July 22-25, 2007; Sydney, Australia. WESS104

Schurmann D; Fatkenheuer G; Reynes J; Michelet C, et al. Antiviral activity, pharmacokinetics and safety of vicriviroc, an oral CCR5 antagonist, during 14-day monotherapy in HIV-infected adults. AIDS. 21(10):1293-1299, June 2007.

Shepherd J, Jacobson L, Qiao W, et al. Analysis of the timing of CXCR4-tropic HIV emergence in the MACS cohort. XVI International AIDS Conference. August 13-18, 2006. Toronto. Abstract TUPE0001.

Yeni P, Rockstroh J, LaMarca A, Madison S, Nichols G, et al. Safety and Antiviral activity of the novel CCR5 Anttagonist Aplaviroc in Combination with Lopinavir/itonavir in HIV Infected Thearpy naïve subjects. 8th International Congress on Drug Therapy in HIV; November 12-16, 2006; Glasgow United Kingdom. Abstract P394.

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