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Maraviroc

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Contents

Abstract

▲ Maraviroc is a specific, slowly reversible, noncompetitive, small-molecule antagonist of the CCR5 chemokine receptor, which also serves as an HIV-1 coreceptor. By acting as an antagonist at the CCR5 coreceptor, maraviroc inhibits HIV-1 from entering host cells.

▲ Clinical data for maraviroc are available from two large, well designed, ongoing phase IIb/III trials (MOTIVATE-1 and MOTIVATE-2) conducted in patients infected with R5-tropic HIV-1 who had previously received at least one agent from three of the four classes of antiretroviral drugs and/or were triple-class resistant.

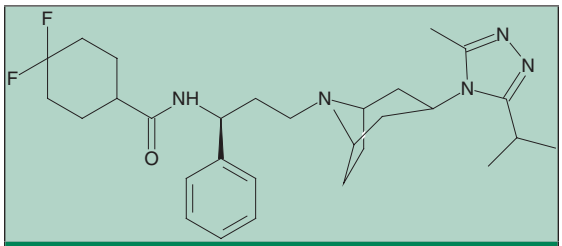
▲ According to 24-week interim results of the MOTIVATE-1 and -2 trials, a significantly greater reduction in viral load occurred in patients receiving maraviroc 150 or 300mg (depending on optimised background therapy [OBT]) twice daily plus OBT compared with placebo plus OBT. This significant difference was maintained at 48 weeks in MOTIVATE-1.

▲ In the MOTIVATE-1 and -2 trials, a significantly greater proportion of patients receiving maraviroc plus OBT achieved an HIV-1 RNA level <400 and <50 copies/mL compared with those receiving placebo plus OBT. In addition, the CD4+ cell count was increased to a significantly greater extent with maraviroc plus OBT compared with placebo plus OBT.

▲ The 48-week results of MOTIVATE-1 also report a significant difference in favour of maraviroc for all these endpoints.

▲ In general, maraviroc at dosages of up to 300mg twice daily was well tolerated in treatment-experienced patients infected with R5-tropic HIV-1.

Features and properties of maraviroc (Celsentri®; Selzentry®)	
Indication	
For use in combination with other antiretroviral agents in adult patients with R5-tropic HIV-1 infection (but not X4- or dual/mixed-tropic HIV-1) who have previously received other antiretroviral medication, and have evidence of viral replication and HIV-1 strains that are resistant to multiple antiretroviral agents	
Mechanism of action	
Antiretroviral	CCR5 coreceptor antagonist
Dosage and administration	
Route of administration	Oral
Recommended dose	150, 300 or 600mg twice daily (depending on concomitant therapy)
Pharmacokinetic profile of maraviroc 150 or 300mg twice daily (bid) in patients infected with R5-tropic HIV-1	
Peak plasma concentration	150mg bid: 273 ng/mL 300mg bid: 618 ng/mL
Time to peak plasma concentration	150mg bid: 3.0h 300mg bid: 3.1h
Area under plasma concentration-time curve	150mg bid: 933 ng • h/mL 300mg bid: 2550 ng • h/mL
Elimination half-life	300mg bid: 22.9h
Adverse events	
Most frequently reported	Upper respiratory tract infection, cough and associated symptoms, pyrexia, rash, musculoskeletal and connective tissue signs and symptoms, dizziness/postural dizziness



Maraviroc

Latest statistics from the Joint United Nations Program on HIV/AIDS estimate that in 2005, 38.6 million people worldwide were living with HIV infection, 4.1 million became newly infected with HIV and 2.8 million deaths were attributed to AIDS.[1]

It has been known for >20 years that the CD4 receptor on T cells and macrophages is the main receptor utilised by HIV-1 for entry into the host cell.[2,3] More recently, the chemokine receptors CCR5 and CXCR4 were identified as essential coreceptors for HIV-1 entry.[2,3] Generally, only viral strains that utilise the CCR5 coreceptor for entry (R5-tropic HIV-1 virus) are detected during early HIV-1 infection whereas X4-tropic viruses, which utilise the CXCR4 coreceptor for host cell entry, tend to develop later on in infection in ≈50% of patients and often herald the onset of AIDS.[2,4]

The development of antiretroviral therapy utilising CCR5 antagonism has been of particular interest since genetic evidence of a naturally resistant human population came to light.[2,5] These individuals have a 32 base pair deletion in the CCR5 coding region, which imparts a natural resistance to HIV-1 infection in homozygotes who fail to express CCR5 on the host cell surface. Heterozygotes have a decreased number of CCR5 receptors and those who become infected with HIV-1 have been found to have a longer disease progression time. Individuals who carry the 32 base pair deletion but do not have HIV-1 appear to be fully immunocompetent with no other obvious abnormalities. This suggested that blocking the function of CCR5 may not be detrimental and thus indicated the potential of CCR5 antagonists in the treatment of HIV infection.

Maraviroc (Celsentri®; Selzentry®)[1] is the first CCR5 coreceptor antagonist to be approved.[6] This profile reviews clinically relevant pharmacological, therapeutic efficacy and tolerability data concerning the use of oral maraviroc in patients infected with R5-tropic HIV-1.

1. Pharmacodynamic Profile

Mechanism of Action

- Maraviroc is a specific, slowly reversible, noncompetitive, small-molecule antagonist of the chemokine receptor CCR5 that normally binds the chemotactic chemokines macrophage inflammatory protein (MIP)-1α, MIP-1β and RANTES (regulated on activation, normal T cell expressed and secreted).[3,7] CCR5 plays an integral role in the process of HIV-1 entry into host cells via interaction with the HIV-1 glycoprotein (gp)120 envelope protein.[2,3] The binding of HIV-1 gp120 to CCR5 causes a conformational change in the HIV-1 envelope protein gp41 allowing fusion of the HIV-1 envelope with the host cell membrane through exposure of a fusion peptide.[2] Thus, with maraviroc acting as a CCR5 coreceptor antagonist, HIV-1 is unable to utilise the receptor and is denied entry into the host cell.
- In an *in vitro* study, available as an abstract and poster, using $HEK_{G\alpha 15}$ cells (human embryonic kidney cells stably expressing the G protein-coupled receptor α15) transiently expressing a cyclic adenosine monophosphate response element-luciferase construct and CCR5, maraviroc appeared to act as a slowly reversible antagonist of the CCR5 coreceptor.[7] The apparent insurmountable antagonism displayed by maraviroc is a consequence of a hemiequilibrium state set up by a slow rate of dissociation from the CCR5 receptor (dissociation constant = 9.4). The dissociation half-life of maraviroc was estimated via a direct method to be 15.95 hours.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Antiviral Activity

In Vitro Studies

- *In vitro* studies conducted on a range of laboratory and primary HIV-1 isolates revealed that maraviroc inhibited R5-tropic HIV-1 replication but was not active against either X4- or dual/mixed-tropic HIV-1 strains.[8] For example, against 43 primary R5-tropic HIV-1 isolates (of subtypes A–J and O), the geometric mean concentration of maraviroc inhibiting replication by 50% and 90% (IC_{90}) was 0.51 and 2.0 nmol/L.
- Maraviroc inhibited all 200 R5-tropic HIV-1 viruses tested *in vitro*, according to the results of a study using HIV-1 envelope-recombinant pseudotyped viruses derived from clinical isolates with (n = 100) or without (n = 100) reverse transcriptase inhibitor or protease inhibitor mutations associated with resistance.[8] Among this panel, 160 viruses were subtype-B in origin and 40 were non-subtype-B. Maraviroc inhibited all 200 viruses with a geometric mean IC_{90} of 13.7 nmol/L.
- No significant difference in susceptibility was demonstrated between subtype-B and non-subtype-B viruses.[8] There was a small statistically significant ($p < 0.001$) difference between viruses with and without resistance mutations, but this difference was not considered biologically significant.
- Maraviroc displayed additive or synergistic interactions when used in conjunction with other antiretroviral agents in an *in vitro* study conducted in PM-1 cells (a CD4+ clone derived from a T-cell line stably expressing a ribozyme targeted to nef) acutely infected with the R5-tropic laboratory strain of HIV-1 Ba-L.[8] A total of 20 approved antiretroviral agents including nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors and the fusion inhibitor enfuvirtide were used in combination with maraviroc. No antagonistic interactions were observed.

In Vivo Studies

- In two short-term monotherapy studies comparing maraviroc, at doses ranging from 25 to 300mg once or twice daily, with placebo over a 10-day treatment period, asymptomatic patients with R5-tropic HIV-1 who received maraviroc at dosages of 100mg twice daily and above had a reduction in viral load of >1.0 $\log_{10}$ copies/mL at nadir.[9] The results of longer-term trials are discussed in section 3.

Viral Resistance

- As maraviroc is selective for R5-tropic viruses, selection for strains that use the CXCR4 rather than the CCR5 coreceptor would lead to virus escape. Early studies (reviewed by Dorr et al.[8]) showed the emergence of X4-tropic strains after treatment with CCR5 antagonists in humanised severe combined immunodeficiency mice infected with R5-tropic HIV-1.[10] It was thought possible that positive selection for HIV-1 strains capable of utilising the CXCR4 coreceptor may have occurred in this instance because the CCR5 coreceptor was no longer expressed on the host cell surface as a result of it being bound by maraviroc.
- However, *in vitro* studies have not demonstrated positive selection of X4-tropic HIV-1 in the presence of maraviroc-bound CCR5 coreceptors. For example, X4-tropic HIV-1 viral strains did not emerge after *in vitro* serial passaging of R5-tropic Ba-L or most R5-tropic primary isolates with maraviroc.[11]
- In an additional analysis[12] of two phase IIa studies[9] in which 64 patients infected with R5-tropic HIV-1 received monotherapy with maraviroc for 10 days, one patient was later shown to have been carrying X4-tropic virus at initial screening, one had no phenotype result post-treatment and two patients had X4-tropic virus detected on day 11. All patients were screened for coreceptor tropism prior to commencing the study and again on days 1 (pre-dose), 11 (post-treatment) and 40 (follow-up).
- The most probable explanation for the emergence of X4-tropic virus in two patients in this study is that they harboured a reservoir of X4-tropic virus (or dual/mixed-tropic virus) pre-treatment.[12] After the successful reduction of total viral load with maraviroc, this small reservoir was then able to be detected. Indeed, results of a tropism substudy in

two large phase IIa/III trials, MOTIVATE (Maraviroc plus Optimized Therapy In Viremic Antiretroviral Treatment Experienced patients)-1[13] and -2[14] (discussed in section 3), have supported this theory.[15]

- Additional data concerning the mechanism by which R5-tropic HIV-1 viruses develop resistance to maraviroc were reported in an *in vitro* study, and suggested that maraviroc-resistant primary isolates (CC1/85- and RU570-derived) had the ability to utilise the CCR5 coreceptor in the presence of bound maraviroc.[11] On serial passaging with maraviroc, resistance developed as mutations in the viral envelope accumulated. The majority of mutations were seen within the V3 loop, with additional mutations seen in the V2, C3 and V4 regions as well as in gp41, with CC1-85-derived maraviroc-resistant viruses, and in the V1, C4, V4 and C5 regions with RU570-derived maraviroc-resistant viruses. These maraviroc-resistant viruses remained susceptible to other CCR5 antagonists.

Other Effects

- In phase I studies, postural hypotension was the dose-limiting adverse effect observed with oral maraviroc at unit doses >300mg.[16] In the first phase I study conducted, postural hypotension was observed in four of nine healthy volunteers who received maraviroc 1200mg. Subsequent phase I studies demonstrated an increased incidence of postural hypotension with unit doses of maraviroc of ≥600mg. Postural hypotension was rare at the dose of 300mg.
- A mild vasodilatory effect was observed in healthy volunteers who received a supratherapeutic dose of maraviroc.[17] Compared with placebo, systemic vascular resistance and stroke index decreased, and cardiac index and pulse rate increased, with maraviroc 900mg (statistical analysis not reported; study available as an abstract).[17] However, there was no change in supine systolic or diastolic blood pressure, indicating a compensatory haemodynamic response.
- An initial phase I study showed a mean increase in the corrected QT (QTc) interval of 7.8 msec in healthy volunteers who received maraviroc 1200mg.[16] A more detailed study revealed no clinically relevant effect on the QTc interval in healthy volunteers who received maraviroc ≤900mg.
- Maraviroc does not appear to have a deleterious effect on immune markers.[18] Data from five phase I/IIa studies (≤28 days' duration) in healthy volunteers or patients with HIV infection (n = 217) revealed that maraviroc did not affect immunoglobulin levels or lymphocyte subset counts. Data from these trials and eight additional phase I studies (n = 214) also revealed no clear effect on the complete differential blood count. Maraviroc did not affect the frequency or severity of reported infections and no cases of malignancy were reported. These analyses were available as an abstract.[18]

2. Pharmacokinetic Profile

Absorption and Distribution

- Maraviroc is moderately lipophilic and is absorbed via a transporter-mediated process, as shown by studies in Caco-2 cells (human-derived colonic adenocarcinoma cell line) and P-glycoprotein knockout mice.[19]
- The absolute bioavailability of maraviroc was 23% in healthy volunteers who received a single oral dose of maraviroc 100mg; with a 300mg dose, the predicted absolute bioavailability was 33%.[20]
- Maraviroc 30–300mg, administered as a single dose, was associated with an increase in dose-normalised exposure as evidenced by increases in both the area under the plasma concentration-time curve (AUC) [from 272 ng • h/mL with 30mg to 537 ng • h/mL with 300mg] and maximum plasma concentration (C_{max}) [from 36 ng/mL with 30mg to 144 ng/mL with 300mg] in healthy men, possibly reflecting the saturation of P-glycoprotein-mediated efflux that may occur at relatively high doses.[19] There was also an apparent increase in the rate of absorption, with the time to C_{max} (t_{max}) decreasing from 2.9 hours with 30mg to 1.6 hours with 300mg. Another study (available as an abstract) observed approximately proportional increases in pharmacokinetic values with maraviroc doses of ≥100mg.[21]

• Maraviroc did not accumulate with repeat administration, according to the results of a study in patients with R5-tropic HIV-1 infection.[9] On days 1 and 10, C_{max} was 585 and 618 ng/mL, and t_{max} was 2.9 and 3.1 hours with maraviroc 300mg twice daily. The minimum plasma concentration (C_{min}) recorded on day 10 was 33.8 ng/mL. With maraviroc 150mg twice daily, C_{max} was 273 ng/mL, t_{max} was 3.0 hours and C_{min} was 19.5 ng/mL on day 10. AUC on days 1 and 10 was 2260 and 2550 ng • h/mL with maraviroc 300mg twice daily. With maraviroc 150mg twice daily, AUC on day 10 was 933 ng • h/mL.

• Steady state was reached within 7 days when maraviroc 100 or 300mg once daily was administered to 54 healthy volunteers (study available as an abstract plus poster).[22]

• A reduction in the rate and extent of absorption of maraviroc occurred when it was coadministered with food, according to *in vivo* and model-based studies.[9,21,23] In the modelling study, AUC was reduced by 50% in the presence of food.[23] It was estimated that mean viral load decline would be reduced by 14% if maraviroc 150mg twice daily was administered with food. In patients infected with R5-tropic HIV-1, a reduction in both AUC (474 vs 933 ng • h/mL) and C_{max} (110 vs 273 ng/mL) was observed when maraviroc 150mg twice daily was administered in the fed compared with the unfed state.[9] However, there was no difference in maximum viral load reduction between these two groups.[9] As a result, maraviroc was deemed appropriate for administration without food restrictions in subsequent studies.[13,14]

• At steady state, ≈76% of maraviroc is bound to plasma protein.[19] Maraviroc appears to have a particular affinity for albumin and α-1 acid glycoprotein.[24] With a blood to plasma ratio of 0.6, it appears that maraviroc is confined mainly to the plasma and has little distribution into red blood cells. The volume of distribution of maraviroc at steady state is ≈194L.[24]

Metabolism and Elimination

• Maraviroc is metabolised predominantly by the cytochrome P450 (CYP)3A4 enzyme.[16]

• Unchanged maraviroc was the major circulating and excreted component in healthy men who received a single oral dose of ^{14}C-labelled maraviroc 3.2 mg/kg.[19] A total of 33% of excreted radioactivity was made up of unchanged maraviroc. The remaining excreted metabolites were made up of a product of hydroxylation of the methyl group of the triazole moiety (10% of total dose), four products of mono-oxidation in the difluorocyclohexyl ring (29% of total dose) and the secondary amine resulting from *N*-dealkylation adjacent to the tropane ring (7% of total dose).

• Maraviroc was mainly eliminated via the faeces.[19] In healthy adult volunteers who received radiolabelled maraviroc, 76.4% of radioactivity was recovered in the faeces, with 25% of radioactivity being accounted for by the unchanged drug. Only a limited amount of the drug excretion occurred renally with 19.6% of the total administered dose recovered in the urine. A total of 8% of the administered dose was eliminated as unchanged drug in the urine. Over 90% of the recovered radioactivity was obtained within 96 hours of administration.

• The mean elimination half-life of maraviroc after administration of a single 300mg dose was 10.6 hours in healthy men.[19] In patients with R5-tropic HIV-1 infection who received oral maraviroc 300mg twice daily, the terminal half-life on day 10 was 22.9 hours. [9]

Drug Interactions

Numerous studies, available as abstracts and/or posters, have examined the potential for drug interactions with maraviroc in healthy volunteers[25-32] or patients with HIV infection.[33]

• *In vitro*, maraviroc, a CYP3A4 substrate, was a weak inhibitor of the major CYP isozymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4).[34] In healthy volunteers receiving midazolam (also a CYP3A4 substrate), maraviroc did not inhibit or induce CYP3A4

to a clinically significant extent.[25] In addition, maraviroc did not affect the pharmacokinetics of the combined oral contraceptive pill ethinylestradiol/levonorgestrel (ethinylestradiol is a CYP3A4 substrate) in healthy women aged 18–45 years.[26]

- The pharmacokinetics of maraviroc were altered by potent inhibitors and inducers of CYP3A4.[27-31,33] The decrease in maraviroc exposure seen with the coadministration of rifampicin (rifampin) and efavirenz (both known CYP3A4 inducers) was adjusted for by increasing the dose of maraviroc in healthy men who received maraviroc 100mg twice daily plus rifampicin, efavirenz or placebo.[30] Compared with placebo, the geometric mean ratio for C_{max} was 30% and 44%, and for AUC was 33% and 49% when rifampicin and efavirenz were coadministered with maraviroc. By increasing the dosage of maraviroc from 100 to 200mg twice daily, the geometric mean ratio increased for both C_{max} (to 97% and 120%) and AUC (to 99% and 110%) for rifampicin and efavirenz.
- In another trial, patients with HIV-1 infection receiving antiretroviral regimens including efavirenz had an ≈50% reduction in exposure to maraviroc.[33] Among patients receiving efavirenz plus lamivudine/zidovudine or efavirenz plus didanosine plus tenofovir, the ratio of geometric means for the AUC from time zero to 12 hours (AUC_{12}) was 46.9% and 48.3% compared with maraviroc monotherapy (historical data).
- By contrast, tipranavir (another inducer of CYP3A4) did not have a clinically significant effect on the pharmacokinetics of maraviroc in healthy volunteers when administered in combination with low-dose ritonavir (a CYP3A4 inhibitor).[32]
- Ketoconazole, saquinavir, atazanavir and ritonavir (all CYP3A4 inhibitors) increased the C_{max} and AUC of maraviroc.[28,29,31,33] Healthy volunteers received maraviroc 100mg twice daily for 7 days in addition to either saquinavir, ketoconazole or placebo for 9 days.[31] Compared with maraviroc plus placebo, maraviroc plus ketoconazole and maraviroc plus saquinavir had geometric mean ratios for C_{max} of 338% and 332% and for AUC of 501% and 425%.
- Similarly, coadministering maraviroc with either atazanavir (with or without ritonavir) or lopinavir/ritonavir increased the maraviroc C_{max} and AUC.[28,33] Patients with HIV-1 infection who received a single dose of maraviroc in conjunction with their normal lopinavir/ritonavir-containing regimen had a geometric mean ratio for AUC_{12} of 265% and for C_{max} of 180% compared with recipients who received maraviroc alone (historical data).[33]
- Moreover, healthy volunteers who received maraviroc plus atazanavir or atazanavir plus ritonavir had a 3.6- and 4.9-fold increase in the maraviroc AUC and a 2.1- and 2.7-fold increase in the maraviroc C_{max} compared with maraviroc alone.[28] These results supported a 50% dose reduction of maraviroc when taken in conjunction with atazanavir (with or without ritonavir).
- The increase in maraviroc exposure seen with coadministration of CYP3A4 inhibitors was reduced by almost 50% when a CYP3A4 inducer was added.[29] In healthy volunteers, treatment with CYP3A4 inhibitor-containing regimens resulted in an increase in both maraviroc AUC (3.9- and 9.8-fold for lopinavir/ritonavir and ritonavir/saquinavir) and C_{max} (2.0- and 4.8-fold). When efavirenz was added, AUC increased only 2.5-fold with lopinavir/ritonavir and 5.0-fold with ritonavir/saquinavir and C_{max} increased only 1.3- and 2.3-fold.

3. Therapeutic Efficacy

The potential of maraviroc as an antiretroviral treatment for patients infected with R5-tropic HIV-1 was established in phase I/IIa studies.[9] However, given the availability of data from larger phase IIb/III trials, these earlier studies will not be discussed further. In addition, a trial examining the efficacy of maraviroc in treatment-experienced patients infected with dual/mixed-tropic HIV-1 is not discussed, as it is beyond the scope of this review.[35]

The efficacy of oral maraviroc, used in conjunction with optimised background therapy (OBT) [three to six antiretroviral drugs with or without low-dose ritonavir], in treatment-experienced adults infected with R5-tropic HIV-1, has been assessed in

two large, randomised, double-blind, placebo-controlled, multicentre, phase IIb/III trials.[13,14]

These trials, known as MOTIVATE-1[13] and MOTIVATE-2,[14] are ongoing and results of a planned 24-week interim analysis are available as abstracts and oral presentations. Additional results from the MOTIVATE-1 trial at 48-weeks are also available as an abstract.[36]

Patients in the MOTIVATE-1[13] trial were gathered from throughout the US and Canada, whereas those recruited for the MOTIVATE-2[14] trial were from Europe, Australia and North America. These patients were triple-class experienced (and/or triple-class resistant) having received ≥6 months of treatment with at least one agent from three of the four classes of antiretroviral drugs (nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors and/or enfuvirtide), had an HIV-1 RNA level of ≥5000 copies/mL and were confirmed to have only R5-tropic HIV-1 strains.

Patients were randomised 2 : 2 : 1 to receive maraviroc once or twice daily plus OBT or placebo plus OBT.[13,14] Those whose OBT contained a protease inhibitor (excluding tipranavir) or the non-nucleoside reverse transcriptase inhibitor delavirdine received maraviroc 150mg once or twice daily. With all other OBT regimens, the maraviroc dosage was 300mg once or twice daily. To ensure a balance between the groups of patients with high and low viral loads, and patients with enfuvirtide-containing and nonenfuvirtide-containing OBT regimens, baseline HIV-1 RNA levels and enfuvirtide use were incorporated as stratification factors into the randomisation process. Given that the once-daily administration regimen is not approved,[20] results pertaining to this regimen will not be discussed.

At baseline, the mean HIV-1 RNA level for maraviroc twice daily plus OBT and placebo plus OBT was 4.86 and 4.84 $\log_{10}$ copies/mL in MOTIVATE-1,[13] and 4.84 and 4.89 $\log_{10}$ copies/mL in MOTIVATE-2.[14] Baseline median CD4+ cell counts with maraviroc twice daily plus OBT and placebo plus OBT were 150 and 163 cells/mm^3 in MOTIVATE-1, and 182 and 174 cells/mm^3 in MOTIVATE-2.

The primary endpoint was the mean change from baseline in HIV-1 RNA level (viral load) 24 weeks into the trial.[13,14] Other endpoints included the mean change in CD4+ cell count from baseline and the percentage of patients who achieved an HIV-1 RNA level of <400 and <50 copies/mL.

Of the 601 patients randomised in the MOTIVATE-1[13] trial, 585 received at least one dose of the study drug. In MOTIVATE-2,[14] 475 patients were randomised and 464 of these received at least one dose of the study drug. Baseline characteristics were considered to be similar across the treatment groups. In both trials, the efficacy data were analysed for all those who received at least one dose of the study drug.

- Maraviroc twice daily plus OBT was superior to placebo plus OBT in treatment-experienced patients infected with R5-tropic HIV-1, according to the 24-week interim results of the MOTIVATE-1[13] and -2[14] trials.
- In both trials, HIV-1 RNA levels were reduced significantly more by treatment with maraviroc

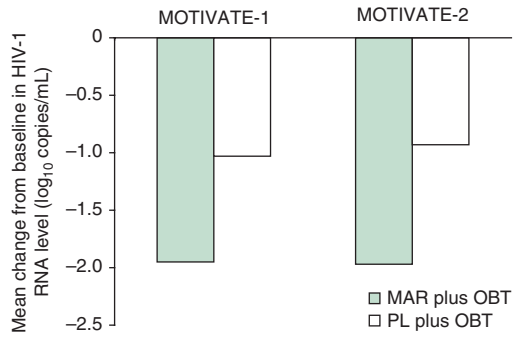


Fig. 1. Efficacy of maraviroc (MAR) in patients with HIV-1 infection. Results of a planned 24-week interim analysis of two randomised, double-blind, placebo (PL)-controlled, multicentre, phase IIb/III trials, MOTIVATE-1[13] and MOTIVATE-2.[14] Patients in these trials were infected with R5-tropic HIV-1 and randomised 2 : 2 : 1 to receive MAR 300mg once daily, MAR 300mg twice daily (bid) or PL along with optimised background antiretroviral therapy (OBT). Given that the once-daily administration regimen is not approved, results pertaining to this regimen are not shown. The primary endpoint was the mean change from baseline in the HIV-1 RNA level. With respect to treatment difference, HIV-1 RNA levels were reduced significantly more by treatment with MAR bid plus OBT than with PL plus OBT in both the MOTIVATE-1 and -2 trials (see text).

twice daily plus OBT than with placebo plus OBT (figure 1). The difference in viral load between those treated with maraviroc twice daily plus OBT and those receiving placebo plus OBT was −0.92 log_{10} copies/mL (97.5% CI −1.28, −0.57) in MOTIVATE-1[13] and −1.04 log_{10} copies/mL (97.5% CI −1.44, −0.64) in MOTIVATE-2.[14]

- In MOTIVATE-1 at 48 weeks, the difference in viral load between those treated with maraviroc twice daily plus OBT and those who received placebo plus OBT remained statistically significant at −1.02 log_{10} copies/mL (97.5% CI −1.39, −0.66).[36]
- Changes in viral load when patients were stratified according to their baseline viral load and whether or not they were receiving enfuvirtide are shown in figure 2.
- The CD4+ cell count increased to a significantly greater extent with maraviroc twice daily plus OBT than with placebo plus OBT in both MOTIVATE-1[13] (+111 vs +52 cells/mm^3; $p < 0.0001$) and MOTIVATE-2[14] (+102 vs +64 cells/mm^3; $p < 0.001$) at 24 weeks.
- At 48 weeks in MOTIVATE-1, the increase in the CD4+ count remained significantly greater in patients who received maraviroc twice daily plus OBT compared with those who received placebo plus OBT (+122 vs +54 cells/mm^3; $p < 0.0001$).[36]
- Significantly more patients receiving maraviroc twice daily plus OBT achieved an HIV-1 RNA level <400 copies/mL compared with recipients of placebo plus OBT in both MOTIVATE-1[13] (60.4% vs 31.4%; $p < 0.0001$) and MOTIVATE-2[14] (61.3% vs 23.1%; $p < 0.0001$). In addition, a significantly greater proportion of patients receiving maraviroc twice daily plus OBT compared with placebo plus OBT recipients achieved an HIV-1 RNA level <50 copies/mL in both MOTIVATE-1 (48.5% vs 24.6%; $p < 0.0001$) and MOTIVATE-2 (40.8% vs 20.9%; $p = 0.0005$).
- At 48 weeks in the MOTIVATE-1 trial, there remained a significantly greater percentage of patients who received maraviroc twice daily plus OBT versus placebo plus OBT with an HIV-1 RNA level of <400 copies/mL (57% vs 22%; $p < 0.0001$) and <50 copies/mL (47% vs 16%; $p < 0.0001$).[36]

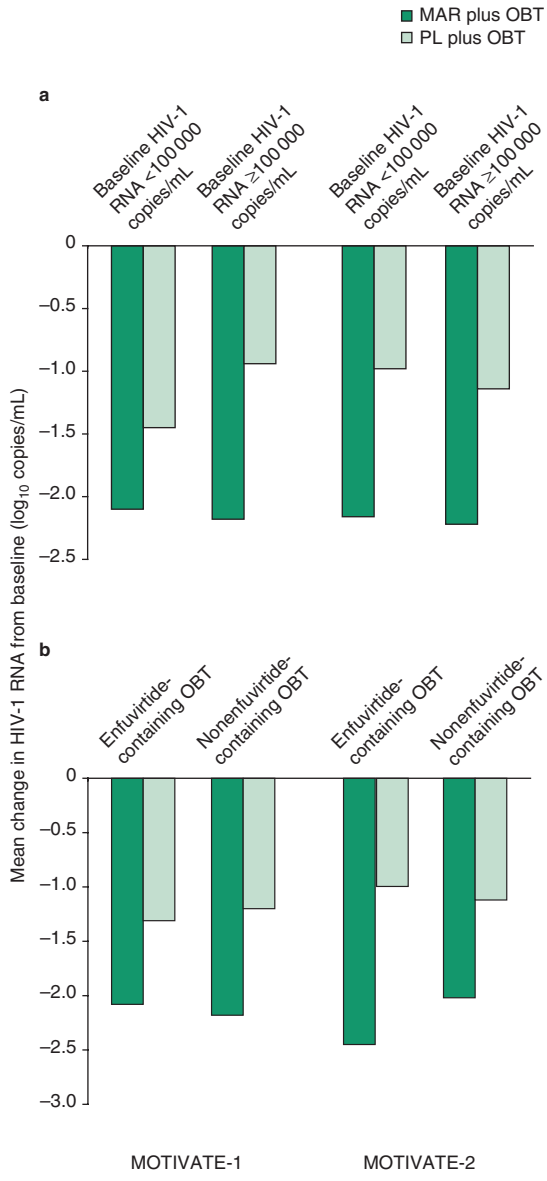


Fig. 2. Response rate in patients with R5-tropic HIV-1 infection who received maraviroc (MAR) following stratification for (**a**) baseline viral load and (**b**) receipt of enfuvirtide. Results of a planned 24-week interim analysis of two randomised, double-blind, placebo (PL)-controlled, multicentre, phase IIb/III trials, MOTIVATE-1[13] and MOTIVATE-2.[14] Patients in these trials were randomised 2 : 2 : 1 to receive MAR 300mg once daily, MAR 300mg twice daily or PL along with optimised background antiretroviral therapy (OBT). Given that the once-daily administration regimen is not approved, results pertaining to this regimen are not shown. No statistical analyses are available for these results.

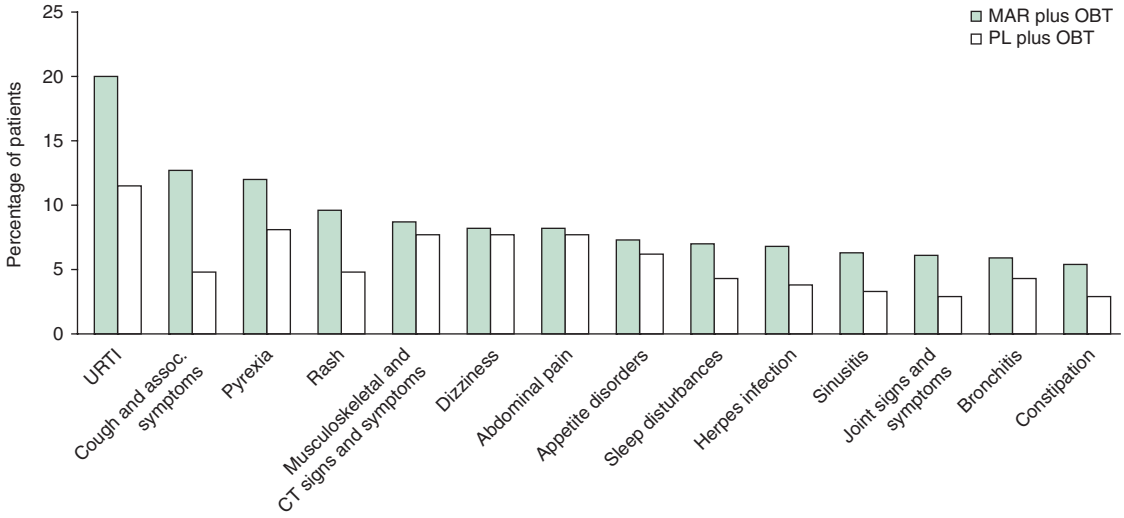


Fig. 3. Tolerability profile of maraviroc (MAR) in patients with R5-tropic HIV-1 infection. Combined results of a planned 24-week analysis of two randomised, double-blind, placebo (PL)-controlled, multicentre, phase IIb/III trials, MOTIVATE-1[13] and MOTIVATE-2.[14] Patients in these trials were randomised 2 : 2 : 1 to receive MAR 300mg once daily, MAR 300mg twice daily or PL along with optimised background antiretroviral therapy (OBT). Given that the once-daily administration regimen is not approved, results pertaining to this regimen are not shown. **assoc.** = associated; **CT** = connective tissue; **URTI** = upper respiratory tract infection.

4. Tolerability

The primary focus of this section is tolerability data from the MOTIVATE-1[13,36] and -2[14] trials (design details discussed in section 3), supplemented by data from the US prescribing information[20] and the US FDA website.[37]

- According to MOTIVATE-1[13] and -2,[14] maraviroc was generally well tolerated in treatment-experienced R5-tropic HIV-1 patients at dosages of up to 300mg twice daily.
- Adverse events that occurred at an incidence of ≥5% in MOTIVATE-1 and -2, and at a numerically higher rate in patients who received twice-daily maraviroc compared with placebo included upper respiratory tract infection, cough and associated symptoms, pyrexia, rash, musculoskeletal and connective tissue signs and symptoms, dizziness/postural dizziness, gastrointestinal and abdominal pain, appetite disorders, sleep disturbances, herpes infection, sinusitis, join signs and symptoms, bronchitis and constipation (figure 3).[20] After adjustment was made for differences in the duration of treatment exposure between maraviroc and placebo recipients (median number of treatment days during the double-blind period of 239 vs 145 days[37]), the majority of these adverse events remained more common in the maraviroc than in the placebo group.[20]
- In addition, the incidence of folliculitis, paraesthesias and dysesthesias, sensory abnormalities, depressive disorders, bladder and urethral symptoms, breathing abnormalities, pruritus and vascular hypertensive disorders also occurred at an incidence of ≥5% and at a numerically higher rate in maraviroc recipients than in placebo recipients when differences in treatment exposure were taken into account.[20]
- After 24 weeks in MOTIVATE-1[13] and -2,[14] discontinuations because of adverse events occurred in 4.3%[13] and 3.7%[14] of maraviroc twice daily recipients and 5.1%[13] and 2.2%[14] of placebo recipients.
- In MOTIVATE-1[13] and -2,[14] deaths occurred in 0.4%[13] and 2.1%[14] of maraviroc twice daily recipients and 0.8%[13] and 0%[14] of placebo recipients. Further investigation revealed no relationship between the deaths and the drug under study.
- After 48 weeks in MOTIVATE-1, discontinuations because of adverse events had occurred in

4.7% of patients who received maraviroc twice daily plus OBT and 5.9% of those who received placebo plus OBT; corresponding numbers for the percentage of deaths in MOTIVATE-1 at 48 weeks were 1.7% and 0.8%.[36] Again, further investigation revealed no relationship between the deaths and the drug under study.

- Similar frequencies of severe adverse events, category C AIDS-defining events and laboratory abnormalities (including abnormalities in liver enzymes) were reported in both treatment groups in MOTIVATE-1[13] and MOTIVATE-2.[14]

- When data from both MOTIVATE-1[13] and -2[14] were combined, liver-related adverse events were reported in 9.2% and 6.2% of patients who received maraviroc 300mg twice daily plus OBT and placebo plus OBT, respectively. Liver enzyme and bilirubin elevations accounted for the majority of these liver-related adverse events.[24] In addition, a case of possible maraviroc-induced hepatotoxicity with allergic features was reported in a healthy volunteer in one study.[20]

- A black box warning appears in the US prescribing information regarding hepatotoxicity and the importance of immediate evaluation of patients who report signs or symptoms of hepatitis or allergic reaction.[20] It is also advised that maraviroc is administered with caution to patients with pre-existing liver dysfunction.[20]

- Cardiovascular adverse events, including myocardial ischaemia and/or infarction, were reported in numerically more patients receiving maraviroc compared with those receiving placebo (1.3% vs 0%) in a combined analysis of the MOTIVATE-1 and -2 trials.[20] In general, patients in whom cardiovascular adverse events were reported had pre-existing cardiovascular dysfunction; the extent to which maraviroc contributed to the cardiovascular adverse events, if any, is not known but it is advised that maraviroc is used with caution in patients who are at increased risk of cardiovascular events.[20]

- In the pooled analysis of MOTIVATE-1 and -2, maraviroc did not appear to increase the risk of developing malignancies (either haematological or non-haematological) [statistical analysis not reported].[24]

5. Dosage and Administration

The recommended dosage of oral maraviroc differs depending upon concomitant medication use.[20] In the US, patients with R5-tropic HIV-1 infection who receive concomitant strong CYP3A inhibitors (including protease inhibitors [except tipranavir/ritonavir], delavirdine, ketoconazole, itraconazole, clarithromycin, nefazodone and telithromycin) have a recommended dosage of maraviroc 150mg twice daily, those whose concomitant therapy includes CYP3A inducers (including efavirenz, rifampicin, carbamazepine, phenobarbital and phenytoin), without a strong CYP3A inhibitor, have a recommended dosage of 600mg twice daily, and in patients receiving tipranavir/ritonavir, non-nucleoside reverse transcriptase inhibitors, nevirapine or enfuvirtide as concomitant medications, the recommended dosage of maraviroc is 300mg twice daily.[20] Maraviroc must be administered in conjunction with other antiretroviral agents.[20]

The US prescribing information contains a black box warning regarding the potential for hepatotoxicity to develop with maraviroc use (see section 4).[20] The warning also cautions that systemic allergic reaction may occur prior to the development of hepatotoxicity. Patients with signs or symptoms of hepatitis or allergic reaction should be assessed immediately.[20] As a result, it is advised that maraviroc is administered with caution to patients with pre-existing liver dysfunction.

Local prescribing information should be consulted for additional information, including dosage and administration, warnings and precautions, adverse reactions, drug interactions and use in special populations.

6. Maraviroc: Current Status

Maraviroc is approved in Europe and the US in combination with other antiretroviral agents for use in adult patients with R5-tropic HIV-1 infection (but not X4- or dual/mixed-tropic HIV-1) who have previously received other antiretroviral medication and

have evidence of viral replication and HIV-1 strains that are resistant to multiple antiretroviral agents.[20,38]

In treatment-experienced patients with R5-tropic HIV-1 infection, two large well designed ongoing phase IIb/III trials, MOTIVATE-1 and MOTIVATE-2, demonstrated a significantly greater decrease in viral load in patients who received maraviroc in conjunction with OBT compared with placebo plus OBT.[13,14] Treatment with maraviroc was generally well tolerated.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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