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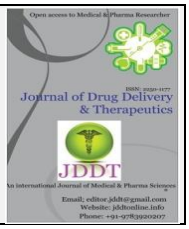

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Review Article

Overview on Chemokine Co-Receptor-5 (CCR-5) HIV-1 Entry Inhibitors

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ABSTRACT

In the 21st century, HIV-1 has turned into a noteworthy global challenge in medication. As per WHO report 2017, HIV is one of the deadliest diseases adding to an aggregate of 36.7 million contaminations until December 2016 among which 1.8 million were analyzed in 2016 itself. In 2016, 19.5 million individuals experienced to anti-retroviral treatment summing up to US$ 11 billion. With regards to rising resistance from anti-retroviral medication in HIV treatment, the advancement of most recent medication classes with a newer mode of action stays essential. The CCR5 co-receptor inhibitors suppress the fusion of HIV with the host cell by upsetting the connection of gp-120 protein with the CCR5 receptor. Though severalCCR5 antagonists are assessed in clinical trials, just Maraviroc has been endorsed for clinical use in the treatment of HIV infected patients. The efficacy and safety profile of CCR5 adversaries with a consideration on maraviroc are assessed here in conjunction with their use in newer and developing clinical trials. In the beginning time of HIV-1 infection in the most of patients, the HIV utilizes CCR5 receptor for passage in CD4 cell of the host (CCR5-tropic infection). Maraviroc did not decrease virus load (compared to optimized background therapy) in patients with CXCR4 or dual-tropic virus. Before prescribing a CCR5 blocker HIV tropism testing is recommended. Viral tropism is defined as the capability of the viruses to enter as well as infect the host cell, and it is based on the binding capacity of the viruses to receptors on those host cells. The co-receptor type should be recognized before the treatment started with a CCR5 blocker.

Keywords: CCR5, CXCR4, HIV-1, CD4 cell, Tropism, CYP3A4.

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INTRODUCTION

In the 21st century, HIV-1 has turned into a noteworthy global challenge in medication. As per WHO report 2017, HIV is one of the deadliest diseases adding to an aggregate of 36.7 million contaminations until December 2016 among which 1.8 million were analyzed in 2016 itself. In 2016, 19.5 million individuals experienced to anti-retroviral treatment summing up to US$ 11 billion. In between 2000 and 2016, new HIV infections fell by 39%, and HIV-related demises reduced by 33% with 13.1 million lives spared due to ART in an exceedingly similar period[1]. In AIDS the system becomes compromised and is unable to fight infections[2, 3]. Due to resistance to many antiretroviral drugs, development of new classes of drugs with a new mode of action is essential. The main productive route for HIV treatment is HAART. It is a mix of different antiretroviral drugs (turn around transcriptase inhibitors, protease inhibitors, integrase inhibitors, co-receptor inhibitors and combination inhibitors). In contrast with different classes, the CCR5 inhibitor is a novel class of HIV-1 inhibitors for HIV-1 treatment approved in recent years. Disclosure of common ligands of CCR5-macrophage inflammatory protein1-α (MIP1-α), RANTES (Regulated upon initiation, Normal T-cell communicated and discharged), and macrophage inflammatory protein1-β (MIP1-β) - as inhibitors quickly discover a method for examine for manufactured ligands to repress the HIV-1 receptor and hinders the viral entry to the cell[4]. The CCR5 receptor is a major co-receptor for viral entry in the host cell, and it is a class of G-protein coupled receptor family having an essential role in the R5- tropic HIV-1 entry.

DEVELOPMENT STAGES

Till now few CCR5 inhibitors are investigated for AIDS treatment. In August 2007 USFDA approve the only drug Maraviroc (Selzentry). Aplaviroc trial was discontinued because of its hepatotoxicity found during clinical trials[5]. INCB009471 an oral antagonist of the CCR5 receptor with prolonged half-life was studied for phase I and II in 2007, but the trials were discontinued by the company. Another drug Vicriviroc was in phase III clinical trial[6, 7]and halted. Anibamine, the first natural product obtained from *Aniba spp*., contains quaternary pyridine alkaloids that are potent CCR5 inhibitors [8]. Recently, there are two new potent CCR5 inhibitors discovered by Takeda (TAK-651 and TAK-220). TAK-652 reported to be a potent inhibitor of CCR5 in preclinical trials and is under phase I pharmacokinetic studies. Promising results of TAK-220 has been found in preclinical stages [9].

ROLE OF CCR5 IN HIV/AIDS

For HIV-1 to enter into a host cell, binding with the CD4 envelope receptor is essential. When HIV-1 binds to the CD4 receptor conformational changes occur in gp120 and the CCR5 binding site is exposed. By this process second conformational change produces in gp41 protein of HIV-1, resulting in fusion of two membranes and viral entry into host cell. Interestingly, Caucasians (1%) in their CCR5 gene has a deletion of homozygous 32 base pairs. In Caucasian individuals expression of CCR5 on the cell surface of CD4 is absent which gives protection against acquiring HIV-1 infection [10].Two main approaches for blocking the entry mechanism of virus entry to host cell is either by interference with protein that binds to CCR5 or by removing the CCR5 from cell surface through carboxy terminus phosphorylation of CCR5.

WHY TROPISM ASSAY IS REQUIRED?

In the early stage of HIV-1 disease in the majority of patients, the virus uses CCR5 receptor for entry in CD4 cell of the host (CCR5-tropic virus). In cases of advanced immuno-suppression around one-half of viral strains enters either through CXCR4 receptor alone, or both CXCR4 and CCR5 receptors (R4 or dual-tropic). About 80% of the HIV-naïve patients are infected with the R5 tropic virus, while approximately 50% of the pretreated patients of the HIV-1 are exclusively infected with CCR5 viral strains. For patients, solely infected with CCR5 tropic viral strains maraviroc has been approved. Maraviroc did not decrease virus load (compared to optimized background therapy) in patients with CXCR4 or dual-tropic virus[11].

European guidelines for the tropism assay

Viral tropism is defined as the capability of the viruses to enter as well as infect the host cell, and it is based on the binding capacity of the viruses to receptors on those host cells. Before prescribing a CCR5 blocker HIV tropism testing is recommended. The co-receptor type should be recognized before the treatment started with a CCR5 blocker[12]. Tropism testing is powerfully suggested in all patients who have medicine failure for whom a CCR5 antagonist is being thought about as a part of the following programme. Tropism testing is moderately counseled altogether patients for whom treatment has did not give insight into future treatment choices. Patients showing adverse events along with its current regimen or unexplained neurological pathology, treatment containing CCR5 co-receptor inhibitors will be of potential worth. In patients who have been diagnosed recently, the role of tropism assay as an indicator for future use of CCR5 antagonist or as a prognostic marker is not sufficiently illustrious to justify any recommendation[13]. In antiviral-naïve patients at high risk of hepatotoxic and neurological abnormalities of first-line treatment, CCR5-tropism testing could be done before initiating any therapy so, if toxic effects develop, a procedure will be changed to include CCR5 antagonists without further tests. Samples ought to be collected as close as possible to the time of beginning treatment. The utilization of maraviroc in HIV-naïve patients is not approved by the European Medicines Agency[12]. Tropism is often assessed with either genotypic or phenotypic technique.

Table1: Some critical methodological characteristics of several phenotypic recombinant method strends within the last years to assess HIV tropism.

Name of the Phenotypic recombinant way	Key methodological characteristics			
	vector Construction	Report gene	Virus Stocks	Sensitivity
XtrackC/PhenX-R In Pheno AG	Clonal technology	β-galactosidase	Defective Replication	1%
Virco NH2-V4 gp120	Recombination	green fluorescent protein	Competent Replication	5-10%
Monogram Biosciences ESTATrofileTM4	Clonal Technology	Luciferase	Defective Replication	0.3-1%
Univ. Toulouse Toulouse Tropism Test (TTT)	Recombination	Luciferase	Competent Replication	0.5%
ISCIII-FISPE Tropitest	Clonal Technology	Luciferase	Competent Replication	1%
VIRalliance Phenoscript	Recombination	β-galactosidase	Competent Replication	5-10%

Phenotypic Assay

The phenotype assays are ordinarily based entirely on recombinant virus's technology. Briefly, the gene is amplified with the aid of PCR (Polymerase Chain Reaction) from plasma samples. In the end, recombinant virions are generated through genetic or clonal recombination. The recombinant virus debris is used to infect cell lines expressing the CD4 receptor and both CCR5 or CXCR4. The phenotypic assay Trofile™ has been appreciably used to provide tropism knowledge in the maraviroc trials, and hence it's been the most extensively used up to now[13-15].

Genotypic Assay

Genotypic assays constitute an extra viable opportunity to phenotypic assays for the reason that they're speedier, less expensive, and extensively to be had among laboratories that specialize in HIV diagnosis. During the early 1990s, numerous rules, and algorithms had been developed to expect HIV co-receptor usage based entirely on V3 sequences, lots of them at the moment are free to be had through publicly accessible websites. The "11/25 rule" was the earliest algorithm advanced for viral tropism interpretation and remained one of the most famous till current times. It's far primarily based on the truth that viruses offering essential amino acids such as arginine (R) or lysine (k) at positions 11 and 25 are regularly related to an X4-tropic phenotype. Conversely, non-existence of R or K in those areas is related to R5-tropic viruses[16]. Despite the fact that this rule shows high specificity (80-90%), it can be afflicted by low sensitivity (30-40%) in figuring out X4-tropic viruses in contrast with phenotypic assays. Currently, a modification of the 11/25 rule has been proposed that improves the predictive cost for viral tropism. It is regarded as the 11/24/25 rule and considers variants as X4-tropic when a position 11, 24, or 25 harbours any essential amino acid; otherwise the virus is classed as R5-tropic[17].

The "net charge rule" is a simple interpretation technique that estimates the global net cost of the V3 region in keeping with the following formula:

(k+R) – (aspartic acid [D] + glutamic acid [E]).

If the end result is ≥ 5, the virus is assessed as X4-tropic; in any other case, it is miles R5- tropic. There is another rule for calculating the net charge that consists of the primary amino acid histidine (H); this is as follows:

(k+R+H) – (D+E).

But, this alternative approach is much less correct than the guideline that does not include H (79 vs 49%). Similar to the 11/25 rule, the net charge rule indicates excessive specificity but suffers from low sensitivity in figuring out X4 variants[18, 19]. During the last decade, efforts have been made to discover residues in the V3 area which can be involved in determining viral tropism. The natural variability of the V3 location has been examined in a couple of HIV isolates phenotypically categorized as R5- and X4-tropic. Consequently, new residues and particular patterns of amino acids have been recognized as influencing viral tropism. No one trade appears to be responsible for the tropism; as a substitute, numerous clusters of genotypes seem in large part decide viral tropism[20, 21]. Many algorithms are free to be had on websites such as Wetcat, Geno2phenocoreceptor, net PSSM, and Fortinbras PSSM.

Table 2: Some critical methodological characteristics of several genotypic recombinant methods trends within the last years to assess HIV tropism

Name of the Genotypic Methodology	Key methodological characteristics		
	Principle	Sensitivity	Specificity
11/25 rule	R or K at position 11/or 25 is related to an X4-tropic makeup	59.5%	93.4%
11/24/25 rule	R or K at positions 11, 24, or 25 is related to X4-tropic makeup	-	-
Net charge	K+R – (D+E) ≥ 5 is associated with an X4-tropic makeup	Low	High
Wetcat	HIV tropism predictions measure inferred from genotypic/ makeup paired dataset using applied statistical ways.	22%	90%
Geno2pheno	These algorithms for HIV tropism interpretation square measure freely obtainable on websites.	50%	90%
WebPSSM	-	84%	96%

CLINICAL EFFICIENCY OF CCR5 INHIBITOTRS

Clinical efficiency of Maraviroc

As Maraviroc is only active against R-5 tropic virus and not against CXCR4 or dual-tropic virus. The maraviroc potency of the HIV-1 virus was studied during the 10-day phase I trial of monotherapy in 63 patients which were previously reported with R-5 tropism. Randomized allocation of patients to treatment with maraviroc 25mg, 100mg, 300mg once daily (QD) or 50mg, 100mg, 150mg twice daily(bid) or placebo for ten days was done. On day 11, mean decrease of viral copies were found to be more in patients treated with maraviroc in comparison to placebo. No difference was reported in the reduction of viral copies in patients who were fasted vs fed individuals [22]. In phase II maraviroc efficacy was also determined in patients pretreated with mixed CXCR4 and R5 tropic virus. In maraviroc treated patients the CD4 cell count was shown to be increased, with a change in CD4 cells/mm^3 +36, +62, and +60 in placebo group, 150mg (bid) and 150mg (QD) maraviroc respectively[11]. Further maraviroc is studied for phaseIII trials, in exclusively pretreated HIV-1 patients. In 2007,

maraviroc was being evaluated in phase III studies MOTIVATE-1 (the USA and Canada) and MOTIVATE-2 (Europe, Australia, and theUSA) in previously treated and ART-naïve subjects in the study of Pfizer. Maraviroc approved by USFDA in 2007 for pretreated patients[23].

Table 3: Efficacy of maraviroc in trials[22]

Doses of the Drug	Mean changes in viral load log_{10} copies/ ml ranges at day 11
25mg QD	-0.03
100mg QD	-1.43
300mg QD	-1.35
50mg bid	-0.66
100mg bid	-1.42
150mg bid(fed)	-1.34

Clinical efficiency of Vicriviroc

A 14 days phase Imonotherapy study in 48 HIV-naïve patients were studied. The patients were treated with 10mg, 25mg, and 50mg bid for 14 days in a randomized design. Decrease in viral copies weredose-related and the mean log_{10} c/ml drop of -1.62(50mg bid), -1.56(25mg bid) and -1.08(10mg bid) [24, 25]. In phase II study is also performed in 92 treatment naïve patients, but the study was terminated due to early virologic breakthrough[26]. The patients are divided into randomized groups to receive vicriviroc with doses of 25mg, 50mg, 75mg once daily and placebo (efavirenz) for 14 days against the AZT/3TCbackground. After two weeks the treatment provides promising results. Duration of this study was 48 weeks, but at 32 weeks this study was terminated due to early viral breakthrough.

A double-blind, randomized trial was studied for phase II in 118 patients who experienced the viral breakthrough. In this study, patients received 5mg, 10mg, and 15mg vicriviroc as an add-on to the failing ritonavir containing HAART. Background treatment was optimized after 14 days of treatment. Study with 5mg vicriviroc dose was discontinued due to high virologic failure[27, 28, 29].An extended follow-up study for phase II for higher doses gives promising results. In 70% patients the mean viral load declines with <50 copies/ml at 24th week and continued to have <50copies/ml at week 48[30]. Vicriviroc was halted in phase III clinical trials because of increased liver malignancies[31].

Table 4: Efficacy of vicriviroc in trials[24]

Dose(QD)	Mean changes in viral load log_{10} copies/ ml ranges at day 15
10mg	-1.08
25mg	-1.56
50mg	-1.62

Clinical efficiency of Aplaviroc

Aplaviroc also a CCR5 inhibitor and promising results are shown in phaseI and IIa study. A decrease was observed in viral load in 0% of the placebo group when compared with 17% of patients receiving 200mg aplaviroc QD, 200 mg aplaviroc bid received by 75% of patients, 63% of those treated with 400 mg aplaviroc QD and 100% of the patients who were receiving 600 mg aplaviroc bid after 10 days of treatment[32]. However, phaseIIb and III trials were discontinued because of hepatotoxicity[33].

Table 5: Efficacy of aplaviroc in trials[32]

Doses	Mean changes in viral load log_{10} copies/ ml ranges at day 11
200mg QD	-0.46
200mg bid	-1.23
400mg QD	-1.03
600mg bid	-1.66

TOXICITY AND ADVERSE EVENTS

In healthy volunteers,oral doses of maraviroc to 900mg was found to be well tolerated[34]. The common adverse effect reported with maraviroc includes nausea, dizziness, headache, gingivitis, and asthenia[11, 22]. But at a 600mg dose or above, orthostatic hypotension occurred more frequently[35]. The safety profile of placebo and maraviroc treatment groups has no difference in a trial with nausea, headache, fatigue, and diarrhoea being most frequent in all groups. A slightly higher chance of drowsiness and respiratory infections was accounted in the maraviroc treated groups[36, 37].

The 48 weeks phase II trial of vicriviroc showed overall good tolerability. No significant differences in adverse effects were seen between the different treatments of vicriviroc (5mg, 10mg, and 15mg) with placebo. No prolongation of QT interval was reported.[38]

MALIGNANCIES

In 2006, the ACTG 5211 trial amongst antiretroviraltherapy-treated adults with the R5 tropic virus who received 10-15mg QD ritonavir-boosted vicriviroc was unblended because of the unexpected production of malignant lymphomas[39]. In patients, randomized in a clinical trial of vicriviroc fatalities occurred in 6 patients with maraviroc and two patients with placebo, from which one had been exposed to vicriviroc treatment for three months. From 6 subjects of vicriviroc group, one was diagnosed with gastric adenoma and one with human papillomavirus-related cell carcinoma, two developed non-Hodgkin lymphoma, and two developed m. Hodgkin (1 had a history of treated Hodgkin disease)[28]. The associations of occurrence of malignancies with vicriviroc treatment remain uncertain but appear to be not drug-related. The data that was available recently through ACTG study showed that there was no further development of malignancies. There is a need for further development to follow up this possible relation of vicriviroc use and malignancies. The data obtained from MOTIVATE 1 and 2 showed that there was no significant difference in the production of malignancies between maraviroc treated patients and placebo groups[35].

PHARMACOKINETICS OF CCR5 INHIBITORS

The pharmacokinetic study of HIV-1 patients revealed that maraviroc is absorbed rapidly with a T_{max} (time to maximum concentration) between 1-4 hours postdose. The plasma half-life ($t_{1/2}$) is from 16-23 hours and is dose dependent[22, 34]. In the presence of food, vicriviroc is absorbed rapidly with T_{max} of approximately 2-3 hours. The plasma $t_{1/2}$ of vicriviroc is 28-32 hours; this data supports that the dose should be once daily[25, 40]. A phase I trial in 24- patients with R5 tropic virus revealed that the steady-state concentration of maraviroc was achieved in 7 days and a fastedstate, the plasma concentration lowered up to 50%. The antiviral effect of maraviroc with dosing of the 150mg bid was found to be independent of food intake and reduces the viral load 1.45 $\log_{10}$ copies/ml and 1.34 $\log_{10}$ copies/ml for fasted and fed condition respectively. The study showed thatthere was no significant effect of food on vicriviroc pharmacokinetic profile. The vicriviroc can be administered with or without food[41].

DRUG INTERACTION

The vicriviroc and maraviroc both are primarily metabolized by CYP3A4, an enzyme that is a member of cytochrome P450 system. When vicriviroc and maraviroc are co-administered with potent CYP3A4 inducer, the drug levels may decrease, and the drug levels may increase when these are co administered with potent CYP3A4 inhibitor. Therefore the drug-drug interactions can be possible especially with a protease inhibitor. Dose of maraviroc reduces up to 50% in presence of protease inhibitor. Consequently, there is a recommendation for potent CYP3A4 inhibitor. An exceptionis with tipranavir which does not lead to any substantial changes, in maraviroc exposure in healthy participants[42]. When protease inhibitor is absent the maraviroc is given with rifampin, the dose of maraviroc has to be doubled[43].Maraviroc and Vicriviroc shows no significant inhibitory effects on any CYP450 enzyme, by making it unlikely that they can alter the metabolism of those drugs which are metabolized by cytochrome 450[43, 44]. Pharmacokinetics studies on healthy volunteers showed that maraviroc does not affect the pK of NRTIs Zidovudine(AZT), Lamivudine (3TC) and Tenofovir(TDF). Metabolism characteristics of the vicriviroc are same to maraviroc.There are no clinically relevant effects on plasma exposure of vicriviroc, AZT, 3TC, and TDF when co-administered to healthy subjects[45, 46].When vicriviroc 10mg QD co-administered with 600mg efavirenzQD resulted in 81% decrease in AUC of vicriviroc[47]. When vicriviroc is co-administered with LPV, the AUC increased by 4.2 fold. The currently reported dose of 100mg ritonavir bid + 15 mg vicriviroc leads to comparable vicriviroc levels as when 15mg is added to ritonavir-boosted PI. Therefore, in future vicriviroc will be added to the ritonavir-boosted Protease Inhibitor (PI) regimen without any dose adaptation[48].

Table 6: Summary of drug interactions

Drug Name	Effect on Maraviroc Exposure Levels	Effect on Dose of Maraviroc
Atazanavir	↑ (5 fold)	↓ (by 50%)
Darunavir	↑ (4 fold)	↓ (by 50%)
Efavirenz	↓ (by half)	Double (in the absence of PIs), ↓(in the presence of a boosting dose of ritonavir)
Ketoconazole	↑ (5 fold)	↓ (by 50%)
Rifampin	↓ (by one third)	Double (in the absence of PIs)
Lopinavir	↑ (4 fold)	↓ (by 50%)
Tipranavir	No change	No dose modification
Ritonavir	↑ (by 2.6 fold)	↓ (by 50%)

CHALLENGES WITH MARAVIROC TREATMENT

There are approximately not more than 50% pretreated patients, infected with the R5 tropic virus and are possible subjects to maraviroc treatment and the remaining almost of 50% of patients with virologic failure owing to HAART resistance are not expected to benefit from maravirocttreatment. Before initiation of the therapy, it is essential to differentiate between R5 or R4 tropic virus. The first requirement of this assay is high-intensity viral load >500 copies per ml, and the major problem with this assay is the cost, i.e. $1500-2000 per single test and the blood samples are shipped to the US for this assay[49].

CONCLUSION

Inside the mild of growing viral resistance in opposition to current antiretroviral drugs, the current improvement of this new class of ARV-therapy with a totally novel mechanism of action is beneficial. The CCR5-antagonists maraviroc and vicriviroc are energetic against current 3 drug-class-resistant R5-tropic HIV-1. The two substances have indicated powerful anti-retroviral action in pre-treated individuals with extreme HIV-disease. The trial results of maraviroc are promising. Vicriviroc was defied with more limitations on its way of clinical assessment. Nevertheless, after preliminary concerns associated with virologic breakthrough in low-dose treatment, sustained antiviral action of vicriviroc can also be suggested as long because it was boosted with ritonavir. Problems

concerning the presence of malignancies in patients treated with vicriviroc could not be affirmed in to boot follow-up assessment of this drug. The CCR5 antagonists are mostly metabolized by the manner of CYP3A4 framework. They don't repress or induce CYP450 at normal concentrations; however the co-administration of CYP3A4-inducers or –inhibitors may have influence on pharmacokinetics of vicriviroc and maraviroc. Consequently, when CCR5 antagonists are combined with different (ARV) drugs dose adjustments can be essential. Herewith two effective new antiretroviral devices are introduced in HIV work on, opening new treatment open doors for patients with multi-resistant strains of HIV. After the maraviroc approvel, the first CCR5 inhibitor in the treatment of HIV-1 infection, trofile testing is required for clinical use. The European concord group on clinical management of trofile testing gives a summary of obtainable published work, evidence-based proposals for the clinical utilization of trofile testing, and directions on uncertain components and improvements. Current information lend support to each the utilization of population genotyping and also the commercially out there increased sensitivity assay for establishing co-receptor response.

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