Maraviroc: integration of a new antiretroviral drug class into clinical practice

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Maraviroc (Pfizer’s UK-427857, Selzentry or Celsentri outside the US) is the first agent in the new class of oral HIV-1 entry inhibitors to acquire FDA and EMEA approval. It is expected that this drug will be effective only in a subpopulation of HIV-1-infected people, namely those harbouring only the R5 virus. The wide use of this drug is currently hampered by the lack of a readily available R5 virus only determination test (tropism test) and by insufficient scientific insight into the dynamics of R5 and X4 viruses during infection. We discuss the challenges associated with the currently available assay, as well as the potential role of alternative assays.

Keywords: tropism, chemokine receptor, co-receptor-blocker, V3 loop sequencing

Introduction

The chemokine receptor antagonist maraviroc is designed to prevent HIV-1 infection by blocking the CCR5 co-receptor. Entry of HIV-1 into a target cell requires interaction between the envelope glycoproteins (gp120) on the surface of the virus and the CD4 receptor and a chemokine co-receptor on the human cell. The two main co-receptors involved in HIV entry are CCR5 and CXCR4. Viruses that have an affinity for the CCR5 co-receptor are called CCR5-tropic or R5, whereas those that bind CXCR4 are known as CXCR4-tropic or X4. A dual tropic (R5/X4) virus can bind both CCR5 and CXCR4. CCR5 antagonists are expected to be of most use in individuals carrying R5 viruses only. For maraviroc, this hypothesis was supported by the results of the MOTIVATE clinical trials: MOTIVATE 1, conducted in the USA and Canada, and MOTIVATE 2, conducted in Europe, Australia and the USA.

MOTIVATE trials

MOTIVATE 1 and 2 were randomized, double-blind studies evaluating potency, safety and efficacy of the addition of maraviroc to an optimized background therapy (OBT) in antiretroviral-therapy-experienced patients with multiple class resistance. The addition of maraviroc twice daily resulted in a statistically significant greater viral load reduction and a significantly greater increase in CD4+ white blood cells compared with OBT alone. Nearly twice as many patients treated with maraviroc plus OBT achieved undetectable viral loads (<50 copies/mL) compared with placebo plus OBT (MOTIVATE 1, 48.5% versus 24.6%; MOTIVATE 2, 40.8% versus 20.9%). Based on the results of the MOTIVATE trials, the FDA and the EMEA recently approved the use of maraviroc for combination antiretroviral treatment of adults with evidence of viral replication and genotypic resistance to multiple antiretroviral agents and with only CCR5 'tropic HIV-1 detectable'.

Challenges associated with tropism diagnostic requirements and maraviroc use

The restriction of maraviroc use to patients with only the CCR5-tropic virus makes determination of the co-receptor tropism a requisite for maraviroc initiation. A recombinant HIV-1 co-receptor tropism assay, Trofile™ (Monogram Biosciences, San Francisco, CA, USA), is currently the only tropism assay that has been clinically validated for determination of co-receptor use. The assay was used in all maraviroc clinical development programmes with over 5000 patients being screened. The two companies, Monogram and Pfizer, have a collaboration agreement to make Trofile™ available for patients on a global basis.

Practical as well as economic challenges are associated with the dependence on Trofile™ for the use of maraviroc. Centralized laboratory testing requires the shipment of fresh blood or plasma specimens from all over the world to one location in California, USA, currently the only location where an assay of this complexity can be conducted. The assay itself is expensive and it is currently unclear who will, in the long term,
pay these additional costs. Besides cost, there are other issues such as the turnaround time of 3–6 weeks and the fact that a minimal viral load of 1000 RNA copies/mL is required for adequate sensitivity (94% to 95% amplification success rate).3

Interpretational challenges associated with the relation between tropism and maraviroc efficiency

Using sensitive clonal methods, Lewis et al.4 and Westby et al.5 were able to show that strains with the same genetic characteristics as the CXCRI4-using viruses isolated at maraviroc failure were already present in small quantities in the baseline samples of these patients but remained undetected by TrofileTM. The limited sensitivity for the detection of minority species is an intrinsic shortcoming of all phenotypic assays (not only Trofile). Each ‘R5 only’ result therefore should be interpreted with caution and is not a foregone guarantee for prolonged maraviroc susceptibility. The FDA label for maraviroc clearly marks that failure might be a consequence of the presence of undetected minorities at baseline.

Mayer et al.6 evaluated the effect of maraviroc in patients with a dual or mixed tropic virus. Although the addition of maraviroc did not result in improved viral suppression compared with OBT alone, patients in the maraviroc group experienced a greater increase in CD4+ T cells than patients in the placebo group (week 24: maraviroc once daily +60, twice daily +62 cells, placebo +35 cells/mm3). The effect of maraviroc in dual or mixed tropic populations definitely needs further evaluation. In particular, the influence of maraviroc on the quantitative distribution of viruses with a different tropism must be looked at in more detail. It might be that, although not beneficial, addition of maraviroc to a dual or mixed tropic virus population is at least harmless. A study presented recently at the Fifteenth Conference on Retroviruses and Opportunistic Infections described a detailed analysis of the tropism of viruses isolated from patients with virological failure in the MOTIVATE 1 and 2 trials.7 Clonal genotypic analysis allowed the classification of viral strains that were scored as dual tropic by TrofileTM, as dual-R or dual-X tropic, based on a comparison of the V3 sequence with known R5 or X4 strains. It appeared that dual-R clones may remain responsive to maraviroc, although in vivo they always co-existed with dual-X clones. The clinical relevance of these findings requires further investigation.

Alternative assays

Although currently the only assay with clinical validation available, TrofileTM cannot be considered the ‘gold standard’ for tropism determination.8 Alternative technologies can be subdivided into two groups: phenotypic and genotypic assays, the latter linked to bioinformatics-driven prediction tools. Phenotypic technologies are always based on the generation of recombinant or pseudo-viruses, starting from a patient’s virus-derived envelope. Such viruses are then used to infect cells presenting the appropriate co-receptor. Tropism is, depending on the assay, deduced from a luciferase, fluorescence or β-galactosidase read-out module.9–11

The genotypic methods are based on the observation that most of the determinants for co-receptor specificity are located within the highly variable V3 loop of the envelope protein. A number of bioinformatic tools have been used to develop prediction algorithms, several of which are now freely available on the Internet.12–16 A recent study by Low et al.,8 however, showed that these genotypic algorithms are inadequate for clinical use. Though the predictive value for X4 use of most of these algorithms is high (between 88% and 97%), their use is mainly limited by a lack of sensitivity of population-based sequencing for the detection of minority species. The study of Low et al. was performed on treatment-naïve patients and thus not on the patient populations studied in the MOTIVATE trials, on which FDA and EMEA approval is currently based. Genotyping assays may perform differently in treatment-experienced patients. In addition, taking into account immunological markers (CD4+) in the genotypic algorithms might further improve their predictive capacity.17

Are diagnostic tropism assays really feasible?

Despite the previously mentioned shortcomings, the use of genotyping methods for tropism prediction is tempting because it would allow most of the routine HIV labs that are fully equipped for the determination of genotypic drug resistance to predict tropism in a more cost-effective and timely manner.8

In the testing cascade recently proposed (Figure 1), genotyping assays are used as first-line assays, whether in combination with immunological markers and treatment history or not.11 If the result of genotypic prediction algorithms indicates the presence of X4 virus, the cascade can be stopped and the patient considered as not eligible for maraviroc treatment. If the results indicate an R5 or unknown tropism, additional testing, preferably phenotypic testing, must be conducted. In a number of clinical studies, analysis for co-receptor tropism in treatment-experienced patients showed that the R5 virus alone was detected in no more than half of these patients (50% to 78%) (for a recent review, see Tsibris and Kuritzkes).8 The possibility of identifying X4 virus in the remaining 32% to 50% by genotyping would reduce the number of samples to be sent for phenotyping by half, thereby reducing the waiting time for advice supporting or discouraging the use of maraviroc in these patients.

But there are a number of drawbacks and several unanswered questions. The result of genotyping is largely dependent on the quality of V3 loop sequencing and, due to high inter-patient variability in the envelope gene, obtaining a good quality sequencing result is not certain. Besides, minority species detection in population sequencing will be at least problematic. The quality of the prediction algorithms needs further clinical validation and cut-offs defining clinical response to maraviroc should be established.

After the first selection by genotyping, additional phenotypic testing could be done using either TrofileTM or one of the alternative assays.9–11 Although for some of these alternative assays comparative data with Trofile are available, none has been evaluated in clinical trials. Efforts to conduct this evaluation must be encouraged.19 The availability of several good quality phenotypic assays will eliminate the need for centralization and sample transport overseas.
Leading article

The problem with minority species

Much remains unknown about the kinetics of R5 and X4 viruses during the course of the HIV infection but increasing data seem to support the statement that the majority of patients carry a mixture of R5- and X4-using HIV strains.\(^1\) Using artificial mixtures of patient-derived viral clones, phenotypic assays available today can detect minority species with a sensitivity approaching 100% when the minority species account for 10% of the population, dropping to ~83% at 5% minority. There is the expectation that, with new sequencing technological breakthroughs (e.g. cyclic array sequencing, ultra-deep sequencing), this detection limit can be lowered considerably.\(^4\) With regard to the prediction of maraviroc susceptibility, the question arises of how deep one needs to look for minority X4 strains. Is it the absolute number of X4 strains in the blood or the relative amount of X4 strains in the total population that is of prognostic value? It might be that the affinity of the virus gp120 for a certain co-receptor presents itself not as a black and white situation, but as a spectrum, going from R5-tropic towards X4-tropic in a gradual scale, realized by a continued accumulation of mutations in V3 and other gp120 domains. Hence, interpretations of the impact of the X4-tropic minority species would require relevant cut-off values for clinical response on such a gradual scale.

Conclusions

The number of patients with limited treatment options as a result of multidrug resistance or intolerance is continuously growing. A promising new drug has been released to the patient’s benefit. The clinical availability of the co-receptor antagonist maraviroc precedes the scientific understanding that is needed to clearly position this class of drugs in the total spectrum of treatment options and this gap must be filled as soon as possible.

Transparency declarations

None to declare.

References


