A prospective evaluation of maraviroc administration in patients with advanced HIV disease and multiple comorbidities: focus on efficacy and tolerability issues

Valutazione prospettica di maraviroc in pazienti con infezione da HIV in fase avanzata e multiple comorbidità: focus su parametri di efficacia e tollerabilità

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INTRODUCTION

In our tertiary-care HIV outpatient centre where over 1,200 patients are currently followed, maraviroc as a novel entry inhibitor (chemokine receptor 5 °C CCR5-antagonist), was introduced since 2010, initially as a part of end-stage salvage antiretroviral therapy. Indeed, according to preliminary literature data, maraviroc demonstrated its effectiveness in both antiretroviral-naïve and experienced patients harbouring a CCR5-tropic HIV, and showed a satisfactory tolerability profile also in patients with multiple comorbidities, including cardiovascular and liver diseases, and tuberculosis [1-7]. The lack of cross-resistance between maraviroc and all other antiretroviral agents due to the unique, specific mechanism of action, makes this drug a very attractive treatment option in patients who are resistant to or intolerant of other anti-HIV compounds [3, 8].

Aim of our study is to assess the background, the therapeutic challenges, and the prospective efficacy and tolerability monitoring of all patients treated with a combination antiretroviral therapy (cART) including maraviroc since at least 12 months, in our cohort of patients living with HIV in North-Eastern Italy, and compare these issues with those coming from registration trials and controlled clinical studies.

Patients and methods

Sixty-six patients, including 40 males and 26 females; 65 caucasians and one black; started a maraviroc-containing cART at standard dosages (depending on concurrent medications and underlying kidney function), when aged 25-74 (mean 43.2±12.8) years. Their history of HIV infection lasted since 3-27 (mean 13.9±10.7) years. A phenotypic virological testing showing the persistence of an “R5” tropic virion (Trofile®, Monogram Biosciences, San Francisco, USA) until 2010, and later an in-house genotypic V3 loop tropism assay, allowed us to select the patients who were expected to have a certain advantage from maraviroc administration.
Our hospital pharmacy informatized dispensary system prospectively followed all patients who received maraviroc and had a continuative follow-up of at least 12 consecutive months. Maraviroc was dispensed according to the international and Italian guidelines of antiretroviral therapy and all manufacturers’ recommendations [9, 10]. In particular, it has been administered at the standard dosage of 300 mg twice daily, reduced to 150 mg b.i.d. when co-administered with a potent CYP3A4 inhibitor, or increased to 600 mg b.i.d. when used with a potent CTP3A4 inducer.

For this interim analysis, patients who received a maraviroc-containing cART for at least 12 months (mean 16.9±12.8, range 12-47 months), were selected. Clinical and electronic charts containing all demographic figures, medical history and laboratory data, informations regarding comorbidities, previous and concurrent medications, and electronic records of all subsequent visits at our outpatient centre for clinical, laboratory and compliance assessment were prospectively matched. In particular, patient’s adherence was monitored through written self-reported written questionnaires released and collected at every clinical access and drug delivery, matched at least every month with drug accountability by our clinical pharmacists.

Statistical analysis included two-tails Student t test and Mantel-Haenszel chi-square test where appropriate, with significance levels posed at p<.05.

RESULTS

One or more (up to 17) therapeutic changes of previous cART lines (due to failure and/or intolerance), prompted the introduction of maraviroc in rescue regimens in the great majority of considered patients (53 out of 66). In 13 cases, maraviroc was given to patients with advanced HIV disease (AIDS in all cases), and showing no immune recovery after three years of a virologically-effective cART. In all the remaining 53 patients, an extensive pattern of viral resistance involved at least the three major classes of antiretroviral drugs (nucleos(t)ide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors). At the time of maraviroc introduction, the most frequent companion antiretroviral agents were: darunavir/ritonavir among protease inhibitors (51 cases), raltegravir among integrase inhibitors (49 subjects), and etravirine among non-nucleoside reverse transcriptase inhibitors (36 cases). These drugs and all other antiretroviral compounds were carefully selected according to previous and current genotypic/phenotypic in vitro resistance assays, previous allergies and intolerances, and underlying diseases and comorbidities. The majority of these patients (47 out of 53: 88.7%) received a four-drug regimen including maraviroc, darunavir/ritonavir, raltegravir, and etravirine.

At the time of the therapeutic switch, and during the follow-up period of at least 12 months, limited changes to the novel, started cART regimens became necessary. In particular, the discontinuation of one or more nucleos(t)ide reverse transcriptase inhibitors, that of non-nucleoside reverse transcriptase inhibitors, and that of protease inhibitors, which proved resistant at genotypic/phenotypic virological assays, or had a poorer tolerability when compared with the novel cART regimens, or did not add anything significant in terms of efficacy, potency, and safety to the remaining components of the last selected cART, thus improving cART simplification, and also containing costs and toxicities of unnecessary drugs.

The most common underlying conditions of our case mix were represented by: a diagnosis of full-blown AIDS (41 patients), liver cirrhosis (25 cases), AIDS-related or other malignancies (20 patients), major cardiovascular events (18 cases), osteonecrosis, and end-stage kidney disease treated with haemodyalisis (3 cases each). Moreover, a chronic HCV or HBV hepatitis were of concern in 25 and 13 patients out of 66, respectively. The patients’ adherence to maraviroc proved to be very elevated (from 90% to 100% of prescribed dosages throughout the study period), together with that of the concurrent antiretroviral regimens (90-100%), based on hospital pharmacists’ monthly interviews, patients’ written records, and computerized drug accountability carried our at least every month.

The switch to an optimized cART based on maraviroc added favourably to clinical and laboratory markers of HIV disease progression, and those of the majority of comorbid conditions. In particular,
with regard to the clinical features of underlying HIV disease, no progression to full-blown AIDS or appearance or recurrence of novel AIDS-related disorders were found throughout the entire study period. With regard to laboratory surrogate markers of HIV disease progression, HIV viremia became undetectable (as expressed by plasma HIV-RNA levels below 20 copies/mL), in 50 patients out of 53 with a previously detectable viral load (94.3%). In these last patients, the time to undetectable viral load varied from 8 to 16 weeks (mean 7.2±1.9 weeks), since maraviroc introduction. No significant difference was detected when adjusting these data according to the different antiretroviral compounds associated to maraviroc. When assessing the extent of immune recovery, an increase of the absolute CD4+ T-lymphocyte count was observed in all the 66 patients treated with a maraviroc-containing cART, as evaluated on the ground of a mean 24.9±19.2% (range 18.2%-143.2%) maximum increase of CD4+ count versus baseline levels, paralleled by an improvement of mean absolute CD4+ lymphocyte count of 134.7±121.1 cells/µL (the range of peak increase of absolute CD4+ count was 79 to 488 cells/µL). The patient subgroup (49 subjects) taking maraviroc plus raltegravir showed a tendency towards an increased mean and peak T-lymphocyte count, although this increase did not reach a statistical significance compared with other patient subgroups.

In particular, chemotherapy and/or radiotherapy cycles were performed as scheduled in all the 21 patients suffering from malignancies. Chronic hepatitis B and C did not progress to liver cirrhosis and/or hepatocarcinoma in the 37 subjects with this relevant comorbidity (as assessed by clinical, laboratory, and instrumental monitoring carried out at least monthly); a first or a repeated treatment with pegylated interferon plus ribavirin became feasible in 18 patients out of 25 with a chronic HCV infection. Liver cirrhosis, end-stage renal disease undergoing haemodialysis, and advanced osteonecrosis, did not show significant signs of progression during maraviroc-containing cART treatment.

Notwithstanding the already compromised clinical and laboratory situation at baseline typical of the large majority of our case mix, no patient experienced remarkable clinical and laboratory adverse events attributable to maraviroc, so that nobody discontinued the study drug during the observation period. In particular, neither skin rash or myelotoxicity, nor cough or upper respiratory tract infections, or a significant, otherwise unexplained increase of serum liver and kidney toxicity parameters were observed, including the proportionally elevated number of patients with HCV or HBV co-infection, liver cirrhosis, malignancies, and end-stage renal disease.

Only mild and transient gastrointestinal disturbances, fatigue and anorexia, were reported during maraviroc administration included in the novel cART regimens, but their relationship with the study drug was extremely difficult to assess because of the multiple comorbidities and polypharmacy experienced by the large majority of our patients; anyway, these events did not affect maraviroc prosecution.

In only 8 cases on the whole of the evaluable 46 (17.3%), a change of companion drugs was deemed necessary during the 12-month follow-up, including: the introduction of darunavir/ritonavir instead of tipranavir/ritonavir in 3 cases, and the adjunct of raltegravir (4 patients) and etravirine (3 cases), to replace enfuvirtide (two subjects), or lamivudine/emtricitabine with or without another nucleos(t)ide reverse transcriptase inhibitor (5 cases).

**DISCUSSION**

Maraviroc is the first available agent of a novel class of antiretroviral drugs, which are addressed to block a host protein located on the CD4+ T-lymphocyte cells parasitized by HIV, rather than a viral target, as exploited by the large majority of other available anti-HIV agents.

A true treatment failure of maraviroc is an extremely uncommon event in properly identified CCR5-tropic virions [3, 8]. It may occur only with an insufficient exposure to drug itself and companion drugs, i.e. a low patient’ adherence which favors the switch to an overwhelming CXCR4-tropic virus population, or failure of the other components of the delivered cART.

Since patients with a prolonged history of previous antiretroviral therapy and multiple drug failures are estimated to carry a non-CCR5 tropic virus in over 50% of cases, as a consequence a timely administration of this drug should be mandatory
in this patient subset, in order to preserve a positive CCR5 tropism for successful maraviroc usage [3, 8, 11-13]. Despite the rapid development of affordable genotyping CCR5 assays, phenotypic recombinant assays are still the benchmark tests, since their elevated sensitivity allows them to detect minor CXCR4-using virions [12-14].

When considering salvage regimens, which remain one of the major maraviroc targets according to the guidelines of antiretroviral therapy issued at the time of our prospective study, maraviroc does not share any cross-resistance with other anti-HIV molecules, has an excellent tolerability profile also in patients with multiple underlying diseases, and the apparently elevated expenses related to maraviroc use are somewhat counterbalanced by the reduced dose, usually applied when ritonavir-boosted protease inhibitor are associated to the cART regimen [9, 10]. Furthermore, recent pharmaco-economic evaluations performed with MonteCarlo simulation models, showed a remarkable advantage in terms of strong efficacy and quality of life end-points in the introduction or maraviroc in individual with limited cART options, regardless of the choice of companion drugs, and taking also into account the expenditures related to the study of viral tropism [12-15].

Our preliminary experience with maraviroc, even taking into account of the numerous limits due to the proportionally reduced patient sample coming from a single centre, the proportionally short period of observation, the extremely frequent patients’ salvage stage on the ground of HIV antiviral resistance profile (occurring in many cases after a prolonged history of HIV disease and multiple previous treatment failures), the already progressed and complicated HIV infection, and the related and unrelated comorbidities and poly-pharmacy, underlines the unique efficacy and safety profile of maraviroc, which exploits a novel mechanism of action, without cross-resistance with all other antiretrovirals, and may be associated with any other effective cART regimen, in order to optimize antiretroviral therapy as far as possible.

When analyzing efficacy figures comparing our data with those of MOTIVATE 1 and MOTIVATE 2 randomized, controlled trials performed on over 1,000 patients versus a placebo-containing optimized cART, from a virological point of view our viremic patients on maraviroc achieved an undetectability level of 94.3% at 12 months of follow-up, versus 39-41% of the registration trials at week 96 [2, 4, 6]. The virological efficacy was comparable with that obtained in the MERIT study, where maraviroc plus lamivudine-zidovudine was compared with efavirenz, lamivudine and zidovudine [1, 16].

A satisfactory immunological response has been also observed in our single-centre cohort, as expressed my a mean peak increase of absolute CD4+ T-lymphocyte count of 134.7 cells/µL, when compared with the randomized MOTIVATE 1 and MOTIVATE 2 trials, where the increase of absolute CD4+ count was comparable: 92-128 cells/µL at week 48 [4, 5, 17], and 89-113 cells/µL at week 96 [6, 17]. In patients treated with maraviroc compared with those receiving a placebo-containing optimized cART, even after adjusting for the greater virological potency of maraviroc-containing regimens, and virological response [5]. The tendency to a further increase of mean and peak CD4+ T-lymphocyte count in the subgroup of patients receiving also raltegravir, failed to reach statistical significance due to the proportionally reduced patient samples in our experience.

The significantly greater increase in CD4+ lymphocyte count in patients under maraviroc may result from a specific action, as well as a better possibility to diffuse in all body compartments [2, 8, 13, 17-19]. Only a recent meta-analysis failed in retrieving a significant increase of CD4+ lymphocyte count in patients treated with maraviroc, compared with other newly available anti-HIV agents [20].

In the early controlled clinical trials (MOTIVATE 1 and 2), a safety profile of maraviroc similar to that of placebo was observed in over 1,000 enrolled patients [5-7, 13, 17]. The 5 most common adverse events associated to maraviroc administration compared to those attributed to placebo were: upper respiratory tract infections (20.0%), cough and associated symptoms (12.7%), pyrexia (12.0%), rash (9.6%), and musculoskeletal or connective tissue signs and symptoms (8.7%) [5]. In the MERIT trial, comparing maraviroc versus efavirenz, both associated with lamivudine-zidovudine, in antiretroviral-naïve patients, fewer adverse event discontinuations, malignancies, and category C events occurred among subjects receiving mara-
viroc [1, 2]. No significant alterations in the serum lipid profile occurred under maraviroc therapy, while patients who were dyslipidemic at baseline improved their laboratory parameters, until a 96-week assessment [17, 21].

In our experience, grade 2-4 adverse events were neither directly observed, nor registered in the self-reported file of possible untoward events, completed every month by our patients at the time of repeated antiretroviral drug prescription, and double-checked prospectively by our hospital pharmacists. As a whole, the discontinuation rate in our 12-month experience was 0%, compared with up to 33% in the MERIT study, and 5% in the MOTIVATE trials [6, 16]. Although a potential risk of liver toxicity has been raised by the pharmaceutical company, this occurrence has not been observed in our clinical practice, regardless of the elevated rate of patients with a chronic hepatic disease or receiving potentially hepatotoxic co-treatments. On the contrary, the discontinuation of some companion drugs at the time of maraviroc introduction and during the 12-month follow-up (especially nucleos(t)ide reverse transcriptase inhibitors, some selected protease inhibitors, and enfuvirtide), acted favourably on the tolerability of the maraviroc-based regimens, especially when checking our patients for serum lipid profile (serum total, LDL-, and HDL-cholesterol, serum triglycerides), serum glucose and HB1c, serum liver enzymes, renal function parameters, and subjective adverse events like gastrointestinal disturbances as a whole, lipodistrophy syndrome, and enfuvirtide-related cutaneous manifestations. In fact, favourable effects on serum lipid profile were observed since early clinical trials with maraviroc, and were confirmed against placebo, and especially against comparators including antiretroviral drugs belonging to nucleos(t)ide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors [2, 17, 21].

Coming to patients with a chronic HCV and/or HBV co-infection, our prospective observational study showed no significant disease progression and an excellent safety profile, also confirmed in patients with HCV- or HBV-related liver cirrhosis. A recent revision of trial figures showed that maraviroc plus an optimized background does not increase the incidence of clinical and laboratory liver-related abnormalities of HIV-patients co-infected with either HCV of HBV, so that also this patient subgroups could exploit all the positive maraviroc effects on their difficult-to-treat co-infections [7, 17]. Among others, Genebat and coworkers conducted a 48-week retrospective review of 46 viremic and CCR5-tropic and antiretroviral-experienced patients with an elevated (48%) rate of HCV co-infection, started on maraviroc-containing cART [22]. After 48 weeks of assessment, 96.3% of patients had achieved HIV undetectability, and a mean CD4+ count increase of 151 cells/µL was observed [22]. The extremely favourable immunological recovery granted by maraviroc could prompt its introduction in cART regimens of patients with a discordant response to previous cART lines, especially when an underlying chronic hepatitis or liver cirrhosis are present, due to the favourable change of a series of laboratory markers of immune activation (i.e. CD38, HLA-DR), senescence (CD28, CD57, Cd45RA and RO), and cell apoptosis (annexin-V), although other studies analyzed different panels of serum mediators of fibrogenesis at different times of treatment of patients co-infected with HIV and HCV introducing maraviroc in their cART, showing different, but promising results [18, 23].

Further pilot experiences demonstrated the efficacy and safety of novel antiretroviral combination sparing both nucleos(t)ide reverse transcriptase inhibitors and protease inhibitors in three-class experienced HIV-infected patients: the association of maraviroc, raltegravir and etravirine seems particularly promising in this setting [24].

In conclusion, in our cohort of heavily experienced patients with frequent comorbidities, the rates of virological and immunological success of the introduction of maraviroc-containing cART regimens and the incidence and severity of untoward events proved at least similar or even better when compared to the registration data belonging to the MOTIVATE and MERIT studies, so that we can consider maraviroc as an effective and safe choice for these difficult-to-treat subsets of HIV-infected patients, also in routine, real-life clinical conditions [1, 7, 13, 16].

The current availability of maraviroc will allow us to prescribe this antiretroviral agent in earlier cART lines, in less compromised patients who have a greatly increased probability to show an “R5” (CCR5) tropic virion, and are expected to
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exploit further the therapeutic potential of this drug in all existing and upcoming cART regimens, including those given to antiretroviral-naïve subjects experiencing their very first antiretroviral treatment [3, 8, 19, 20]. Other issues to be addressed are: the diffuse availability of an easy and affordable CCR5 genotypic tropism testing, the possibility to deliver potent and metabolically stable CCR5 inhibitors once daily, and possibly the development of CXCR4 inhibitors, which are expected to greatly improve the available treat-

ment options for patients harboring an X4- or a dual-tropic strain, although at this time only few novel CCR5 inhibitors are assessed in preliminary, pipeline studies [3, 12, 13].

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Keywords: HIV infection, antiretroviral therapy, maraviroc, prospective assessment, efficacy and tolerability.

SUMMARY

In our HIV outpatient centre where over 1,200 patients are followed, maraviroc as an entry inhibitor was introduced in 2010. We aimed to assess the background, the therapeutic challenges and the prospective monitoring of all patients treated with a combination antiretroviral therapy (cART) including maraviroc. Sixty-six patients started a maraviroc-containing cART with a history of HIV infection lasting 13.9±10.7 years. This interim analysis presents patients who had at least 12 (mean 16.9±12.8) months of follow-up. One to 17 previous cART changes prompted the introduction of maraviroc in rescue regimens in the great majority of patients considered (53 of 66); in 13 cases, maraviroc was given to patients with advanced HIV disease and no immune recovery after 2-3 years of a virologically-effective cART. The most frequent companion antiretroviral agents were: darunavir/ritonavir (51 cases), raltegravir (49 subjects), and etravirine (36 cases). The most common underlying conditions were: AIDS (41 cases), liver cirrhosis (21), AIDS-related or other malignancies (20 cases), major cardiovascular events (18 cases), osteonecrosis and haemodialysis-treated kidney failure (3 cases each). A chronic HCV and HBV hepatitis were of concern in 25 and 13 patients. The addition of maraviroc added favourably to clinical-laboratory markers of HIV disease progression, and those of comorbid conditions. HIV viraemia became (or remained) undetectable in 55 patients of 66 (83.3%). An improvement in CD4+ count was observed in all 66 patients, based on a mean 24.9±19.2% increase versus baseline, paralleled by an improvement in mean absolute CD4+ count of 134.7±121.1 cells/µL. A tendency towards an increased mean and peak CD4+ count was observed in the subgroup receiving a maraviroc-raltegravir-based cART. As no clinical-laboratory adverse events attributable to maraviroc occurred, nobody discontinued the study drug. Only mild-transient gastrointestinal disturbances, fatigue and anorexia, were reported during maraviroc administration, but their relationship with the study drug was difficult to assess because of the multiple comorbidities and polypharmacy. Our preliminary experience with maraviroc, even considering the limits of the proportionally reduced sample, the patients’ salvage stage of advanced disease and the related-unrelated morbidities, underlines its excellent efficacy and safety profile.

 RIASSUNTO

Nel nostro Centro, dove sono seguiti oltre 1,200 pazienti, l’inibitore dell’ingresso maraviroc è stato introdotto fin dal 2010. Questo studio è stato condotto nell’intento di valutare il background, le sfide terapeutiche, e il monitoraggio prospettico di tutti i pazienti trattati con una terapia antiretrovirale di combinazione (cART) contenente maraviroc. Sessantasei pazienti hanno iniziato una cART contenente maraviroc con una storia di infezione da HIV di durata pari a 13.9±10.7 anni. In questa analisi ad interim, presentiamo i pazienti che hanno almeno 12 (media 16.9±12.8) mesi di follow-up. La grande maggioranza dei pazienti considerati (53 su 66) necessitava di terapie di salvataggio contenenti maraviroc, dopo 1-17 precedenti linee terapeutiche; in 13 soggetti con malattia da HIV avanzata, si introduceva maraviroc in presenza di mancata immunoriconversione, dopo 2-3 anni di CART virologicamente efficace. Gli antiretroviral più frequentemente associati erano: darunavir/ritonavir (51 casi), raltegravir (49), ed etravirina (36 casi). Le più frequenti patologie concomitanti erano: AIDS conclamata (41 casi), cirrosi epatica (21), neoplasie correlate o non correlate...
La nostra esperienza preliminare con maraviroc, pur tenendo in considerazione i limiti della casistica relativamente ridotta, la necessità di cART di salvataggio e le comorbidità correlate e non, sottolinea l’eccellente profilo di efficacia e tollerabilità di maraviroc.

REFERENCE


