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A Randomized, Double-Blind, Placebo-Controlled Clinical Trial of a Chemokine Receptor 5 (CCR5) Antagonist to Decrease the Occurrence of Immune Reconstitution Inflammatory Syndrome in HIV-Infection: The CADIRIS Study

Juan G. Sierra-Madero, MD¹, Susan Ellenberg, PhD², Mohammed S. Rassool, MBCHB³, Ann Tierney, MS², Pablo F. Belaunzarán-Zamudio, MD¹, Alondra López-Martínez, MD¹, Alicia Piñeirúa-Menéndez, MD¹, Luis J. Montaner, DPhil⁴, Livio Azzoni, MD⁴, César Rivera Benítez, MD⁵, Irini Sereti, MD⁶, Jaime Andrade-Villanueva, MD⁷, Juan L. Mosqueda-Gómez, MD⁸, Benigno Rodriguez, MD⁹, Ian Sanne, FRCP^{3,10}, Michael M. Lederman, MD⁹, and the CADIRIS study team¹¹

¹Departamento de Infectología, Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán”. Vasco de Quiroga 15, Col. Sección XVI, Del. Tlalpan. México DF, México. CP 14000

²Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine. 611 Blockley Hall. 423 Guardian Drive, Philadelphia, PA 19104-602. USA

³Clinical HIV Research Unit, Department of Internal Medicine, Faculty of Health Sciences, University of Witwatersrand. Perth Ave, Westdene. Johannesburg, South Africa

⁴HIV-1 Immunopathogenesis Laboratory, The Wistar Institute. 3601 Spruce Street, Philadelphia, PA 19104. USA

⁵Servicio de Infectología, Hospital General de México, Dr. Balmis 148, Col. Doctores. México DF, México. CP 06726

⁶HIV Pathogenesis Unit, Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases/National Institutes of Health. 10 Center Drive, Building 10, 11C-103. Bethesda, MD 20892

⁷Unidad de VIH, Hospital Civil de Guadalajara. Calle Hospital 278 S.H. Col. Alcalde Barranquitas. Guadalajara, Jalisco, México. CP 44280

⁸Centro de Ambulatorio de Prevención y Atención en SIDA e Infecciones de Transmisión Sexual León. Calle 20 de enero # 927, Col. Obregón. León, Guanajuato, México CP 37000

Corresponding author and contact information: Pablo F. Belaunzarán-Zamudio, Departamento de Infectología, Instituto Nacional de Ciencias Médicas y Nutrición, Vasco de Quiroga 15, Tlalpan. México DF 14000. México, Telephone: 52(55)54 87 0900 ext. 5502, Fax: 52 55 13 8106, p_belaunzarán@yahoo.co.uk.

¹¹Members of the CADIRIS team are listed in the acknowledgements

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⁹Center for AIDS Research, Case Western Reserve University. 2061 Cornell Rd, Cleveland OH 44106. USA

¹⁰Center for International Development, Boston University. USA

Abstract

Background—Immune Reconstitution Inflammatory Syndrome (IRIS) is a common complication of antiretroviral therapy (ART) in HIV-infected patients. IRIS is associated with an increased risk of hospitalization and death. We ascertained whether CCR5 blockade using maraviroc reduces the risk of IRIS.

Methods—The CADIRIS study was a randomized, double-blind, placebo-controlled, clinical trial that accrued subjects from five clinical sites in Mexico and one in South Africa between November 2009 and January 2012, and followed them for one year. The primary outcome was occurrence of IRIS by 24 weeks. HIV-infected adults, naïve to ART, with CD4 cells <100/μL, and HIVRNA >1,000 copies/mL were eligible. We screened 362 subjects; 279 met inclusion criteria, 3 refused participation, and 276 were randomized. Participants received maraviroc 600 mg twice daily or placebo added to an ART regimen that included tenofovir, emtricitabine, and efavirenz for 48 weeks.

Findings—There were 276 patients randomized (140 received maraviroc and 136 placebo). There was no difference in the time to IRIS events between treatment arms (HR 1.08, 95% CI (0.66, 1.77), log-rank test $p=0.743$). In total, 64 (23%) patients had IRIS events, 33 (24%) in the maraviroc arm and 31 (23%) in the placebo arm ($p=0.88$).

Interpretation—Maraviroc had no significant effect on frequency, time or severity of IRIS events after ART initiation. Including a CCR5 inhibitor in an initial treatment regimen does not confer a meaningful protection from the occurrence of IRIS in persons with advanced HIV infection.

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Trial Registration—*ClinicalTrials.gov*. ID: NCT00988780 (<http://clinicaltrials.gov/ct2/show/NCT00988780>)

Introduction

Immune reconstitution inflammatory syndrome (IRIS) manifests as the clinical deterioration in HIV-infected patients initiating antiretroviral treatment (ART).¹ IRIS may present as a paradoxical worsening of opportunistic infections (OIs) on treatment or as the unmasking of an undiagnosed, untreated infection.^{1,2} Overall, 13% of patients starting ART worldwide experience IRIS during the first weeks of treatment.² The incidence and manifestations of IRIS vary widely depending on the type and prevalence of opportunistic infections (OIs) in the population, and can be significantly higher in people with severely depressed CD4 counts when starting ART.² IRIS has been associated with increased hospitalizations, longer hospitalizations, and death.^{3,4} The major risks for IRIS are low CD4 cells,^{5,6} high

plasma HIV RNA levels, OIs when starting ART,^{3,5,6} and a short time between ART start and treatment initiation for OIs.⁶

Most IRIS events occur during the first phase of immune restoration as T cells, especially effector T cells, are released from lymphoid tissues where they had been sequestered during HIV replication.⁷ Patients with IRIS have increased plasma levels of inflammatory cytokines,^{8,9} CD4 and CD8 cell activation,^{8–10} increased CD4 cell production of pro-inflammatory cytokines in response to pathogen-derived antigens.^{9–11} Patients with IRIS characteristically have inflammatory infiltrates of affected organs.^{12,13} IRIS therefore, might be related, at least in part, to heightened or inadequately regulated pathogen-directed cellular immune responses.^{1,14,15}

Since inflammatory chemokines may help mediate the influx of CC-chemokine receptor 5 (CCR5)-expressing immune cells to sites of infection and inflammation,¹⁶ we hypothesized that maraviroc, a CCR5 antagonist¹⁷ with proven efficacy for the treatment of R5-tropic HIV,¹⁸ could retain these inflammatory cells in circulation by blocking the interaction of CCR5 with its endogenous ligands, preventing the local inflammatory reaction characteristic of IRIS. Thus, the primary objective of this study was to test whether maraviroc would decrease the occurrence of IRIS. Our secondary objectives were to assess the effects of maraviroc on IRIS severity, AIDS-defining events (ADEs), non AIDS-defining events (non-ADEs), deaths, suppression of plasma HIV RNA levels during CD4 cell recovery, and safety and tolerability.

Methods

Study Design

In this randomized, double-blind, placebo-controlled clinical trial, subjects were randomized 1:1 to receive either maraviroc 600 mg twice daily (BID) or placebo, added to a standard ART regimen consisting of efavirenz 600 mg, tenofovir 300 mg and emtricitabine 200 mg daily (QD) for 48 weeks. Because the primary objective was to assess the immunoregulatory effect of maraviroc, HIV tropism tests were not performed. Substitution of ART backbone components was allowed to treat serious toxicities. If efavirenz required substitution, it was replaced by atazanavir 300 mg with ritonavir 100 mg QD and the dose of maraviroc adjusted to 150 mg BID.

Endpoints

The primary endpoint was the time to an IRIS event by week 24. IRIS events were defined by ACTG revised criteria^{5,9} (see *Study procedures and definitions* section). We also compared proportions of patients with suppression of plasma HIV RNA and AIDS-defining events (ADEs), the rate of CD4 and CD8 cell count changes to week 48, emergence of any adverse events (AEs) during treatment (TE AEs) and deaths.

Study Population

Patients were recruited from one site in South Africa and five in Mexico. The South African site is an HIV referral clinic based at a tertiary care, university-affiliated hospital in

Johannesburg. In Mexico, patients were accrued in three HIV tertiary care clinics in university-affiliated hospitals; one sexually transmitted diseases clinic, and one HIV clinic proximal to a hospital. All centers enrolled both outpatients and hospitalized patients.

Eligible subjects were HIV-infected, 18 years old, ART naive, had a CD4 cell count $<100/\mu\text{L}$ and plasma HIV RNA $>1,000$ copies/mL. Additional inclusion criteria are listed in eTable 1 (see supplemental material). Patients with opportunistic or HIV-related infections were included if they were otherwise ready to start ART. Pregnancy and breastfeeding were exclusionary, as was systemic cancer chemotherapy or use of investigational agents, or immunomodulators within 180 days, or systemic corticosteroids within two weeks prior to randomization. We excluded persons with decompensated liver disease or other serious medical illnesses, altered mental status or active substance abuse that could compromise adherence to study requirements.

The study was approved by the Institutional Ethics Review Committee at each site or Institutional Review Boards at participating institutions and was registered with ClinicalTrials.gov (NCT00988780). All patients provided written informed consent.

Randomisation and masking

To ensure balance, randomization was stratified by country using permuted block randomization (eFigure 1). Patients, care providers, and members of the research team were blinded to treatment allocation. Identical maraviroc and placebo tablets were produced by Pfizer Inc, New York, USA.

Study procedures and definitions

Clinical and laboratory evaluations were performed at baseline, and weeks 2, 4, 8, 12, 16, 24, 48 and 60. Study treatment was discontinued for pregnancy, toxicity requiring treatment termination or withdrawal of consent for any reason. Clinical and laboratory procedures to identify sub-clinical OIs in all participants included fundoscopy, mycobacterial blood cultures, serum assays for cryptococcal antigen, Hepatitis B surface antigen, Hepatitis B core and Hepatitis C virus antibodies, tuberculin skin tests, and chest radiographs. Follow-up visits included structured questionnaires to assess adherence to ART, use of concomitant medications, signs and symptoms of IRIS or other AIDS-related conditions, a targeted physical examination and clinical laboratory evaluation. ART adherence was recorded by participants assisted by clinicians using the AIDS Clinical Trials Group (ACTG) Adherence Follow up Questionnaire.¹⁷ Signs and symptoms of IRIS were sought by clinicians at each visit using a semi-structured questionnaire and entered on case report forms (CRFs).

IRIS events were pre-defined as symptoms consistent with an infectious or inflammatory condition, temporally related to the initiation of ART and associated with an increase in CD4 cells count, a decrease in HIV RNA level or both, not explained by a newly acquired infection, the expected clinical course of a previously diagnosed infection, or side effects of ART according to the ACTG IRIS criteria. The ACTGIRIS criteria have been used^{5,9} and validated¹⁸⁻¹⁹ previously. Clinicians employed the above criteria to make a provisional diagnosis of IRIS, documenting the criteria in an Electronic Data Management System (EDMS). To ensure that all possible cases were reported, the coordinating center in each

country actively monitored the CRFs and EDMS of all patients' visits. When adverse events or symptoms compatible with IRIS were found and IRIS was not reported in the EDMS, the site was queried to confirm or deny an IRIS event. The EDMS report contained a checklist of *ACTG IRIS Criteria*, a brief clinical narrative of the event and its severity, and pathologic, radiologic and laboratory evidence for the IRIS diagnosis.

An endpoint committee of four experts not involved in the study implementation or data collection reviewed all IRIS cases and determined the ultimate classification of all IRIS events by consensus. IRIS events were severe if they resulted in death, hospitalization, need for invasive diagnostic or therapeutic intervention (e.g. bronchoscopy, surgery, biopsy, etc.) or threatened vision. Events reported in the EDMS included in the Centers for Diseases Control and Prevention (CDCs) case definition for AIDS surveillance²⁰ that did not meet criteria for IRIS were excluded from the primary analysis.

A composite outcome of non-IRIS and non-AIDS-defining events (non-ADEs) included any cardiovascular or cerebrovascular event, non AIDS-defining malignancies, liver cirrhosis, or renal failure. Viral failure was defined as either (a) confirmed failure to achieve one log₁₀ reduction from baseline in plasma HIV RNA by week 8 or (b) a confirmed HIV RNA >400 copies/mL after week 24.²³ Safety and tolerability were evaluated by assessing the emergence of *any* clinical or laboratory toxicities during the study (TE AEs).²⁴ Serious adverse events were defined by US Food and Drug Administration guidelines.²⁴ Toxicities were graded as per the Division of AIDS Table for Grading Adult Adverse Experiences.²⁵

Statistical Analysis

With 138 subjects per arm, we calculated an 80% power to detect a 50% reduction in risk of IRIS events during the first 24 weeks of ART, using a two-tailed log-rank test stratified by country at a 0.05 significance level, assuming a 10% loss to follow up rate and 30% occurrence in the control group. This would have yielded 56 IRIS cases. All randomized subjects contributed to the primary time-to-event analysis from the date of ART initiation until week 24, the time of an IRIS event or death. Binary outcomes were compared using Fisher's exact test. Continuous outcomes (transformed if necessary) were compared using t-tests. Trajectories of CD4 and CD8 cells were compared using mixed effect models after using a square root transformation to improve normality (SAS, Proc Mixed).

Role of the funding source

Pfizer Inc. had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; in the decision to publish the study; in the preparation, review, or approval of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication

Results

Baseline characteristics and patient disposition

Three hundred sixty-two subjects were screened between November 2009 and January 2012. Two hundred seventy-six met inclusion criteria, consented to participate and were

randomized to receive maraviroc (n=140) or placebo (n=136) in addition to the ART regimen. Baseline OI's are shown in eTable 2. Patient disposition during the study is shown in Figure 1. As summarized in Table 1, demographic and clinical characteristics, CD4 and CD8 cell counts, and plasma HIV RNA levels at entry were similar between treatment arms. Only two patients received the reduced dose drug kit, one from each arm.

Effect of maraviroc on occurrence of IRIS

At week 24, 130 subjects remained in the maraviroc arm and 126 in the placebo arm. (eTables 3 and 4 show the frequency of IRIS events proposed by local investigators that were adjudicated by the central experts committee as IRIS and the frequency of type of IRIS events by pathogen, respectively). There was no difference in the time to IRIS events between treatment arms (HR 1.08, 95% CI (0.66, 1.77), log-rank test $p=0.74$, Figure 2). In total, 33 (24%) subjects in the maraviroc arm had an IRIS event and 31 (23%) in the placebo arm ($p=0.88$). There was also no difference when only severe IRIS events were considered (nine receiving placebo *vs.* seven receiving maraviroc, $p=0.6$). No differences were found in the proportions of unmasking or paradoxical TB-associated IRIS events between treatment arms (Table 2). Among the 16 patients with severe IRIS, five died of associated IRIS events (Maraviroc arm: Kaposi's sarcoma, n=1 and unmasking TB, n=1. Placebo arm: paradoxical disseminated TB, n=1 disseminated histoplasmosis, n=1 and cerebral toxoplasmosis, n=1).

Changes in T cell counts and plasma HIV RNA levels

There were 124 patients in each arm by week 48. A mixed model analysis comparing the trajectories of T cell counts over the 48-week observation period showed a greater increase of CD8 cells ($p=0.002$) (but not of CD4 cells, $p=0.19$) in patients receiving maraviroc, (See Table 3 and eFigure 2). The proportions of patients with viral failure and of patients with HIV RNA <50 copies/mL at all time-points did not differ between treatment arms (Table 3).

Safety and tolerability

The proportions of patients with any treatment emergent adverse events (TE AEs) were not different between groups (see eTable 5). Patients receiving maraviroc had a higher proportion of grade 3 or 4 TE AEs but this difference was not significant (maraviroc n=37, 26.4% *vs* placebo n= 24, 17.6%; $p=0.07184$). There were 25 subjects with serious TE AEs (18%) in the maraviroc arm and 21 (15.4%) in the placebo arm ($p=0.63$). ART discontinuation or substitution for toxicity occurred in five subjects (three in the maraviroc arm and two in the placebo arm). Reasons for treatment discontinuation on the maraviroc arm were one Grade 3 increase in liver function tests (attributed to alcohol intake), one severe toxic hepatitis (attributed to the study drug), and dizziness (attributed to the study drug). One patient in each arm with toxicity attributed to efavirenz had the study drug discontinued due to temporary unavailability of the reduced dose formulation.

Eleven patients died during the study, seven in the maraviroc arm and four in the placebo arm ($p=0.5$). One of these subjects died at week 49 (maraviroc was discontinued at week 48). Deaths in the maraviroc arm included unmasking TB-IRIS (n=1), pneumonia of unknown aetiology (n=2), septic shock of unknown aetiology (n=1), cryptococcal meningitis in a patient with tuberculosis (n=1), multiple organ failure due to Kaposi's sarcoma-

associated IRIS in a patient with concomitant Castleman disease (n=1), and complications of intestinal ischemia (n=1). For subjects on placebo, deaths were attributed to hypoglycaemia (n=1), paradoxical cerebral toxoplasmosis-associated IRIS (n=1), unmasking histoplasmosis-associated IRIS (n=1) and paradoxical TB IRIS (n=1).

Discussion

In this multicentre, randomized, double-blind, placebo-controlled trial in patients initiating ART, we observed no difference in the emergence, severity or timing of IRIS events between patients receiving maraviroc and those receiving placebo. Virologic suppression was comparable in the two arms and while greater CD8 cell rises were seen in the maraviroc arm, this was not accompanied by a sustained and significant CD4 cell difference. The frequency of AEs was not different between treatment arms.

This trial was designed to test the hypothesis that the CCR5 blockade by maraviroc would decrease the occurrence of IRIS by modulating immune cell trafficking and by blocking chemokine-induced cellular activation in tissues. This is, to our knowledge, the first clinical trial designed to prevent IRIS in HIV-infection. In the MERIT trial, maraviroc was compared to efavirenz as part of an initial ART regimen in treatment-naïve patients. Half as many patients receiving maraviroc experienced Category C ADEs during the first year of treatment and this was largely due to differences in the emergence of tuberculosis during the study.²⁶ This suggested a possible protective effect of CCR5 blockade on the risk for tuberculosis-associated IRIS. Maraviroc has since been applied in different settings as an immunomodulator with apparent beneficial effects in graft versus host disease but no clinical impact in rheumatoid arthritis.^{27,28} Preliminary reports also suggest that maraviroc may, by affecting inflammatory cell trafficking into the central nervous system, have helped to prevent and treat progressive multifocal encephalopathy (PML)-related IRIS in one patient with AIDS and in another with immune reconstitution after receiving natalizumab for multiple sclerosis.^{29,30} During this trial we observed no PML-associated IRIS so we cannot address the utility of maraviroc to prevent this condition. In the current study we evaluated IRIS events irrespective of aetiology and found no differences in the occurrence of these endpoints. Since it is possible that the pathogenic determinants of IRIS are heterogeneous,¹ our study was limited by lack of power to detect differences in specific pathogen-associated IRIS events. Thus an effect of CCR5 blockade in any particular IRIS entity, such as for example, IRIS events in the central nervous system, might have been missed. Future intervention studies should attempt to target specific IRIS events such as those seen in high frequency or those associated with substantial morbidity such as TB associated IRIS or IRIS involving the central nervous system. Our results suggest however, that CCR5 is not a central pathogenic aspect of IRIS. Either pre-existing tissue resident cells or cells trafficking in response to other signals may be the primary inflammatory mediators. Alternatively, CCR5 blockade may lead to the compensatory increases of chemokine ligands that signal via other promiscuous receptors.³¹

There was no difference in CD4 cell increases over the 48-week observation period between treatment arms ($p=0.19$). We observed an early, modest increase in circulating CD4 cells in persons treated with maraviroc, but in contrast to previous studies^{26,32,33} this increase was

not sustained longer than 12 weeks. This may be related to the more advanced disease of patients in this trial.³⁴ Ongoing sub-studies are characterizing the maturation phenotype of circulating T cells that were increased during the study to understand these findings better. Absolute gains in circulating CD8 cells over the 48-week interval were significantly greater in the maraviroc arm than in the placebo arm ($p=0.002$). As CCR5 expression typically increases with T cell maturation and is greater on CD8 than on CD4 cells,³¹ this finding is not surprising and is consistent with previous reports.^{26,34,35} It also indicates that CCR5 blockade was effectively attained with maraviroc in this trial. For instance, in HIV-infected patients with viral suppression on ART but who failed to increase circulating CD4 cells, Hunt *et al.* presented evidence suggesting that the increase of circulating CD8 cells in patients receiving maraviroc depends on inhibition of the distribution of CD8 cells from peripheral blood to gut mucosa.³¹

The frequency of severe AEs and AEs leading to study drug discontinuation in patients receiving maraviroc was similar to that in the placebo arm, and was similar to that reported in other studies in patients with advanced disease starting ART with either efavirenz or protease inhibitor-based regimens.^{36–38} The death rate was also similar to those in other clinical trials^{36,37} and observational cohort studies^{38,39} among patients starting ART with CD4 cells $<200/\mu\text{L}$ in comparable settings.

A limitation of the study is the lack of a gold standard to diagnose IRIS, and the possible differences in diagnostic resources across participating sites. While these factors may decrease the reliability of IRIS diagnosis⁴⁰ and increase misclassification bias, several procedures were implemented to homogenize diagnostic criteria and event classification. The use of pre-established IRIS diagnostic criteria and systematic valuation of patients to identify possible cases, and the validation of suspected cases by experts have been used in previous IRIS studies to reduce ascertainment and classification errors.^{5,9, 42,41} We implemented each of these measures to enhance accurate case ascertainment and classification. As the diagnosis of IRIS still required application of clinical consensus criteria and despite engaging an independent blinded review committee to confirm these diagnoses, there is a possibility that some events were incorrectly categorized. The randomization, double-blinding and the observed distribution of IRIS events across arms make the probability of misclassification bias towards a particular treatment unlikely. Our study has the strength of being generalizable to most settings where HIV-infected patients receive routine clinical care in a large array of developing countries. Participants were accrued in clinical centres in two different regions of the world with different HIV epidemics and OIs distributions. Our results reflect the diagnostic approach and management of OIs and IRIS in secondary and tertiary care units in these countries. Nonetheless, our study population may not fully represent the spectrum of IRIS associated pathogens in other regions of the world. In addition, exclusion of patients for safety reasons and altered mental status that impaired their ability to consent may have limited the applicability of our results for particular types of IRIS.

In summary, our study does not support the hypothesis that CCR5 blockade has therapeutic value in the prevention of IRIS. Thus, based on our results, we conclude that including a CCR5 inhibitor in an initial treatment regimen does not confer a meaningful protection from

the occurrence of IRIS. Inpatients with advanced AIDS, the addition of maraviroc as immunomodulator appears to have no effect on CD4 cell recovery or the occurrence of OIs during the first year of therapy. While this agent has proven antiviral activity, safety and tolerability as part of an ART regimen, its use as an immunomodulator to prevent IRIS is unwarranted.

Discussion panel

Systematic review

We searched PubMed using the terms “Immune Reconstitution Inflammatory Syndrome”, “IRIS”, “Immune Reconstitution Disease” and “prevention”, restricted to 2009–2014. We found the report of a secondary analysis of two trials to assess the timing for the initiation of antiretroviral therapy (ART) in relation to the start of antituberculosis therapy^{6,43} and three expert’s reviews about pathogenesis, prevention and treatment^{44–46} of immune reconstitution inflammatory syndrome (IRIS). We did not identify trials to prevent the incidence of IRIS. This is the first report of a clinical trial in which a drug has been used to attempt to prevent IRIS in patients at risk. In this study, we observed that the CCR5-blocker maraviroc in addition to a standard combination ART for patients with low CD4 cells have no effect on the frequency, severity and time to presentation of IRIS after ART initiation.

Interpretation

This trial shows that including a CCR5 inhibitor in an initial treatment regimen does not confer a meaningful protection from the occurrence of IRIS. In patients with advanced AIDS, the addition of maraviroc as immunomodulator appears to have no effect on CD4 cell recovery or the occurrence of OIs during the first year of therapy. While this agent has proven antiviral activity, safety and tolerability as part of an ART regimen, its use as an immunomodulator to prevent IRIS is unwarranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Author Contributions

Susan Ellenberg and Anne Tierney had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: PBZ, SE, MML, BR, I Sanne, I Sereti & JSM

Acquisition of data: JAV, JMG, ALM, APM, CRB, MR, BR, I Sanne, I Sereti & JSM

Analysis and interpretation of data: LA, PBZ, SE, MML, LM, APM, MR, I Sanne, I Sereti, JSM & AT

Drafting of the manuscript: LA, PBZ, SE, MML, LM, I Sanne, I Sereti & JSM

Critical revision of the manuscript for important intellectual content: JAV, LA, PBZ, SE, ML, ALM, LM, JMG, APM, BR, MR, CRB, I Sanne, I Sereti, JSM & AT

Statistical analysis: Susan Ellenberg, PhD and Ann Tierney, M.S. (Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine. Philadelphia PA, USA)

Obtained funding: SE, MML, I Sanne & JSM

Administrative, technical, or material support: I Sanne, JSM

Study supervision: I Sanne & JSM

Declaration of interests

Drs. Andrade-Villanueva, Piñeirúa-Menéndez, Rassool, Rivera Benítez and Sereti have nothing to declare. Dr. Azzoni reports other from Pfizer during the conduct of the study, and other from Gilead outside the submitted work. Dr. Belaunzarán reports support as scholarships from Instituto Científico Pfizer Mexico in 2006 and from Johnson & Johnson during 2007–2008, outside the submitted work. Dr. Ellenberg reports grants from Pfizer during the conduct of the study; has consulted for a number of companies over the past three years, some of which manufacture antiviral drugs. These include Merck, GSK and BMS; served on a DMC for Wyeth Pharmaceuticals, which was taken over by Pfizer prior to its completion, so received some consulting fees from Pfizer for that service in 2011. Dr. Lederman has served as consultant and has received grant support for this work from Pfizer. Dr. López-Martínez reports other from Pfizer during the conduct of the study. Dr. Montaner reports grants from Pfizer and personal fees from University of Pennsylvania during the conduct of the study. Ms. Tierney reports grants from Pfizer during the conduct of the study. Dr. Sanne reports grants from Pfizer Laboratories during the conduct of the study and personal fees from Pfizer Laboratories, outside the submitted work. Dr. Sierra-Madero reports grants from Pfizer during the conduct of the study; also, personal fees from Janssen Pharmaceutical; grants and personal fees from MSD; grants from BMS; grants, personal fees and non-financial support from Gilead; non-financial support from Roche; personal fees and non-financial support from Viiv Healthcare, all outside the submitted work.

The CADIRIS Trial Team

Investigators: J Andrade-Villanueva, L Azzoni, PF Belaunzarán-Zamudio, S Ellenberg, MM Lederman, LJ Montaner, M Magaña-Aquino, JL Mosqueda-Gómez, A Piñeirúa-Menéndez, C Rivera-Benítez, B Rodríguez, I Sanne, I Sereti, JG Sierra-Madero, Ann Tierney

Site Personnel: Audelia Alanís (Center Pharmacist, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán), Rosa Brena Arellano & Maru Zghaib, MD (Study coordinators, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán), Juana del Carmen Báez Cruz (Study coordinator, Hospital Central Dr. Ignacio Morones Prieto, San

Luis Potosí, México), Vuyokazi S. Jezile (Head of Data Management, Clinical HIV Research Unit, Helen Joseph Hospital, Johannesburg, South Africa), Iris A Jiménez Vieyra (Center Pharmacist, Hospital Civil de Guadalajara), Mónica López-Segura (Center Coordinator and Pharmacist, Hospital General de León, Guanajuato, México), Silvia Martínez (Center Coordinator, Hospital General de México, México City), Jorge Martínez-Lozano and Miguel Herrera (Center Coordinator, Hospital Central Dr. Ignacio Morones Prieto, San Luis Potosí, México), Karina E. Montes-Salcedo (Center Coordinator and Pharmacist, Hospital Civil de Guadalajara, Jalisco, México), Tracey Webster (Center Coordinator, Clinical Research Africacc., South Africa), Doreen Schulze (Head of Data Management, Clinical HIV Research Unit, Helen Joseph Hospital, Johannesburg, South Africa)

End-point committee: Benigno Rodriguez, Irini Sereti, Graeme Meintjes and anonymous member

Data and Safety Monitoring Board: Juan J Calva-Mercado, James Hakim & other anonymous member

Coordinating centres: Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (Mexico) & Faculty of Health Sciences, University of the Witwatersrand (South Africa)

Trial Steering Committee: S. Ellenberg, M. Lederman, L. Montaner, I. Sanne, J Sierra-Madero,

Figure 1.

Patients' progress through the study.

^aPatients who required change in ART regimen due to toxicity or viral failure were taken off study drugs but still followed, except for these 2 patients who did not return for further visits. ^b due to social conditions that compromised adherence to the protocol^c The patient did not meet eligibility criteria and was enrolled by mistake

Figure 2.

Probability of remaining free of IRIS by treatment arm during the first 24 weeks of ART

^aTwo-tailed log-rank test stratified by country. Hazard Ratio = 1.08, 95% CI (0.66, 1.77)

Table 1

Baseline characteristics of randomized patients.

Characteristic	Maraviroc (N=140)	Placebo (N=136)
Female, n (%)	51 (36.4)	47 (34.6)
Age, mean (SD)	36.7 (8.1)	37.5 (9.3)
Subjects with history of AIDS-Defining Conditions ⁽²⁴⁾, n (%)	80 (57.1)	83 (61.0)
Mexico	50/62 (80.6)	48/62 (77.4)
South Africa	30/78 (38.5)	35/74 (47.3)
<i>Mycobacterium tuberculosis</i> in any site, n (%)	29 (20.7)	35 (25.7)
<i>Mycobacterium tuberculosis</i> , disseminated or extra-pulmonary, n (%)	14 (10.0)	20 (14.7)
CD4 cells/μL, median (IQR)	36.0 (15.5–57.0)	32.0 (19.0–60.5)
Mexico	32.0 (13.0–53.0)	27.0 (16.0–52.0)
South Africa	38.0 (20.0–61.0)	38.0 (22.0–68.0)
%CD4 cells, median (IQR)	4.4 (2.3–6.6)	4.0 (2.5–7.0)
Mexico	3.6 (1.8–6.0)	4.0 (1.9–7.0)
South Africa	4.9 (2.7–7.1)	4.2 (2.7–7.1)
CD8 cells/μL, median (IQR)	468.0 (355.0–738.0)	492.0 (335.0–746.0)
Mexico	507.5 (396.0–804.0)	458.0 (330.0–753.0)
South Africa	447.5 (305.0–650.0)	516.0 (341.0–722.0)
%CD8 cells, median (IQR)	61.9 (54.1–70.4)	63.1 (53.4–71.3)
Mexico	63.9 (55.1–71.2)	63.4 (55.6–73.3)
South Africa	60.5 (53.5–69.9)	62.9 (52.1–70.0)
Plasma HIV-1 RNA ($\log^{10}$ copies/mL), mean (SD)	5.3 (0.6)	5.4 (0.6)
Hemoglobin (g/dL), mean (SD)	12.2 (1.8)	12.1 (1.8)

Table 2

Comparison of event rates of primary and secondary outcome

Endpoints	Maraviroc n (%) ^a	Placebo n (%) ^a	P-value ^b
Subjects with IRIS events ^c	33 (24.4) ^c	31 (23.3) ^c	0.74
Subjects with severe IRIS events ^d	7 (5.1)	9 (6.8)	0.59
Subjects with non-cutaneous IRIS events ^d	16 (11.7)	16 (12.0)	0.98
Subjects with tuberculosis related IRIS ^e	10 (7.3)	13 (9.8)	0.50
Unmasking	2 (1.5)	4 (3.0)	0.39
Paradoxical	8 (5.8)	9 (6.8)	0.80
Subjects with non-AIDS related clinical events by 48 weeks ^f	12 (9.1)	7 (5.4)	0.26
Deaths by 48 weeks ^g	6 (4.6)	4 (3.1)	0.56

^a Column percentages are based on Kaplan-Meier estimates at 24 weeks for IRIS events and at 48 weeks for other clinical events.

^b Log Rank Test, adjusted for country, for comparison of event rates.

^c There were 71 IRIS events in 64 patients (36 events in the maraviroc arm and 35 events in the placebo arm).

^d Subjects with severe, non-cutaneous and tuberculosis-related IRIS events had single IRIS events.

^e Only tuberculosis-related IRIS events were reported separately for comparisons and by categories because the low frequency of *other* IRIS events does not allow for statistical comparisons. Patients with tuberculosis-related IRIS had single IRIS events

^f Cardiovascular, cerebrovascular, non- AIDS related neoplasia, cirrhosis, renal failure and death.

^g One additional patient on maraviroc died after 48 weeks.

Table 3

Comparison of immunological and virological outcomes by treatment arm

Endpoints	Maraviroc	Placebo	<i>P</i> -value ^a
CD4 cells/mL, median (IQR)			
Baseline (n=140, 136)	36 (16–57)	32 (19–61)	0.88
Week 12 (n=128, 127)	148 (105–211)	137 (82–180)	0.04
Week 24 (n=127, 124)	165 (113–225)	142 (113–198)	0.09
Week 48 (n=122, 120)	209 (151–274)	191 (147–257)	0.24
CD8 cells/mL, median (IQR)			
Baseline (n=140, 136)	468 (355–738)	492 (335–746)	0.99
Week 12 (n=128, 127)	936 (601–1365)	729 (520–965)	<.001
Week 24 (n=127, 124)	831 (562–1175)	640 (486–952)	0.002
Week 48 (n=122, 119)	841 (612–1213)	695 (506–919)	<.001
Subjects with CD4 cells >100 cells/mL, n (%)			
Week 24 (n=127, 124)	106 (83.5)	100 (80.6)	0.62
Week 48 (n=122, 120)	109 (89.3)	109 (90.8)	0.83
Subjects with CD4 cells >200 cells/mL, n (%)			
Week 24 (n=127, 124)	44 (34.6)	30 (24.2)	0.07
Week 48 (n=122, 120)	69 (56.6)	55 (45.8)	0.12
Subjects with virological failure, n (%) ^b			
Week 8 (n=131, 129)	3 (2.3)	3 (2.3)	0.50 ^c
Week 24 (n=128, 126)	5 (3.8)	3 (2.3)	
Week 48 (n=100, 100)	5 (3.8)	3 (2.3)	
Subjects with HIV VL 50 copies/mL, n (%)			
Week 8 (n=132, 128)	33 (25.0)	35 (27.3)	0.67
Week 24 (n=127, 123)	96 (75.6)	105 (85.4)	0.06
Week 48 (n=120, 121)	101 (84.2)	102 (84.3)	>.999

The sample sizes shown on each line represent the number on each arm with a measurement at that time point.

^aFishers Exact test was performed for dichotomous outcomes. The Wilcoxon Rank Sum Test was used for continuous outcomes.

^bLog Rank Test, adjusted for country, for comparison of event rates.

^cData shown are Kaplan-Meier estimates of proportions with viral failure by specific time points, with numbers remaining at risk at these times shown in parentheses