

Maraviroc, a future treatment of sarcoidosis? An unexpected drug effect

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Maraviroc is a selective inhibitor of C-C chemokine receptor type 5 (CCR5) that has been approved only for the treatment of HIV infection, in combination with other antiretroviral drugs (ARV). Unlike other ARVs, maraviroc does not target HIV but the host's CCR5 cell receptor, which is key to HIV entry into CD4+ T-cells [1]. CCR5 is involved in the Th1 signaling cascade, not only in HIV infection but also in various disorders such as hepatocellular carcinoma, liver steatosis, arterial pulmonary hypertension, and sarcoidosis [2,3]. Maraviroc has immunomodulatory effects in HIV-infected patients and treatment intensification with maraviroc has been used in patients with controlled HIV viremia to enhance CD4+ T-cell recovery when immune restoration was suboptimal or in the treatment of primary HIV infection [1,4]. These immunomodulatory properties of maraviroc have led to evaluate its potential benefit in immunologic disorders [3].

We report here on an HIV-1 infected patient who developed pulmonary sarcoidosis and was given maraviroc because of CD4 lymphocytopenia. Treatment intensification with maraviroc led to both immune restoration and the alleviation of respiratory symptoms.

A 44-year-old man, who had been diagnosed with HIV-1 infection in 1995, had undetectable plasma HIV viral load while on combined antiretroviral treatment (CART) for six years when he was diagnosed with a stage II pulmonary sarcoidosis in 2011. The diagnosis of sarcoidosis was based on the combination of dyspnea, cough, diffuse micronodular infiltrates predominantly in the upper right lobe and bilateral mediastinal adenomegaly on CT-scan (Online-supplemental file), lymphocytic alveolitis (22% of total cell count) at the bronchoalveolar lavage (BAL) fluid, non-caseous giant-cell granulomas on lymph node biopsy, and negative mycobacterial cultures on BAL and lymph node samples. At that time, the patient's CD4+ T-cell count plummeted progressively from 329/mm³ (27%) in August 2008 to 22/mm³ (5%) in May 2012, while plasma HIV viral load remained undetectable throughout this period. Immune deterioration translated clinically in the development of profuse warts on the four limbs. Oral steroid treatment was initiated in August 2011 to treat sarcoidosis, well after the deterioration of the CD4+ T-cell count began, but failed to improve the respiratory symptoms and chest CT-scan images despite an increase of lung function parameters. In June 2014, while patient's CART included didanosine, etravirine, and raltegravir, maraviroc (300 mg b.i.d.) was substituted for didanosine in order to restore immunity. Consequences of this treatment change were twofold. First, as expected, CD4+ T-cell counts gradually rose from 42/mm³ (8.4%) in June 2014 to 259/mm³ (24%) in December 2018 while the warts progressively vanished. Second, the previously steroid-dependent sarcoidosis rapidly improved, with the disappearance of dyspnea, cough, the clearing of lung lesions, and the normalization of lung function parameters (Online-supplemental file). Corticosteroids were tapered over three months and discontinued in September 2014. No relapse was observed over the subsequent 66-month follow-up period.

Although well tolerated, maraviroc has moderate antiretroviral activity, and consequently is not a first-line treatment for HIV infection. Its effect on immune restoration in HIV-infected patients has been evaluated in several studies with conflicting results [1,4]. Besides, a non-HIV patient with idiopathic CD4 lymphocytopenia and progressive multifocal leukoencephalopathy was successfully treated with maraviroc [5]. CD4+ T-cells are key to the development of granulomas in sarcoidosis, as illustrated by the fact that in HIV-infected patients, that granulomatosis usually develops once immune restoration has been achieved [6]. It has been shown that both CCR5 and its ligands (CCL2, CCL3, CCL5) are overexpressed in sarcoidosis granulomas [7]. Furthermore, CCR5 mRNA is overexpressed in the BAL fluid of patients with pulmonary sarcoidosis [2]. It has also been suggested that CCR5 not only plays a role in the development of sarcoidosis granulomas, but also in the subsequent evolution towards pulmonary fibrosis [8]. The inhibition of CCR5 pathway induced by maraviroc, could decrease the chemotaxis and the migration of leukocytes involved in the formation of the granuloma and subsequently the migration of fibroblasts [9]. Altogether these findings might explain that the use of maraviroc alleviated sarcoidosis symptoms in our patient. If the dramatic improvement observed in our patient's respiratory symptoms were associated with the introduction of maraviroc, one could hypothesize that this effect resulted from the immune restoration and the immunomodulatory effects of maraviroc within granulomas. To the best of our knowledge, maraviroc has not yet been tested in the treatment of sarcoidosis, except in a proof-of-concept trial that was intended to evaluate the impact of maraviroc on CD4+ T-cell counts in BAL fluid in sarcoidosis patients but failed to enroll (ClinicalTrials.gov Identifier: NCT02134717). Our findings suggest that maraviroc should be further evaluated in the treatment of sarcoidosis. This could obviously be done in HIV-

infected patients but also in non HIV infected patients, given that maraviroc should be looked at as a selective CCR5 inhibitor rather than as an anti-HIV drug.

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