An Unexpected Effect of Maraviroc Could Make It a Future Treatment for Sarcoidosis

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J Investig Allergol Clin Immunol 2021; Vol. 31(1): 83-84
doi: 10.18176/jiaci.0537

Key words: Maraviroc. HIV infection. Sarcoidosis. CD4+ lymphocytopenia. T_H1 inflammation.

Palabras clave: Maraviroc. Infección por VIH. Sarcoidosis. Linfocitopenia CD4+. Inflamación Th1.

Maraviroc is a selective inhibitor of C-C chemokine receptor type 5 (CCR5). It is approved only for the treatment of HIV infection in combination with other antiretroviral drugs (ARVs). Unlike other ARVs, maraviroc does not target HIV but rather the host's CCR5 cell receptor, which is key to HIV entry into $CD4^+$ T cells [1]. CCR5 is involved in the T_H1 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 intensification of ARV therapy with maraviroc has been used in patients with controlled HIV viremia to enhance $CD4^+$ T-cell recovery when immune restoration is suboptimal or in the treatment of primary HIV infection [1,4]. These immunomodulatory properties of maraviroc have led to the evaluation of its potential benefit in immunologic disorders [3].

We report the case of an HIV-1–infected patient who developed pulmonary sarcoidosis and was given maraviroc because of CD4 lymphocytopenia. Intensification of ARV therapy with maraviroc led to both immune restoration and the relief of respiratory symptoms.

A 44-year-old man, who had been diagnosed with HIV-1 infection in 1995, had had an undetectable plasma HIV viral load for 6 years while on combined ARV treatment, when he was diagnosed with 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 enlarged mediastinal lymph nodes on a computed tomography (CT) scan (Online supplemental file), lymphocytic alveolitis (22% of the total cell count) in bronchoalveolar lavage (BAL) fluid, noncaseating giant-cell granulomas on lymph node biopsy, and negative mycobacterial cultures in BAL and lymph node samples. At that time, the patient's $CD4^+$

T-cell count decreased progressively from 329/mm^3 (27%) in August 2008 to 22/mm^3 (5%) in May 2012, while plasma HIV viral load remained undetectable throughout this period. Immune deterioration manifested clinically as profuse warts on all 4 limbs. Oral corticosteroids were initiated in August 2011 to treat sarcoidosis long after deterioration of the CD4$^+$ T-cell count began, although they failed to improve the respiratory symptoms and chest CT images despite an increase in lung function parameters. In June 2014, when the patient's combined ARVs included didanosine, etravirine, and raltegravir, didanosine was replaced by maraviroc (300 mg bid) in order to restore immunity. The consequences of this treatment change were 2-fold. First, as expected, CD4$^+$ T-cell counts rose gradually from 42/mm^3 (8.4%) in June 2014 to 259/mm^3 (24%) in December 2018, while the warts progressively vanished. Second, the previously corticosteroid-dependent sarcoidosis improved rapidly, with resolution of dyspnea, cough, and lung lesions and the normalization of lung function parameters (Online-supplemental file). Corticosteroids were tapered over 3 months and discontinued in September 2014. No recurrences were 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]. On the other hand, a non–HIV-infected 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, granulomatosis usually develops once immune restoration has been achieved [6]. Palchevskiy et al [7] showed 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 plays a role not only in the development of sarcoidosis granulomas, but also in subsequent progress towards pulmonary fibrosis [8]. The inhibition of the CCR5 pathway induced by maraviroc could decrease chemotaxis and the migration of leukocytes involved in granuloma formation and, subsequently, the migration of fibroblasts [9]. Altogether, these findings might explain the resolution of sarcoidosis symptoms with maraviroc in the present case. If the dramatic improvement observed in the patient's respiratory symptoms was associated with the introduction of maraviroc, we might 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 sufficient volunteers (ClinicalTrials.gov Identifier: NCT02134717). Our findings suggest that maraviroc should be further evaluated in the treatment of sarcoidosis. While such an evaluation could obviously be made in HIV-infected patients, it should also be made in non–HIV-infected patients, given that maraviroc should be looked at as a selective CCR5 inhibitor rather than as an anti-HIV drug.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Manuscript received April 8, 2020; accepted for publication June 16, 2020.

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