Immune Reconstitution Inflammatory Syndrome (IRIS) Manifesting as Anogenital HSV-2 Infection in a HIV-1-Infected Patient After Initiation of Raltegravir

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Citation


Abstract

Objective: To report a case of immune reconstitution inflammatory syndrome (IRIS), manifesting as anogenital HSV-2 infection after initiation of raltegravir-based antiretroviral (ARV) therapy.

Case Summary: We report a case of a 30-year-old HIV-1-infected woman, who presented to an outpatient clinic to reinitiate HAART. Her CD4+ T cell count and HIV-1 RNA level were <20 cells/mm3 (3%) and >100,000 copies/ml, respectively. Due to patient's previous inability to tolerate multiple HAART combinations, she was initiated on raltegravir and emtricitabine/tenofovir. The patient presented after one month of therapy with anogenital lesions that were subsequently diagnosed as HSV-2 infection based on culture results. Her CD4+ T-cell count at that time increased to 229 cells/mm³ (35%) and HIV-1 RNA level declined to 2,860 copies/ml.

Discussion: Immune reconstitution inflammatory syndrome (IRIS) is a complication of highly active antiretroviral therapy (HAART) initiation, especially in patients with extremely low CD4+ T-cell counts and high HIV-1 RNA levels. It is suspected that this patient experienced IRIS, manifested by anogenital HSV-2 infection. This case represents the first published descriptive report of IRIS associated with raltegravir-based HAART.

Conclusions: The strong temporal relationship that was seen in this case suggests the possibility of an association between the initiation of raltegravir and IRIS. Health care providers treating HIV-infected patients should consider this potential adverse reaction after initiation of raltegravir.

INTRODUCTION

With the initiation of highly active antiretroviral therapy (HAART) in both treatment-experienced and treatment-naïve HIV-1 infected patients, approximately 10-25% of patients will experience immune reconstitution inflammatory syndrome (IRIS) in the first 6 months of therapy. IRIS is thought to result from restored immunity to specific infectious or non-infectious antigens, combined with specific host genetic susceptibility. A definite case definition and pathogenesis of IRIS remain unclear. In the face of improving CD4+ T-cell counts and decreasing HIV-1 RNA levels, patients experience paradoxical clinical deterioration characterized by an unusual presentation or worsening of an existing condition, or ‘unmasking’ of a new condition. The most commonly reported events include genital herpes, genital warts, followed by infections secondary to Mycobacterium avium complex, Mycobacterium tuberculosis, Cryptococcus neoformans, cytomegalovirus, Pneumocystis jiroveci, herpes zoster, hepatitis B and C and Kaposi's sarcoma. Risk factors for development of IRIS include CD4+ T-cell counts below 100 cells/µL at the time of HAART initiation, rapidly decreasing viral loads (mean time of 29 days to onset of IRIS), and the use of potent treatment regimens that include ritonavir-boosted protease inhibitors (PIs), and/or non-nucleotide reverse transcriptase inhibitors (NNRTIs). The first drug in a new class of HIV-1 integrase inhibitors, raltegravir selectively inhibits integrase activity in order to block integration of viral cDNA into the host genome; raltegravir has demonstrated potent efficacy and excellent tolerability in clinical trials. Raltegravir product labeling includes a warning/precaution regarding immune reconstitution.
events in phase II/III studies with Raltegravir. The manifestations of these events are not described. To our knowledge, this case report represents the first documented descriptive IRIS event with the initiation of raltegravir-based therapy.

CASE REPORT
A 30-year-old African American female presented to our outpatient clinic after a hospitalization secondary to Pneumocystis jirovecci pneumonia. She was diagnosed with HIV-1 during pregnancy 7 years ago. Since that time, her HAART regimen was changed multiple times due to poor tolerance and low levels of adherence. At the time of presentation, she was not taking any antiretrovirals, and her CD4+ T-cell count and HIV-1 RNA levels were <20 cells/mm³ (3%) and >100,000 copies/mL, respectively. An HIV-1 genotype obtained at that time did not indicate any resistance mutations. Results from previous resistance testing were unknown. After counseling, the patient was eager to restart HAART, but was intolerant to a regimen that would include a boosted PI or an NNRTI. She was initiated on raltegravir 400mg twice daily and emtricitabine/tenofovir 200/300mg fixed dose combination (Truvada) 1 tablet daily.

One month after regimen initiation, the patient presented for follow-up, complaining of a painless ‘bump’ in her vaginal area for approximately 2 weeks. Physical exam revealed a firm, circular, nontender mucocutaneous ulcer on the prepuce, as well as smaller, nontender ulcers in the perianal region. The patient reported exceptional compliance and tolerance of her current HAART regimen. Laboratory results revealed an increase in the CD4+ T-cell count to 229 cells/mm³ (35%), and a decline in the HIV-1 RNA level to 2,860 copies/ml. RPR (rapid plasma reagin test) was non-reactive, but an HSV-2 culture was positive. Raltegravir and emtricitabine/tenofovir were continued, valacyclovir therapy was initiated and the lesions resolved.

DISCUSSION
Although widely described in the literature, the pathogenesis of IRIS remains unclear, current theories indicating the need for an underlying antigenic trigger, combined with a significant degree of immune restoration and host genetic susceptibility. Our patient was at a risk for IRIS, given her low CD4+ T-cell count and high HIV-1 RNA level. Her remarkable response to HAART in the first month of therapy likely resulted in IRIS, manifesting as anogenital HSV-2 infection. Culture-positive genital herpes infections are widely linked in the literature to patients having absolute CD4+ T-cell counts below 100 cells/mm³ and high plasma HIV-1 RNA levels, and IRIS events.

This case is unique in that the potent regimen did not include a boosted PI and/or NNRTI, as previously described; rather, her therapy included raltegravir, a HIV-1 integrase inhibitor. In phase II and III studies with raltegravir, IRIS was reported as a serious adverse event in 3 patients; 2 patients in the raltegravir treatment group in the double-blind cohort, and 1 patient in the open label post virologic failure (OLPVF) phase who was originally randomized to placebo. IRIS was thought to be drug-related in only the one patient in the OLPVF phase. One patient in the double-blind phase interrupted treatment; 2 patients recovered from IRIS; 1 patient had ongoing IRIS at the time of database freeze for FDA submission.

The relationship between raltegravir-based HAART initiation and patient's IRIS was supported by the application of a Naranjo scale, which is a method that assesses the causality of adverse drug reactions in a variety of clinical situations. Using this method, points are assigned to each category in a questionnaire and the final score (ranging -4 to +13) indicates the probability that a certain treatment caused a specific adverse reaction in a patient. A 'possible' causal relationship (score = 4) between initiation of raltegravir and our patient's IRIS was deduced when the events of this case were applied to the Naranjo criteria.

SUMMARY
As more clinicians incorporate raltegravir into their clinical practice, they should be vigilant in regards to possible IRIS events after the initiation of raltegravir-based therapy in their patients. Further research should be conducted on the incidence and types of IRIS events after initiation of raltegravir in order to determine if there are any significant differences in such events as compared to the incidence and types of IRIS after initiating HAART regimens containing NNRTIs and boosted PIs.

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References
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