Pediatrics & Therapeutics
ISSN: 2161-0665

Dreyfus, Pediat Therapeut 2013, 3:4
DOI: 10.4172/2161-0665.1000172

Review Article Open Access

Evidence that Raltegravir (Isentress, Merck), a Retroviral Integrase Inhibitor is Effective against Recurrent Human Herpes Simplex Virus Infection Associated with NK-cell Deficiency

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Recurrent or severe infection with Herpes Viruses may reflect an acquired underlying immune deficiency such as AIDS/HIV-1 infection but also is typical of some types of hereditary immune deficiency presenting in childhood. In utero exposures to reactivation or primary maternal infection with herpes simplex type 1 and 2 (HSV-1, HSV-2) and cytomegalovirus (CMV or HHV-4) remain a significant cause of infant mortality are also a major cause of both congenital deafness (CMV) as well as other pediatric morbidity and mortality (HSV and CMV). Molecular defects have been identified in toll-receptors, related interferon signaling pathways associated with herpes simplex encephalitis andshingles due to VZV (varicella zoster virus) as well as defects in NK (natural killer)-cells associated with overwhelming EBV (Epstein-Barr Virus or Human Herpes 4) infection in the syndrome of XLP (X-Linked Immunoproliferative syndrome). Specific defects in these and other mechanisms of herpes pathogenesis remain an active subject of research, however it is clear that additional therapy options for severe herpes virus infection are needed in both the adult and pediatric population.

Human and veterinary herpes virus pathogens encode conserved recombinases in the DDE recombinase family that also includes the retroviral integrases [1,2]. Raltegravir inhibits additional conserved terminase proteins in the DDE family required for herpes virus replication at therapeutic doses in vitro [3]. Thus, at least two conserved enzymes present in all herpes viruses could potentially be targeted by retroviral integrase inhibitors. Retroviral integrase inhibitors including raltegravir (Isentress, Merck) have been approved for clinical therapy of AIDS/HIV (Acquired Immune Deficiency Syndrome/Human Immunodeficiency virus-1) infection since successful clinical trials reported in 2008 [4]. However, the effects of retroviral integrase inhibitors on herpes virus related pathology have not been investigated independently of the effects of raltegravir on HIV- replication with the exception of a single case report [5].

This report is the first to present evidence that retroviral integrase inhibitors may be an effective therapy for herpes virus related illness in an HIV-negative patient with a deficiency of NK-cells. A 34 year-old HIV negative woman was referred for severe episodes of oral cold soresbeginning in childhood which were unresponsive to oral and topical acyclovir and/or Valtrex combined with oral corticosteroids. She had a history of hepatitis C that had responded to interferon therapy, and had repeatedly tested negative for HIV. Laboratory evaluation confirmed HIV negative status and showed evidence of past infection with hepatitis C, HSV (herpes simplex virus) type 1, varicella (HHV3), Epstein Barr Virus (HHV4), and HHV6 but no previous infection with HSV2, cytomegalovirus (HHV5), HHV7, 8 or HIV. CBC, liver and kidney function, and immunoglobulin levels were normal. Cellular immunology showed a borderline or low number of CD16/56 NK lymphocytes with normal CD4, CD8 and B lymphocytes (Table 1). IgM to herpes simplex was reported by the reference laboratory as equivocal (Quest Diagnostics, Wallingford, CT).

She signed a written consent for off-label use of Raltegravir for herpes simplex which was to be started at the onset of her typical prodrome of fever and chills, a standard dose of 400 mg twice a day. Within 12 hours of starting the medication she noted rapid resolution of her symptoms as well as "crusting over" of several herpes oral cold sores that in the past had progressed to multiple lesions over 1-2 weeks. Seen in the office three months after the initial visit examination remained normal and shereported several subsequent occasions she had experienced a prodrome of fever and chills, responding completely to a single dose of raltegravir. She has continued to use the medication "as needed" several times per three month interval for the past two years without any evidence of developing resistance to therapy. Because of a theoretical concern that retroviral integrase inhibitors such as Raltegravir might trigger or worsen autoimmune disease based on observations in a murine model, ANA and anti-DNA antibodies, thyroid function was normal and there was no evidence of anti-thyroid antibodies at follow-up.

Because the RAG-1 recombinase required for generation of the T and B lymphocyte repertoire is a DDE recombinase potentially inhibited by retroviral integrase inhibitors, lymphocyte subsets and immunoglobulin levels were monitored and unchanged (Table 1) [1,2]. PCR for hepatitis C remained negative. Laboratory testing at follow-up visits at three month intervals until the present showed evidence of improved immunity to HSV1 infection (equivocal levels of HSV specific IgM present at visits April, July and October 2012, but negative to HSV in January, 2013) and minimal changes in cellular immunity with the exception of a slightly improved absolute number and percentage of CD16/56 NK cells. Immunoglobulins A, E, G and M were also normal and unchanged at all visits (not shown). Thus, it

	12-Apr	12-Apr	12-Jul	12-Jul	24-Oct	24-Oct	23-Jan	23-Jan
	#	%	#	%	#	%		
cd4	1113	47	1191	40	1045	45	736	44
cd8	864	36	1045	35	861	37	563	33
nk	77	3	385	13	114	5	144	8
cd19	238	10	280	9	284	13	209	12
wbc	7.6						6.4	
hct	35.7						37.2	
HSVIgM		borderline		borderline		borderline		negative

Table 1: Immunologic Parameters During Treatment Interval April, 2012 To January, 2013.

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Received July 12, 2013; **Accepted** September 26, 2013; **Published** September 28, 2013

Citation: Dreyfus DH (2013) Evidence that Raltegravir (Isentress, Merck), a Retroviral Integrase Inhibitor is Effective against Recurrent Human Herpes Simplex Virus Infection Associated with NK-cell Deficiency. Pediat Therapeut 3: 172. doi:10.4172/2161-0665.1000172

is plausible that the benefits of Raltegravir in this patient were due to direct effects upon herpes virus replication, rather than non-specific changes in her NK cells or other aspects of her immune system both because of the observed change in herpes virus specific serology, and the lack of significant changes in other immunologic parameters during the treatment interval (Table 1).

Raltegravir might be offered on a case by case basis to pediatric or adult patients with non-HIV related herpes pathology not responsive to conventional therapy such as acyclovir and related nucleotide inhibitors since this class of medication seems relatively safe even in patients with severe defects of cellular immunity due to AIDS.Since the patient described in this report is currently planning pregnancy she is planning to continue therapy during pregnancy to prevent both avoid flares of infection during pregnancy and in theory reduce the risk maternal to fetal transmission of HSV-1 infection. Raltegravir is currently considered class C in pregnancy (no adverse events in animal models but limited clinical experience in humans), however the safety of Raltegravir and other retroviral integrase inhibitors should be examined in larger studies of pregnant women both with respect to maternal and fetal safety. Anotherapproach to confirm or refute the hypothesis presented in this study that Raltegravir may have anti-viral properties against herpes simplex at doses clinically suggested for therapy of HIV-1 infection would be to retroactively examine prevalence and incidence of herpes virus pathology in a cohort of HIV-1 patients treated with Raltegravir compared to a cohort of HIV-1 patients with similar levels of HIV-1 virus, with the expectation that herpes virus pathology such as herpes simplex, herpes zoster, or EBV related pathology such as auto-immune syndromes might be decreased in the Raltegravir-treated groups over time when viewed retrospectively [5].

Therapy of HIV with retroviral integrase inhibitors is associated with emergence of viral resistance that could also alter the response of herpes viruses to therapy [6]. As additional retroviral integrase inhibitors are introduced for therapy of HIV, the author suggests that it will be important to monitor not only the effects of these medications on HIV replication but also upon co-morbidity due to herpes virus infections. It is possible or likely that some of the benefits of retroviral integrase inhibitors in both pediatric and adult HIV positive patients are due to their direct ability to block replication of herpes virus co-infection, and thus that clinical benefits and effectiveness of different retroviral integrase inhibitors as well as emergence of viral resistance may vary independently from the effects of this class of medication upon HIV replication.

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