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Maraviroc Induced CCR5 Blockage for HIV Infected Individuals is Associated with Increased Rates of Respiratory Tract Infections

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Abstract

Background: Maraviroc is an allosteric, non-competitive blocker of CCR5, interfering with its ability to bind to the HIV GP120 and thus preventing HIV cell entry. CCR5 is involved in recruiting immune cells to sites of viral invasion in the respiratory tract.

This postulated role of CCR5 led us to perform a meta-analysis of the largest clinical drug trials that evaluated CCR5 antagonists, as part of antiretroviral regimens, with focus on the occurrence of respiratory infections in general and viral infections in particular in CCR5 antagonist recipients.

Data source and eligibility criteria: Clinical trials involving administration of Maraviroc to HIV infected individuals were reviewed with emphasis on reported respiratory infections. We included in the analysis those studies enrolling more than 100 participants in the maraviroc treatment arm.

Results: We compared individuals treated with optimized background regimen plus placebo to those receiving the background regimen along with the CCR5 anatagonist maraviroc. We found in the clinical data significantly more respiratory infections in the CCR5 blocker treated arm than in the control arm.

Limitations: The studies had limited microbiological analysis of respiratory infections and the categorization differs between the studies included.

Conclusions: This observation suggests that the CCR5 blockade may lead to more infections caused by other viruses and respiratory pathogens in HIV infected patients and the incidence of such infections needs to be carefully assessed.

Keywords: CCR5; Maraviroc; HIV; Viral respiratory infection

Introduction

The CCR5 protein is a member of the beta-chemokine-receptor family and is expressed primarily on T cells, macrophages and dendritic cells surface. CCR5 is considered to play a role in mediating leukocyte chemotaxis in response to several stimuli including response to ligands such as RANTES, MIP-1α and MIP-1β. As such, CCR5 is believed to be important in the homing of several immune cell subsets, including regulatory T cells and Th17 cells to sites of infection. CCR5, along with CXCR4, is also well known as a co-receptor for HIV viral cell entry. Until recently, understanding of the role of CCR5 in supporting the antiviral immune response was limited to the role of CCR5 receptor deficiency in protecting from HIV infection and disease progression. Individuals who are homozygous for the CCR5Δ32 allele, a condition in which a 32 bp deletion in the CCR5 gene prevents its expression on the cell surface, have been shown to have reduced susceptibility to HIV infection and the heterozygous state delays HIV disease progression [1-4]. However, it was only recently shown that homozygosity of the Δ32 allele was also associated with an increased risk of neuroinvasive disease and fatality caused by West Nile virus (WNV) infection [5,6]. This association is also consistent with a role for CCR5 in lymphocyte trafficking during infection in a mouse model of WNV [7]. A case report of an adverse reaction to the Yellow Fever virus vaccine in a CCR5Δ32 heterozygote as well as a link with severe tick-borne encephalitis suggest that CCR5 may play a pivotal and broader role in human immune response to other flavivirus infections as well [8,9]. It is possible that CCR5 activity is not limited to flaviviruses and retroviruses. In mouse models, CCR5 is important in the recruitment of CD8+ T cells to the lung airways during Sendai virus challenge [10]; similarly, $CCR5^{-/-}$ mice exhibit increased mortality following Influenza A infection [11]. We have recently reported an over-representation of the CCR5Δ32 allele among Caucasians with severe pandemic H1N1 influenza virus infection [12].

Maraviroc is an orally administered, noncompetitive inhibitor of CCR5 with potent in-vitro activity. It binds to the trans-membrane coreceptor cavity with ensuing conformational changes. These changes in turn render the CCR5 coreceptor incapable of interaction with the V3 loop of gp120 of the HIV virus [13-15]. Maraviroc was the first agent with CCR5 blocking activity to gain FDA approval in 2007 for the therapy of advanced HIV. This approval was based primarily on the MOTIVATE 1 and MOTIVATE 2 clinical trials in which the drug demonstrated superior antiviral and immunological efficacy compared to an optimized backbone regimen with placebo in HIV infected patients [16-18].

Rationale and objectives

Given the presumed role that CCR5 plays in generation of the cellular immune response to a growing list of various viral infections, we sought to determine the occurrence of respiratory infections with specific attention to viral Upper and Lower Respiratory Tract Infections

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Publication	N=; Drug	Trial Name	LRTI among CCR5 antagonist	LRTI Control arm	LRTI
Cooper JID [16]	721; maraviroc	MERIT: Maraviroc in treatment Naïve	2 Lobar Pneumonia; 1PCP	0	
Saag JID [17]	186(OBT versus OD and BID maraviroc	Maraviroc in treatment experienced	5 Bronchitis; PCP 4	0 bronchitis PCP-0 Pneumonia-1	
Gulick NEJM [18]	1049; maraviroc	MOTIVATE 1+2: (601+474) PLACEBO-209	2 PCP; Pneumonia 4		URTI 16+20 (PLACEBO=1)
			11 LRTI; 7 PCP	**1 LRTI; 0 PCP**	

Table 1: Maraviroc large RCT's- comparison of respiratory infections among treatment and control arms.

(URTI and LRTI) in the aforementioned randomized controlled Maraviroc trials.

The Study

We extracted data regarding the occurrence of respiratory infections including lower respiratory tract, upper respiratory tract as well as PCP, from the data in the major clinical trials enrolling more than 100 individuals in the CCR5 antagonist treatment arm. The major clinical trials comparing maraviroc to controls were included. In trials with a range of maraviroc dosages, all lower respiratory adverse events were pooled for the maraviroc treatment arms.

Results

The main 3 randomized controlled trials included in this analysis were: the MERIT trial that compared maraviroc to efavirenz along with zidovudine-lamivudine in treatment-naive individuals. [17] shows a phase 2b trial of maraviroc aimed to determine the safety and efficacy of the drug in combination with optimized background therapy, in treatment experienced individuals. The MOTIVATE 1 and 2, were two randomized, placebo controlled trials studying maraviroc in treatment experienced individuals on optimized backbone therapy, with resistance to 3 anti-retroviral classes.

As shown in (Table 1), lower respiratory tract infections were more common in the maraviroc treatment arms. All cases of PCP occurred in the maraviroc treatment arms, however the numbers of these pulmonary infections were small and failed to reach statistical significance. The occurrence of upper respiratory tract infections was more common among maraviroc recipients in the MOTIVATE trials but were not reported in the two other trials.

Limitations

Attempts at documentation of the bacterial or viral cause of respiratory infections were limited in the analyzed studies, and the description of upper respiratory tract infections was incomplete, thus prohibiting the identification of specific pathogens as the cause of respiratory infections.

Conclusions

CCR5 antagonists are becoming an important addition to HIV treatment arsenal and provide a novel drug target. The role of the chemokine receptor in migration of T-lymphocytes to the site of infection is beginning to be appreciated, with an expanding range of infections in which it is thought to play a role, including flaviviruses and possibly influenza.

In the three large maraviroc randomized controlled clinical trials, the combined number of LRTI was higher among maraviroc treated individuals, with all the cases of *pneumocystis jirovecii* occurring in the maraviroc treated patients. The proportion of upper respiratory tract infections was also higher among maraviroc treated patients, in the MOTIVATE studies, the only studies that reported these infections.

The analysis is limited by the differences of adverse events reporting method, the terminology and classification of respiratory infections between the trials. An incomplete microbiological investigation in the original trials limits the etiologic diagnoses. Partial investigations were reported for LRTI and URTI but no viral cultures were reported.

Our analysis along with the mounting evidence for the role that CCR5 plays in an array of viral infections, suggest that careful documentation and better definition of the respiratory adverse events is warranted. Specifically, identifying the agents causing lower and upper respiratory tract infection is required in order to gain a better understanding of the role of CCR5 blockage in the pathogenesis of other infections and how it can be optimally employed in the treatment regimen against HIV. The post-marketing data, with larger numbers of patients should provide insights into the effects of CCR5 blockage on respiratory tract infections.

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