Blockade of CCR5 to protect the liver graft in HIV/HCV co-infected patients

Stéphanie Haim-Boukobza1,2,3,9, Karl Balabanian4,5,9, Elina Teicher2,3,7,9, Marion Bourgeade2,3,9, Gabriel Perlemuter3,4,8,9, Anne-Marie Roque-Afonso1,2,3,9, Jean-Charles Duclos-Vallee2,3,6,9,*

1AP-HP, Hôpital Paul Brousse, Département Virologie, Villejuif, France; 2INSERM, U785, Villejuif, France; 3Univ Paris-Sud, Faculté de Médecine Paris-Sud, Le Kremlin Bicêtre, France; 4Univ Paris-Sud, Laboratoire Cytokines, Chimiothérapies et Immunopathologies, UMR S996, Clamart, France; 5INSERM, Laboratoire of Excellence in Research on Medication and Innovative Therapeutics (LERMIT), Clamart, France; 6AP-HP, Hôpital Paul Brousse, Centre Hépato-Biliaire, Villejuif, France; 7AP-HP, Hôpital de Bicêtre, Service de Médecine Interne, Le Kremlin-Bicêtre, France; 8AP-HP, Hôpital Antoine Béclère, Département Hepato-Gastroenterologie, Clamart, France; 9Hepatinov, Villejuif F-94800, France

Abstract: Background: Graft-versus-host disease (GVHD) is a major barrier to successful allogeneic hematopoietic stem-cell transplantation (HSCT). The chemokine receptor CCR5 appears to play a role in alloreactivity. We tested whether CCR5 blockade would be safe and limit GVHD in humans.

Methods: We tested the in vitro effect of the CCR5 antagonist maraviroc on lymphocyte function and chemotaxis. We then enrolled 38 high-risk patients in a single-group phase 1 and 2 study of reduced-intensity allogeneic HSCT that combined maraviroc with standard GVHD prophylaxis.

Results: Maraviroc inhibited CCR5 internalization and lymphocyte chemotaxis in vitro without impairing T-cell function or formation of hematopoietic-cell colonies. In 35 patients who could be evaluated, the cumulative incidence rate (±SE) of grade II to IV acute GVHD was 11.7 ± 5.6% without excessive rates of relapse or infection. Serum from patients receiving maraviroc prevented CCR5 internalization by CCL5 and blocked T-cell chemotaxis in vitro, providing evidence of antichemotactic activity.

Conclusions: In this study, inhibition of lymphocyte trafficking was a specific and potentially effective new strategy to prevent visceral acute GVHD. (Funded by Pfizer and others; ClinicalTrials.gov number, NCT00948753.)

Introduction

Chemokines play a major role in the health of the immune system. CCR5 is a receptor present at the surface of monocytes/macrophages and activated T-lymphocytes. Its natural ligands include the CC chemokine ligands (CCL)-3, -4 and -5. CCR5 is a CD4 coreceptor for the entry of HIV into cells. Maraviroc is a CCR5 inhibitor that is usually used as an antiretroviral agent in HIV-infected individuals, in combination with other antiretrovirals. The CCR5-Δ32 mutation is a 32-base-pair deletion within the CCR5 coding region that results in a non-functioning receptor. It was with great interest that we read the recent article by Reshef et al. in the New England Journal of Medicine, dealing with the immunomodulatory properties of maraviroc used as an inhibitor of T-cell trafficking in graft versus host disease (GVHD) that frequently compromises allogeneic hematopoietic stem cell transplantation. During this study, maraviroc prevented in vitro internalization of CCR5 on effector T-cell subsets and inhibited T-cell migration following exposure to CCL3 and CCL5. Moreover, combining this drug with standard GVHD prophylaxis induced a lower incidence of GVHD, especially affecting the liver and gut, in the 35 patients evaluated. Interestingly, serum from maraviroc-treated patients displayed antichemotactic activity in vitro. This elegant study reinforces previous findings that highlighted a lower rate of graft rejection when the CCR5 pathway was inhibited. For example, lower renal transplant rejection rates were observed in recipients homozygous for the CCR5-Δ32 allele [1]. Moreover, mice that were either deficient for the membrane expression of CCR5 or CCL5, or treated with CCR5 monoclonal antibodies (mAb), presented with less cardiac graft rejection [2]. Similarly, primates receiving maraviroc demonstrated an improved survival of heart allografts [3].
Despite a lack of data regarding the use of maraviroc in liver-transplanted HIV/HCV coinfected patients, maraviroc could be indicated for two reasons: firstly, to lower liver graft rejection (LGR) rates in the same way as maraviroc in the context of GVHD [as presented by Reshef et al.], and secondly, to reduce liver fibrosis after liver transplantation (LT), because HCV reinfecation can induce rapid-kinetic liver fibrosis on the liver graft. These two points are detailed below and in Fig. 1.

### Expected effects of maraviroc in reducing liver graft rejection

In some patient series, the occurrence of LGR was significantly higher among HIV/HCV-coinfected patients than among HCV mono-infected recipients [4]. LGR is mainly due to the migration of circulating peripheral CD8 T lymphocytes (CTL) which infiltrate the liver graft and are attracted by CCL3, CCL4, and CCL5, leading to Kupffer cell activation, necrosis and rejection of the graft [5]. In this case, inhibiting the CCR5 pathway should reduce the chemotaxis involved in CTL recruitment into the liver graft (Fig. 1). In support of this assumption, a CCR5-Δ32 mutation has been described as a protective genetic factor against LGR, and one research team proposed minimized immunosuppressive therapy in patients harboring the homozygous CCR5-Δ32 mutation [6]. However, two other studies showed an increase incidence of biliary complications in CCR5-Δ32 patients after LT, especially among those with primary sclerosing cholangitis, but the small number of homozygous subjects included in that series needs to be taken into account [7,8]. It is therefore necessary to further study the long-term management of maraviroc in these patients.

### Expected effects of maraviroc on reducing fibrosis induced by HCV reinfecion after LT

The natural course of HCV infection in HIV-infected patients differs significantly from that seen in HCV mono-infected patients, even when effective antiretroviral therapy has been started [9]. LT is now currently indicated in HIV/HCV-coinfected patients, but the severity of HCV reinfecion (as observed in forms involving fibrosing cholestatic hepatitis) appears to be the principal challenge [10]. The mechanisms involved in this accelerated progression remain a subject of debate. The CCR5 pathway is thought to be involved in liver fibrosis; for example, the administration of anti-CCR5 mAbs was shown to decrease liver inflammation in a mouse model of liver failure [11]. The mechanisms that are
probably involved are shown in Fig. 1. Briefly, injured hepatocytes activate Kupffer cells, which in turn secrete pro-inflammatory (e.g., IL-6) and fibrogenic (e.g. TGF-β) cytokines as well as inflammatory chemokines (e.g., CCL3, CCL4, CCL5), resulting in the activation of hepatic stellate cells (HSC). HSC-derived myofibroblasts secrete collagen and drive fibrosis. Convergent observations have supported attempts to inhibit CCR5 in HIV/HCV coinfected patients. Firstly, HCV infection induces inflammation and liver injury, leading to the activation of Kupffer cells, the synthesis of chemokines and TGF-β, and the secretion of CCL5 by vascular endothelial cells. Secondly, intrahepatic lymphocytes from HCV-infected patients and fibrotic liver express high levels of CCR5 [11]. Thirdly, HIV envelope glycoprotein directly promotes HCV replication through an increase in TGF-β secretion by macrophages in a CCR5-dependent manner, inducing HSC activation and collagen synthesis by myofibroblasts [12]. Moreover, HIV-infected HSCs have been shown to overexpress collagen and pro-inflammatory cytokines, thus increasing fibrogenesis [13]. Lastly, HCV-infected patients who are homozygous for CCR5-Δ32 or harbor CCL5 polymorphism may experience attenuated liver disease with moderate fibrosis [11].

A recent prospective study comparing patients on antiretroviral therapy that did or did not contain maraviroc demonstrated a non-progression of liver elastometry and inflammatory markers of fibrosis in serum (i.e., TGF-β, matrix metalloproteinase-2, tissue inhibitor of matrix metalloproteinase-1, APRI score) in the maraviroc arm vs. the control arm [14].

With respect to tolerance, some authors have already suggested a weak hepatotoxicity of maraviroc, unlike aplaviroc [15], a CCR5 inhibitor whose development was halted. The package insert for maraviroc thus includes some specific warnings (http://www.emea.europa.eu). It is also necessary to document age insert for maraviroc thus includes some specific warnings (http://www.emea.europa.eu). It is also necessary to document

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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