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Immune-mediated complications of the graft in interferon-treated hepatitis C positive liver transplant recipients

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Hepatitis C virus (HCV) re-infection of the graft is universal and interferon based antiviral therapy remains at present the treatment of choice in HCV liver transplant recipients. Apart from the antiviral effects, interferon and ribavirin have both potent immunomodulatory properties resulting in a broad range of immune-related disorders including acute cellular rejection and chronic ductopenic rejection as well as *de novo* autoimmune hepatitis. Further complicating the picture, HCV infection *per se* is associated with a variety of autoimmune phenomena. We discuss here the immune-mediated complications and their relationship to chronic HCV and interferon based antiviral therapy.
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Introduction

Hepatitis C virus (HCV) related end-stage liver disease is the leading indication for liver transplantation worldwide. HCV re-infection of the graft is universal and associated with accelerated progression of fibrosis, leading to graft cirrhosis in 10–30% of patients within 5 years [1,2]. The long-term survival of HCV-positive liver transplant recipients is, therefore, impaired [3,4].

HCV elimination through interferon alpha (IFN) based antiviral therapy has been shown to improve survival [5–7]. However, the efficacy of antiviral therapy in liver transplant recipients remains suboptimal, most studies reporting sustained virological response (SVR) rates that are at least 10–20% lower than those of a non-transplant population [6,8,9]. Contributing factors likely include the obvious need for concomitant immunosuppressive therapy, the high prevalence of HCV genotype 1 infection responding poorly to current antiviral regimens [7,10–12] and, last but not the least, the limited tolerability preventing optimal dosing of pegylated interferon alpha (PEG) and/or ribavirin (RBV) in a large proportion of patients [6–9,13].

Apart from the antiviral effects mediated through the Jak-Stat signaling pathway, IFN is a potent immunomodulator affecting both the innate and the adaptive immune system [14–16]. While the exact mechanism(s) responsible for the anti-HCV effect of RBV remain(s) to be elucidated, RBV has been shown to exert antiviral, as well as immunomodulatory effects [15,17]. Given the immunomodulatory properties of both agents, it is not surprising that a broad range of immune-related phenomena and disorders have been reported in association with IFN-based therapy of HCV patients [18,19]. In the non-transplant setting, this includes an autoimmune-type thyroiditis, and rarely, entities, such as systemic lupus erythematosus, type 1 diabetes, and even autoimmune-type hepatitis (AIH) [20–22]. Acute cellular rejection (ACR) and chronic ductopenic rejection are unique to the post-transplant setting. Both, as well as an ill-defined autoimmune-type graft hepatitis, have been reported in association with IFN-based therapy of recurrent HCV after liver transplantation [7,9,13,23]. Moreover, HCV infection *per se* is known to be associated with a variety of autoimmune phenomena and diseases, thus further complicating the issues of rejection and autoimmune phenomena associated with IFN-based therapy of recurrent HCV [24].

In the following we will focus on acute and chronic rejection, as well as autoimmune-type graft hepatitis and discuss their characteristics and potential relationship to recurrent HCV infection *per se* and/or IFN-based antiviral therapy.

Acute cellular rejection

The overall incidence of ACR in HCV transplanted recipients varies between 30% and 50% in various studies [25]. The majority of these studies have examined an early ACR (<6 weeks) post LT. ACR is a relatively rare, but serious side effect of IFN-based antiviral therapy of HCV recurrence after liver transplantation. The association between ACR and antiviral therapy was initially described in renal transplant recipients and was subsequently reported in liver transplant patients [26,27]. The initial lack of experience in management of ACR and the fear that it might lead to a subsequent risk of developing chronic rejection (CR) and ultimately graft loss have hindered for years the acceptance and generalization of antiviral therapy for recurrence of chronic HCV

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Abbreviations: ACR, acute cellular rejection; AIH, autoimmune hepatitis; CR, chronic rejection; HCV, hepatitis C virus; IFN, interferon; PEG, pegylated interferon; RBV, ribavirin; SVR, sustained virological response.

post liver transplantation. Today, with better knowledge of the management of ACR and its outcomes, this side effect of IFN-based antiviral therapy appears less worrisome than in the past.

The reported incidence of ACR during IFN-based therapy ranges from 0 to 35% (Table 1) [28]. This wide range is partly explained by heterogeneity among the studies regarding (1) performance of protocol liver biopsies during therapy looking for evidence of subclinical rejection even in the absence of abnormal liver tests, (2) the use of PEG rather than regular IFN with or without RBV, and (3) differences in the baseline immunosuppression regimens [29]. In a retrospective analysis of 23 HCV recipients who underwent antiviral therapy for HCV recurrence post liver transplantation, Stravitz et al. reported an incidence of 35% of ACR diagnosed in a post treatment liver biopsy [30]. The authors argue that several features of their protocol might have contributed to this high rate of ACR; these included the practice of protocol biopsies pre- and post-antiviral therapy allowing the detection of subclinical ACR, the use of the PEG as opposed to regular IFN, and, finally, the late administration of IFN therapy post-transplant (when maintenance immunosuppression is usually less intense) [30]. Protocol biopsies (pre- and post-IFN therapy) and PEG regimens are currently the standard of practices in many centers that do not observe a similarly high incidence of ACR. An important point of the Stravitz study is the fact that only 4 of the 23 patients received a full course of RBV therapy [30]. This might, at least in part, explain the high incidence of ACR, as it is known that RBV suppresses proliferation of immune cells *in vitro*, and, thus, might protect against ACR [31]. This seems corroborated by the study of Dumortier et al. who observed an ACR incidence of 25% among 20 patients treated for HCV recurrence [32]. Here again only 3 of the 20 patients received a full dose RBV. Indeed, the reported rate of ACR in most recent studies using the combination of both drugs is below 10% [7,33–35]. Most importantly, in all recent randomized studies, the incidence of ACR in HCV-positive liver transplanted recipients treated with combination antiviral therapy for HCV recurrence does not seem to be higher than that observed in non-treated HCV-positive liver transplant recipients [36–38].

ACR is often associated with concomitant low or negative serum HCV RNA. It has been suggested that HCV clearance during IFN-based therapy improves hepatic microsomal function, which in turn leads to lower immunosuppressant levels in blood putting

Table 1. Summary of the acute cellular rejection and chronic rejection in the larger antiviral studies for HCV recurrence post liver transplantation.

Author	n	regimen	SVR %	Incidence ACR %	Outcome	Incidence CR %	Outcome
Berenguer 2006	36	PEG + RBV	50	5	One death due to graft failure In other cases, resolution with bolus of steroids	8	One patient died from graft failure One patient underwent re-LT, two other patients improved with adjustment of IS
Carrion 2007	54	PEG + RBV	48	7	-	5	-
Castells 2005	24	PEG + RBV	35	4	Resolution with increased IS	0	-
Dumortier 2004	20	PEG + RBV	45	25	Resolution with increased IS	-	-
Fernandez 2006	47	PEG + RBV	23	2	-	2	-
Firpi 2002	54	INF + RBV	30	5	One graft failure, two others resolved	0	-
Mukherjee 2006	39	PEG + RBV	31	0	-	0	-
Oton 2006	55	PEG + RBV	44	0	-	2	Controlled by adjustment of IS
Rodriguez-Luna 2004	19	PEG + RBV	26	5	-	0	-
Selzner 2009	172	PEG + RBV	50	5	All resolved with either bolus of steroids or increase IS	4	Three died, two from graft failure, one from liver unrelated cause Four patients have cirrhosis
Stanca 2007	70	PEG + RBV	-	5	-	17	Five died of sepsis. Two were re-LT and one was listed for re-LT
Stravitz 2004	23	INF + RBV	35	7	Resolution in 3 cases Re-LT in one patient	1	Graft failure

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