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Progression of liver fibrosis in post-transplant hepatitis C: Mechanisms, assessment and treatment

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Summary

Liver fibrosis results from an excessive wound healing response in most chronic liver diseases, such as hepatitis C. Despite great advances in antiviral therapy in recent years, progressive liver fibrosis remains a major problem for patients with recurrent hepatitis C after liver transplantation. Liver biopsy remains a central tool in the management of HCV-positive liver transplant recipients, but reliable non-invasive methods for the assessment of liver fibrosis, such as ultrasound elastography, are increasingly being incorporated in the management of post-transplant patients, helping predict prognosis, guide treatment decisions, and stratify patients for emerging antifibrotic therapies.

In this manuscript, we will review the natural history as well as tools to monitor fibrosis progression in the HCV-positive liver transplant recipient, the mechanisms underlying rapid fibrosis progression in up to 30% of these patients, the effect of antiviral therapies and highlight promising antifibrotic approaches.

Fibrosis progression monitoring: justification and tools

Natural history of fibrosis progression in post-transplant hepatitis C

The deposition of fibrotic tissue in most HCV transplanted livers is highly accelerated with development of bridging fibrosis and cirrhosis in 20–54% at 5 years and 32–51% at 7 years (Table 1) [1–13]. Reasons to tightly monitor fibrosis progression after liver transplantation include: (i) poor correlation between liver function tests and histology, both in HCV and non-HCV recipients [1–4,14,15]; in one recent study where 165 biopsies were taken at the time of normal liver function tests, histologic abnormalities were found in almost one third of biopsies (11.5% of which were considered to be clinically significant), including fatty liver disease, low-grade/low-stage recurrent hepatitis C or primary biliary cirrhosis, or central venulitis [16]; (ii) the usually high speed of fibrosis progression in transplant compared to non-transplant patients, with medium annual rates ranging from 0.2 to 0.8 Metavir stages/year (Table 2) [1,2,10,12,17–23] compared to 0.1–0.2 in non-transplanted, immune competent patients [24]. Moreover, fibrosis progression often is not linear [19,20] and can have an early exponential increase [12,21,25] as well as a late start [26]. In fact, the lack of linearity was recently confirmed by a non-Markov analysis based on 901 histological fibrosis assessments in 401 patients [27]. Moreover, this model showed that the risk of progression decreased as time spent at a given fibrosis stage increased, however, a longer time to reach that stage did not predict risk of progression to a higher stage. In other words, this indicates that disease activity is variable over time and that current time at a given stage rather than the prior time in earlier stages is most predictive of future progression [27]; (iii) the potential to predict outcome. Indeed, the course of progression appears to be determined early after transplantation [28,29], and the stage of fibrosis within the first year has been shown to be strongly associated with subsequent progression to cirrhosis as well as with graft and patient survival. Additional information that can be used to predict the risk of fibrosis progression includes the degree of necroinflammation in early biopsies, the age of the donor, viral load, the degree of immunosuppression as well as concurrent complications occurring during the first months post-transplantation, mainly biliary complications [1,2]. In particular, the degree of necroinflammation helps identify those at increased risk of fibrosis progression and with impaired survival [1–5,9,10,21,22,30–34] (Table 3A and B). Overall, patients in whom at least moderate fibrosis (Metavir F $\geqslant$2) is found in the first-year have a significantly greater risk of progressing to cirrhosis and a lower graft and patient survival than those with minimal or absent fibrosis; (iv) limited efficacy but high toxicity of antivirals in transplant recipients [35–44] (see

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Table 1. Progression to bridging fibrosis or cirrhosis in HCV-infected liver transplant recipients.

Author, yr [Ref.]	n	Outcome measure	3 yr outcome	5 yr outcome	7 yr outcome
Gane *et al.,* 1996 [3]	149	Cirrhosis		20%	
Prieto *et al.,* 1999 [4]	81	Actuarial rate of cirrhosis	16%	28%	
Sreekumar *et al.,* 2000 [5]	47	F ≥2	47%		
Sanchez-Fueyos *et al.,* 2002 [7]	134	Actuarial rate of graft damage (cirrhosis + FCH + submassive liver fibrosis)	15%	33%	44%
Berenguer *et al.,* 2002 [6]	189	Actuarial risk of cirrhosis	25%	44%	51%
Wali *et al.,* 2003 [8]	49	Severe fibrosis (F5-6)		24% non-GT4 *vs.* 85% GT4	
Neumann *et al.,* 2004 [9]	183	Cirrhosis or death	17%	25%	24%
Yilmaz *et al.,* 2007 [10]	227	Bridging fibrosis or cirrhosis Cirrhosis	11% 2%	25% 6%	41% 10%
Belli *et al.,* 2007 [11]	354	Bridging fibrosis or cirrhosis	18%	27%	32%
Walter *et al.,* 2007* [12]	105	Bridging fibrosis or cirrhosis		18% at a mean of 4.7 yr	
Lai *et al.,* 2011 [13]	1264	Bridging fibrosis or cirrhosis	38% for women 33% men	54% for women 45% men	

*Surviving the first year, 67% having received early antiviral therapy.
FCH, fibrosing cholestatic hepatitis; yr, year.

Table 2. Fibrosis progression rates described in liver transplant recipients infected with HCV.

Author, yr [Ref.], n	1 yr FPR	3 yr FPR	5 yr FPR	6-10 yr FPR
Berenguer *et al.,* 2000 [20], n = 284	0.3 FU/yr			Time to F ≥1: 2-2.3 yr Time to F ≥2: 4.5-4.7 yr Time to F ≥3: 5.9-6 yr Time to F4: 9.5-11.6 yr
Wali *et al.,* 2002 [19], n = 56	0.78 FU/yr DA <40 yr: 0.6 FU/yr DA >50 yr: 2.7 FU/yr			Time to F4: 7.7 yr 10 yr 2.2 yr
Neuman *et al.,* 2004 [21], n = 183	1.2 FU/yr	0.25 FU/yr	0.08 FU/yr	
Firpi *et al.,* 2004 [22], n = 264	0.8 FU/yr			
Walter *et al.,* 2007 [12], n = 105	0.33 FU/yr	0.33 FU/yr	0.16 FU/yr	0.08 FU/yr
Selzner *et al.,* 2008 [23], n = 201	0.19 FU/yr in DDLT *vs.* 0.11 FU/yr in LDLT			

FU, units of fibrosis (Metavir scale); yr, year; FPR, fibrosis progression rates; DA, donor age; DDLT, deceased-donor liver transplantation; LDLT, live-donor liver transplantation.

section on antiviral therapy). The discrimination between patients with slow and rapid fibrosis progression would avoid starting unnecessary antiviral therapy in patients with an expected good long-term survival, while urging early treatment in those at high risk of disease progression; (v) improved efficacy and reduced toxicity if antiviral therapy is started at less advanced stages of fibrosis, particularly before the development of cirrhosis [40–44]. This is exemplified by a single center study, where lower sustained viral response (SVR) rates were achieved by recipients treated during a more recent period of time (2001–2005: n = 71, 42% *vs.* 2006–2007: n = 36, 24%; $p = 0.043$). One likely explanation is the greater proportion of patients treated at advanced stages, which is associated with lower rates of viral clearance. Most specifically, of 22 patients with baseline cirrhosis, only 4 (18%) achieved SVR, whereas 34 out of 83 (41%) non-cirrhotic patients reached an SVR [43]. Increased SVR rates (from 25% to 54%) were later achieved in the same center after treatment policy was changed to start therapy at lower fibrosis stages (the number of cirrhotic patients decreased from 20.5% to 7%) coupled with higher ribavirin doses [44]. Others showed that among 113 patients with a 38% SVR rate, tolerability of therapy decreased significantly in those with fibrosis stage $\geqslant 3$ at baseline liver biopsy. A total of 20% of the advanced patients died or were re-transplanted due to liver failure as opposed to 1% of patients with fibrosis stage <3 [40]. Whether the same will hold true in the era of new direct oral antivirals remains to be seen; (vi) potential co-existence of other lesions, some of which should be excluded before initiating antiviral therapy with interferon-based regimes, such as rejection or autoimmunity [32,33,35,36]. In a recent study, autoimmune features (mainly plasma cell hepatitis) in liver biopsies collected before peg-interferon therapy were one of the main risk factors for the development of