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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.

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

patients at higher risk of development of ACR [39,40]. In an analysis of 36 HCV patients treated for recurrence of HCV post liver transplantation, Kugelmas et al. showed that the mean cyclosporine and tacrolimus trough levels measured immediately after becoming HCV RNA negative were significantly lower than those at baseline (pre-therapy) [39]. Furthermore, they demonstrated that the overall decrease of calcineurin inhibitor levels after HCV clearance averaged 32% in responders to antiviral therapy compared to only 0.98% in non-responders. These data, albeit preliminary, have alerted transplant physicians to monitor calcineurin inhibitor levels closely during the course of antiviral therapy, in particular in patients who respond favorably and clear the virus. Our practice is to routinely increase baseline immunosuppression in all HCV recipients at the initiation of antiviral therapy in order to lower the probability of triggering ACR at the time of viral clearance.

The typical manifestation of ACR during antiviral therapy is a secondary increase of liver function test, in particular the transaminases, after an initial improvement or normalization with treatment. This is, however, non-specific and the diagnosis requires a liver biopsy (Fig. 1). In 1997, The Banff Working Group [41], developed a consensus for a common nomenclature along with a set of histopathological criteria for the diagnosis and grading of ACR. These include: (a) a mixed, but predominantly mononuclear portal inflammation, containing blastic (activated) lymphocytes, neutrophils, and frequently eosinophils; (b) bile duct inflammation/damage; and (c) phlebitis of portal veins or terminal hepatic venules. Portal inflammation, bile duct damage, and venous endothelial inflammation/damage are each scored semi-quantitatively on a scale of 0 to 3 (0 = absent, 3 = severe) [41]. The individual scores are then added to generate an overall rejection score (rejection activity index, RAI) that can reach a maximum of 9 in case of severe rejection. Applying this scoring system presupposes that the diagnosis of rejection is first made based on the aforementioned histological pattern, thus becoming eligible for severity scoring.

To facilitate the acceptability and in the interest of simplicity, the Banff group agreed to further provide a global assessment of the ACR grading based on the overall biopsy appearances. Rejection is indeterminate if the portal inflammatory infiltrate fails to

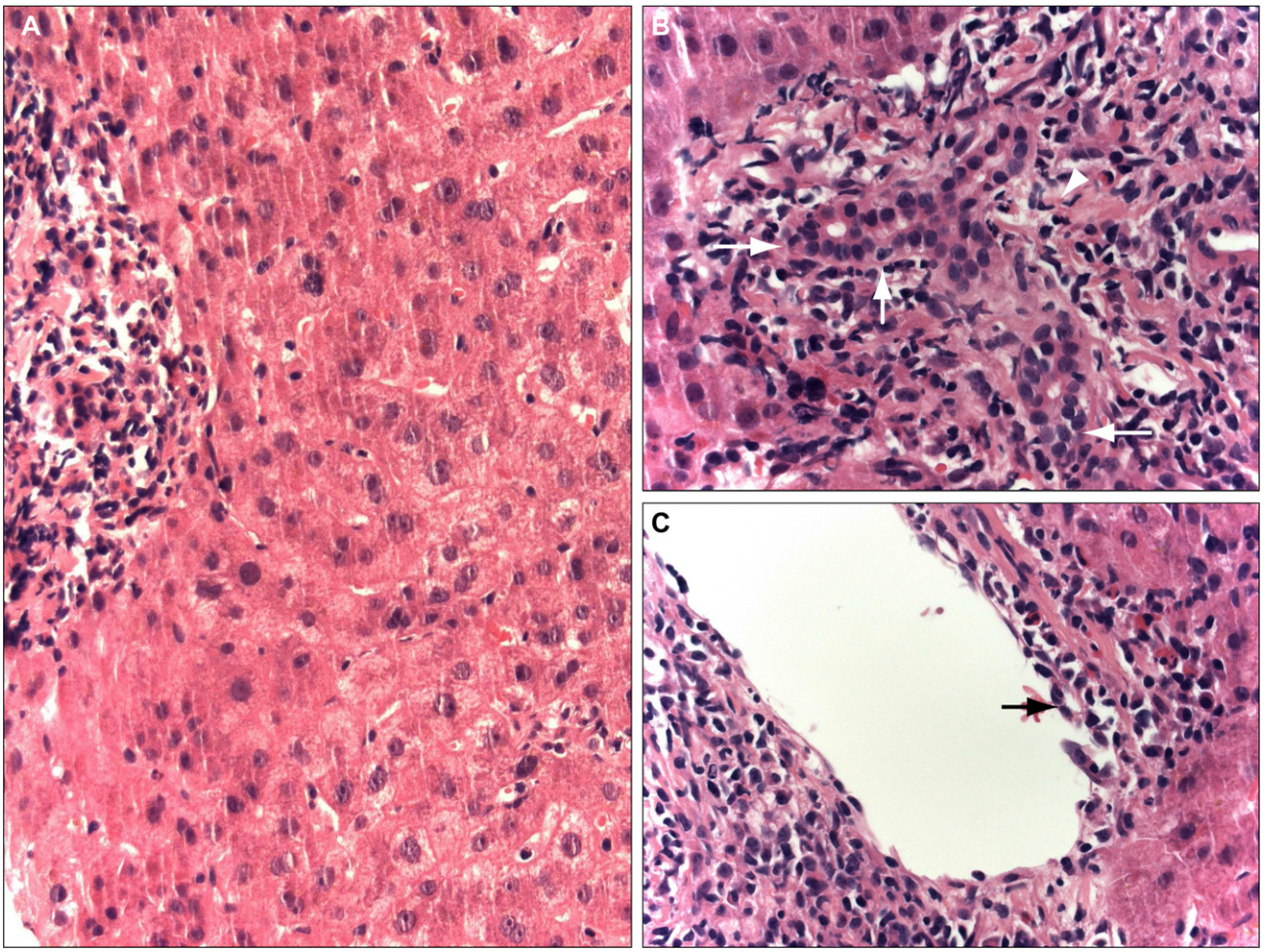

Fig. 1. Acute cellular rejection occurring in a patient transplanted for HCV cirrhosis. (A) Liver parenchyma showing sparse lymphocytosis (hematoxylin and eosin, magnification 100×). (B) Portal tract lymphoid inflammation with few eosinophils (arrowhead) and bile duct epithelium infiltration by lymphocytes (hematoxylin and eosin, magnification 400×). (C) Portal tract showing portal vein phlebitis. There is subendothelial infiltration by lymphocytes and lifting of endothelial cells (arrow) (hematoxylin and eosin, magnification 200×).

meet the criteria for the diagnosis of ACR, as above. Rejection is mild if the infiltrate fulfils the criteria, and is present in a minority of the triads, confined within the portal tracts. In moderate rejection, the infiltrate expands most or all of the portal tracts. In severe rejection, in addition to expanding infiltrate to most or all of the portal tracts, there is spill over into periportal areas and perivenular inflammation that extends into the hepatic parenchyma and is associated with perivenular hepatocyte necrosis [41].

Because of the potential for progressive injury and graft loss, it is recommended that any biochemical abnormalities secondarily appearing during antiviral therapy should prompt an immediate liver biopsy to rule out histological evidences of ACR. For mild ACR, the current management is to increase baseline immunosuppression level. For moderate to severe forms of ACR (RAI >4), i.v. boluses of steroids are recommended. A follow up liver biopsy should be considered in patients with elevated liver enzymes persisting after treatment of ACR.

Whether antiviral therapy should be discontinued when ACR is diagnosed is a matter of debate. Many transplant hepatologists will stop antiviral therapy, at least in case of a moderate or severe ACR requiring i.v. bolus steroids. Some programs have started to continue antiviral therapy even in severe ACR cases. Based on our personal experience, the prognosis of ACR in HCV recipients during the course of antiviral therapy is not worse than the ACR in HCV recipients without antiviral therapy. Clearly more data are required to resolve this important issue.

Chronic rejection

The reported incidence of chronic rejection (CR) in HCV-positive liver transplant recipients in the absence of IFN treatment varies between 4% and 8% [42]. Five small studies using PEG IFN therapy have reported a total of seven cases of CR [30,37,43–45]. Three of these seven patients had severe ACR which casts some doubt on the role of IFN-based therapy in directly triggering CR. Recently, Stanca et al. reported a 17% rate of CR among 70 HCV liver transplant recipients treated with a PEG based regimen in their center [46]. In contrast to the previous reports, only four of these patients had previously developed ACR while receiving antiviral therapy. The authors argue that pegylated formulation of IFN together with a longer length of therapy may explain this unusual high rate of CR. Indeed in their series, CR was diagnosed after a median of 12 months of therapy with PEG and RBV. Six of the 12 patients with CR were treated for more than 12 months with antiviral therapy when CR was diagnosed. The presence and severity of previous ACR did not appear to play a role in the development of CR in this study.

In another series of 67 HCV patients treated for HCV recurrence post liver transplantation with either the standard IFN ($n = 31$) or PEG ($n = 36$), Berenguer et al. reported a total of 4 patients with CR. The rate of rejection was 3% in those treated with standard INF compared to 14% in the PEG group [42]. Three of the 4 patients achieved SVR of whom two were listed for re-transplantation.

In our series of 172 LT recipients who underwent IFN based regimen for HCV recurrence, we observed histological evidence of CR on the liver biopsies performed during or after antiviral therapy in only seven (4%) patients, of whom three had achieved SVR [7]. Three of the seven patients were treated with standard IFN and the four remaining with PEG. None of these patients had experienced ACR during the course of antiviral therapy.

Similar to the observation in ACR, it appears that the clearance of the virus might be associated with CR. In the series by Berenguer et al., all cases of CR occurred after the patients had achieved SVR [42]. Similarly, in our series, CR was diagnosed after 12 (4–17) months of therapy when 70% of the patients had undetectable HCV RNA [7]. Similar to the report from Stanca et al. [46], a majority of patients developing CR in our series had been treated with INF based regimens for more than one year, thus raising the question of whether the length of antiviral therapy may have an impact as a risk factor on the development of CR. No significant decrease in calcineurin inhibitor levels was observed in association with CR [7]. Further studies with larger population are required to clarify the role of PEG regimen and the length of antiviral therapy in the development of CR.

CR is defined by histological evidence of atrophy and loss of both small bile ducts (Fig. 2) and small branches of the hepatic artery essentially in the portal tracts and perivenular regions [47]. The bile duct damage in CR appears to be caused by both, (a) direct immunologic attack and (b) indirectly via ischemic bile duct injury mediated by changes of the microvasculature (obliterative arteriopathy, small artery/arteriolar loss, and destruction of the peribiliary capillary plexus) [48].

CR is suspected when a cholestatic liver enzyme pattern develops during antiviral therapy and imaging has excluded large bile duct and/or hepatic artery changes as potential etiology of abnormal liver tests. The diagnosis requires a liver biopsy demonstrating small duct loss in the portal tracts (vanishing bile duct syndrome). The aforementioned vascular changes are usually not sampled in a percutaneous liver biopsy.

CR is histologically divided into early and late stages according to the Banff staging system [47]. The clinical implication of staging is that patients with early stage CR have lesions that are potentially reversible with increased immunosuppression and, therefore, may not require re-transplantation. However, in patients with late CR and no ongoing necroinflammatory activity, additional immunosuppressive therapy is unlikely to be beneficial and re-transplantation may be required.

Overall CR seems to be a relatively rare, but serious complication of interferon based therapy for HCV recurrence after liver transplantation. Thus, out of the seven patients developing CR in our series, three had achieved an SVR, two of the latter died from graft failure secondary to CR while awaiting liver re-transplantation. Moreover, the pathologic mechanisms involved and their link to IFN-based therapy remain ill understood.

De novo "autoimmune hepatitis" (AIH)

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease of unknown cause. Multiple factors are felt to play a role in its pathogenesis. Thus, it is thought that, on a predisposing genetic background (HLA DR3 and DR4), environmental, pharmacological or infectious agents may trigger the condition. The diagnosis is based on a scoring system proposed by a group of experts and recently simplified to criteria [49]. Among patients transplanted for autoimmune related end-stage liver disease, recurrent disease occurs infrequently in the early post-transplant period but may become an issue with prolonged follow-up, with an incidence in adults ranging from 8% at 1 year to 60% after

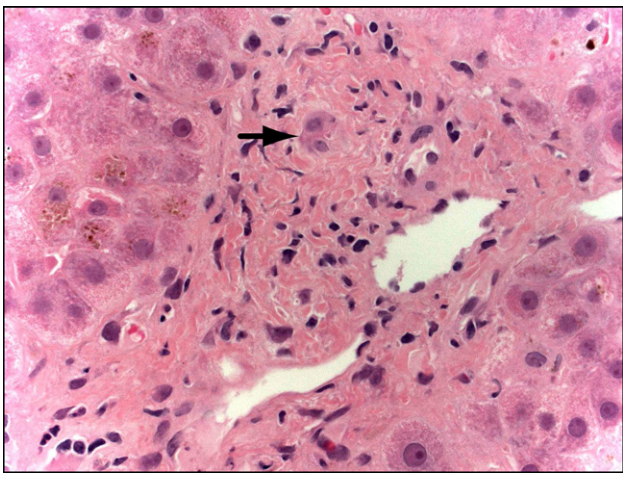

Fig. 2. Chronic rejection. Portal tract with a markedly atrophic bile duct (arrow). The duct epithelial cells show senescent changes. Their epithelium is attenuated, more eosinophilic and their nuclei are unevenly spaced. There is no ductular reaction at the periphery of the portal tract (hematoxylin and eosin, magnification 400×).

5 years of follow-up. The risk is higher in children. While no specific immunosuppression has been linked to a higher risk of recurrence, most studies have emphasized the hazards of discontinuing immunosuppression, particularly steroids. Its reintroduction is frequently accompanied by an improvement in liver function tests, generally but not always associated with histologic resolution.

Idiopathic hepatitis with histological characteristics of AIH, namely the presence of a plasma-cell rich centrilobular infiltrate on liver biopsy [50,51] (Fig. 3), have been described in patients undergoing liver transplantation for indications other than AIH [51–55] particularly in the pediatric transplanted population. In this setting, rejection and steroid dependence are risk factors associated with this complication. This has been termed *de novo* AIH, AIH-like recurrence, graft dysfunction mimicking AIH, or plasma cell hepatitis. It remains controversial though whether these cases represent a true AI (alloimmune) process, as opposed to an atypical manifestation of recurrent disease or of acute or chronic allograft rejection [50,52,56,57]. Due to the heterogeneity of patient populations studied, the histological features described, and the small number of patients included in different series, these and many questions remain currently unresolved.

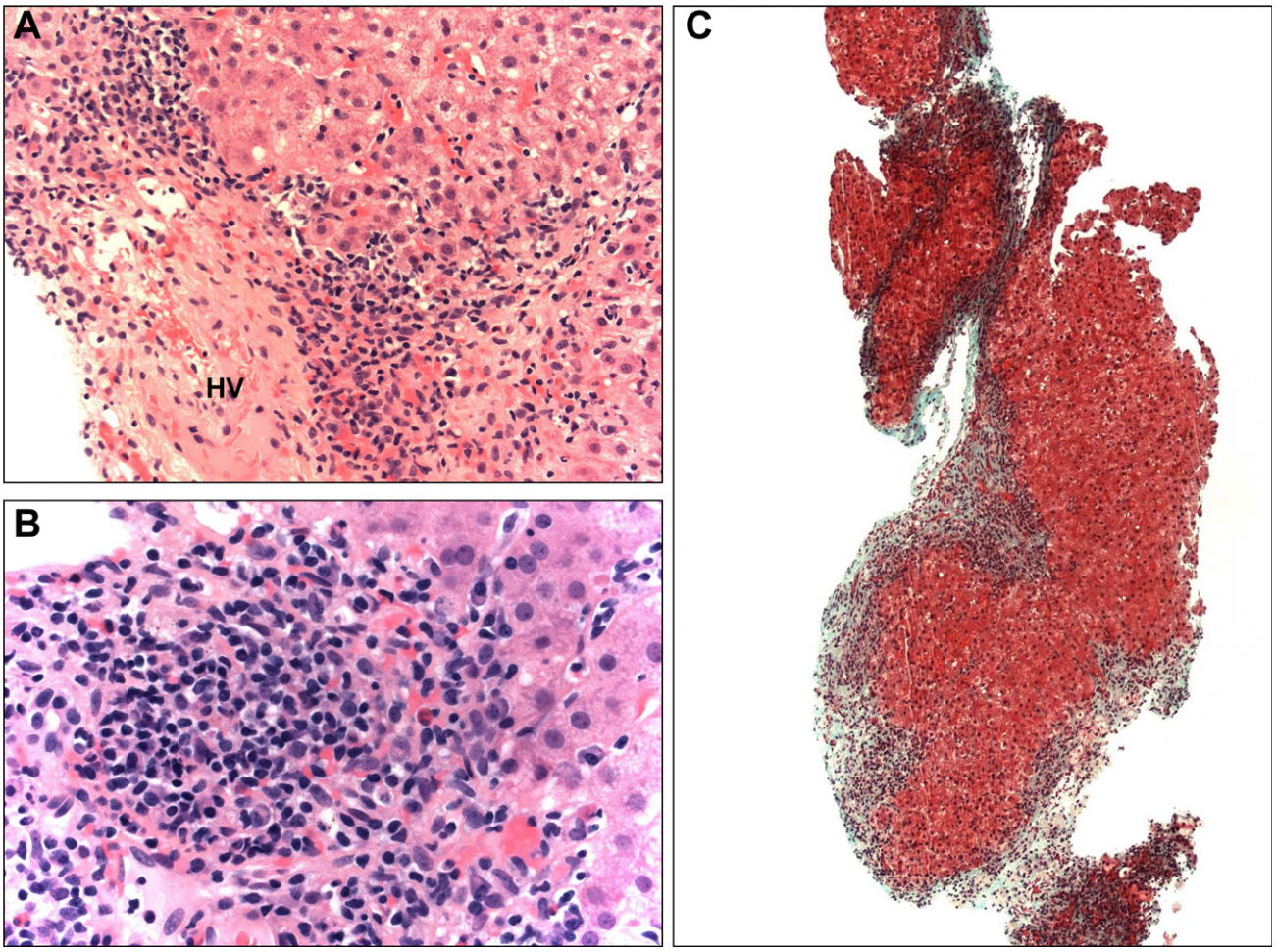

Fig. 3. *De novo* AIH hepatitis/plasma-cell rich hepatitis post HCV treatment with HCV RNA clearance. (A) Perivenular inflammation in zone 3 (hematoxylin and eosin, magnification 100×). (B) Portal tract with lymphoplasmacytic infiltrate and mild interface activity (arrow) (hematoxylin and eosin, magnification 400×). (C) Repeat biopsy showing advanced fibrosis with rounded parenchyma contours surrounded by curved septa (green) (Masson trichrome, magnification 25×). HV, hepatic vein.

Interestingly, an increasing number of such cases with AIH like features have been reported in recent years in transplant recipients infected with HCV [56,58]. This includes several cases in which AIH like features developed in the setting of antiviral therapy for recurrent HCV infection [58]. The implications are important because of the potential risks associated with increased immunosuppression in HCV-infected recipients [59,60]. Indeed, while the addition of corticosteroids may reduce the severity of liver inflammation in these patients, it occurs at the expense of enhanced viral replication, potentially resulting in progressive HCV-related fibrosis and impaired viral clearance with antiviral therapy [60,61].

The diagnosis is challenging and requires the exclusion of alternative aetiologies of allograft dysfunction, including recurrent disease, rejection, biliary complications, and acquired viral infections, together with a clinical presentation resembling classic AIH, with a particular emphasis on histological features of AIH, such as centrilobular necrosis with or without bridging necrosis and a prominent plasma-cell rich infiltrate (Fig. 3). This pattern of immune mediated hepatitis is different from that usually seen in recurrent HCV (Fig. 4). Rapid response to corticosteroids remains an important diagnostic tool [55].

Fiel et al. reported one of the largest studies to date describing 38 HCV-positive liver transplanted recipients with histological changes compatible with autoimmunity in a post-transplant liver biopsy performed a mean of 17 (3.6–173.4) months after transplantation [62]. About half of the patients had a history of ACR. In this series, the histological changes compatible with autoimmunity were more frequently observed in association with a recent lowering of maintenance immunosuppression (47% of cases), or subtherapeutic calcineurin inhibitor levels (35%). This might suggest the presence of a variant form of ACR, rather than a true *de novo* AIH [62]. Rapid resolution of the histological changes (as early as one month) following therapy (see below), and low titers of auto-antibodies (<1/160) in the majority of the patients are additional arguments against the diagnosis of true *de novo* AIH [62].

A small number of patients in Fiel's series were treated. In those who received specific therapy, treatment was variable, consisting in either the addition of azathioprine, mycophenolate mofetil, prednisone, and/or an increase of the calcineurin inhibitor. The fact that steroid therapy was associated with worse results than with the optimized calcineurin inhibitor dose seems to imply that steroid therapy may have improved autoimmune features, but may ultimately have led to a more severe recurrence of HCV.

Fiel et al. [62] argued that the development of a plasma-cell rich infiltrate in HCV patients post liver transplantation is a variant of rejection rather than AIH based on the following: (i) the early occurrence of the histological features post liver transplantation,;(ii) previous episodes of ACR; (iii) a rapid resolution of plasma cell infiltrate with increased immunosuppressive treatment in some patients, (iv) absence or low titers of auto-antibodies; and (v) suboptimal immunosuppressive levels or recent lowering of the immuosuppression in many patients. Interestingly, the fact that an increasing number of such cases were reported in recent years may be due to the recent trend of more aggressively weaning immunosuppression in patients transplanted for HCV.

In another study by Khettry et al., 10% of HCV patients developed histological "AIH like" features with moderate to severe portal, periportal, and lobular necroinflammation and prominent plasma cells [63]. Serologic evidence of autoimmunity, with

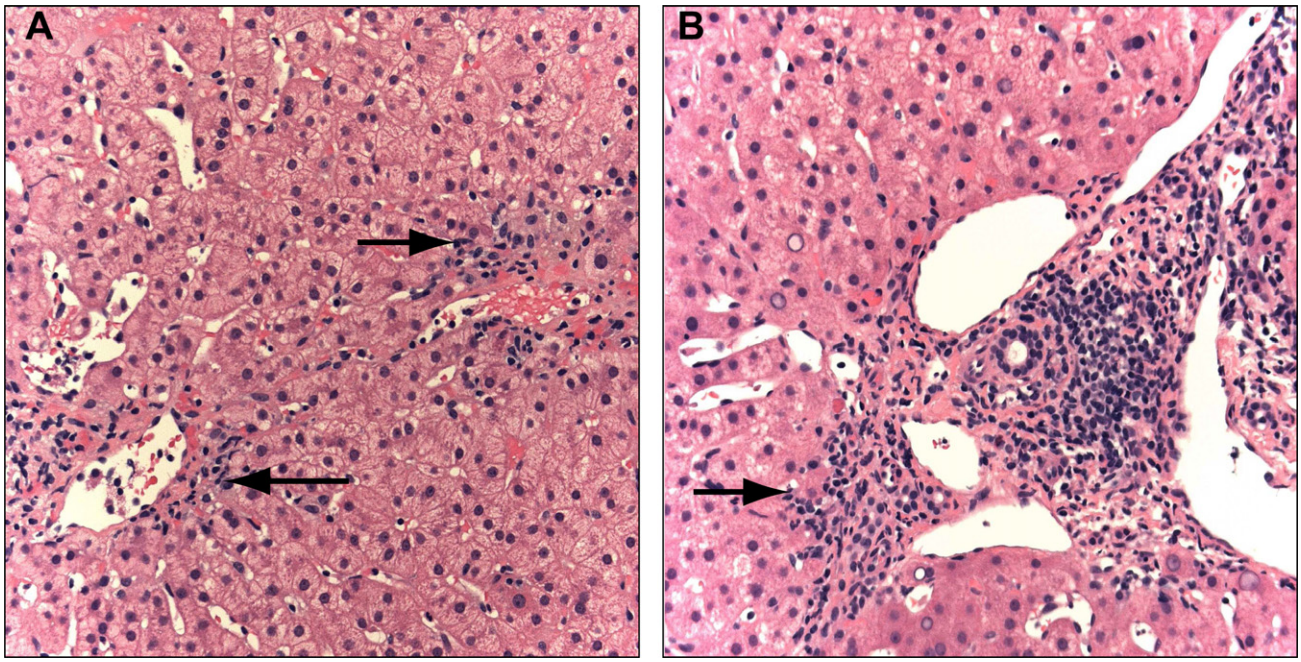

Fig. 4. Recurrent hepatitis C with involving zone 3 in the same patient depicted in Fig. 3 prior to HCV clearance. (A) mild necroinflammation in zone 3 (arrows) around the hepatic vein (hematoxylin and eosin, magnification 100×). (B) Portal area of same biopsy showing lymphoid infiltrate with a small amount of focal interface activity (arrow) (hematoxylin and eosin, magnification 100×).

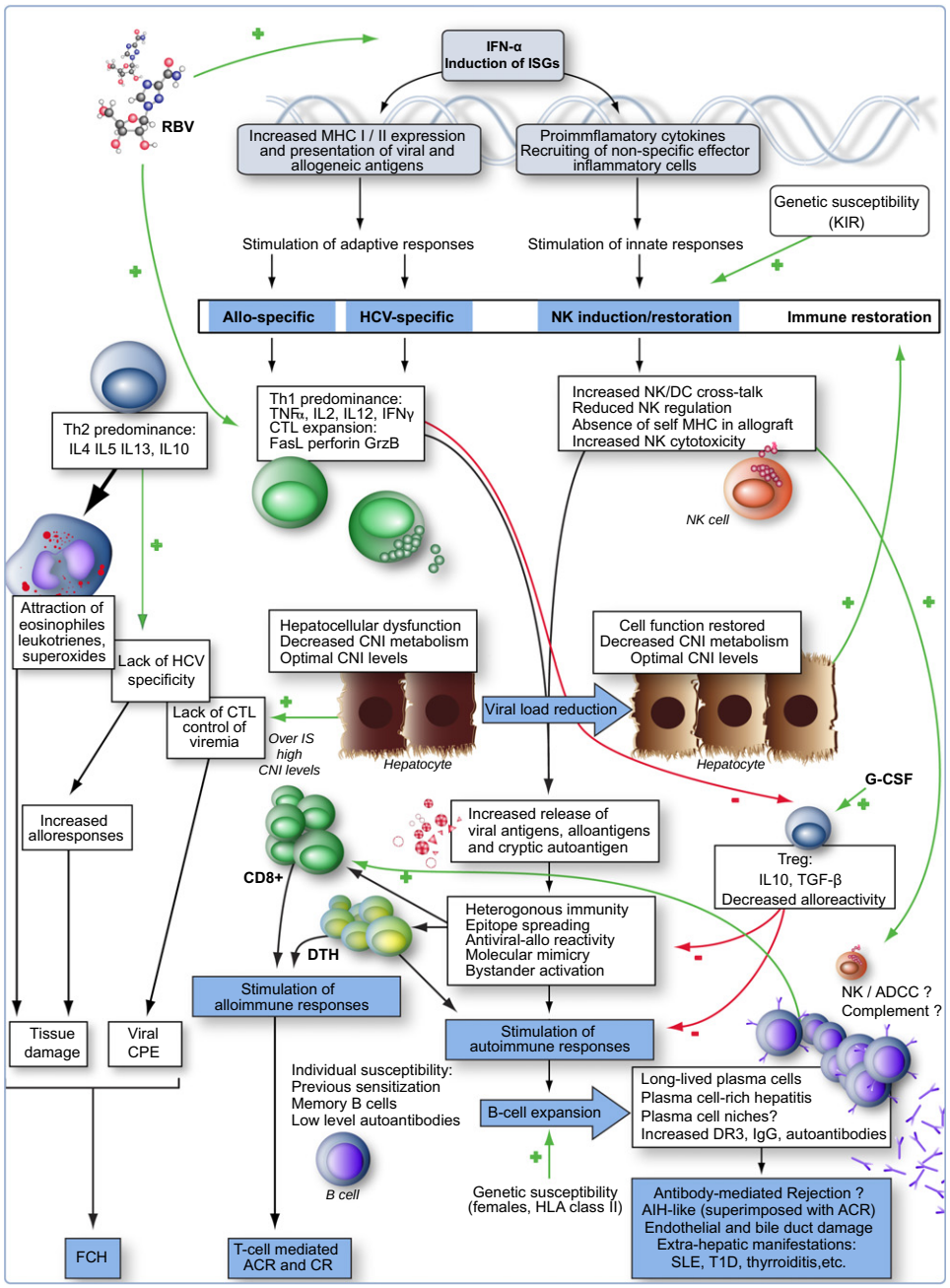

Fig. 5. Possible mechanistic pathways for immune mediated complications in interferon-treated HCV positive liver transplant recipients. Interferon alpha (IFNα) activates a large number of interferon stimulated genes (ISGs), which combined with the upregulation of MHC antigen expression results in increased antigen presentation, T-cell activation and dominance of a Th1 response including release of TNF α, IL2, IL12, IFNγ, FasL, perforin and GrzB activities, and decrease on IL10 and Treg activity, collectively leading to tissue damage and inflammation. Similarly ribavirin (RBV) also potentiates ISGs expression and skewing toward TH response. IFNα also enhances recruitment and activity of other non-specific cell types such as natural killer (NK) cells, macrophages, neutophiles, and monocytes. Stimulated virus-specific T-cells and NK cells may also lyse allogeneic graft cells, by allo-recognition or lack of self-MHC, respectively. An increased cytolitic activity by NK cells and T-cells may potentially increase the antigen release, both viral, self (cryptic) and allogeneic, which in turn can trigger proliferation of memory T-cell subsets previously sensitized to viral, and alloantigens. While expansions of T-cell clones directed to viral antigens contribute to viral load reduction and clearance, expansions of T-cell clones to alloantigens may trigger autoimmunity. The mechanism underlying the enhancement of autoimmune responses by IFNα may be amplified in predisposed individuals. Previous B-cell sensitization (even without detectable auto-antibodies prior to transplantation) and genetic susceptibility (female gender and certain HLA phenotypes) may be risk factors for IFNα-mediated autoimmunty in HCV patients. Potentially, the increased Ag release induced by IFNα may induce expansion of B-cell clones sensitized to allo- and auto-antigens that can even lead to accumulation of long-lived plasma cells niches inside the allograft, which in turn produce an elevation of IgG, auto-antibodies, and consequently, antibody-mediated autoimmune disease including extra-hepatic manifestations. The abundance of auto and allo-antibodies could potentially lead to antibody-mediated rejection mechanisms through NK/ADCC and complement pathways. Lastly, activated B cells may also amplify T-cell responses, potentially explaining the superimposition of autoimmune-like hepatitis with acute/chronic cellular rejection.

either auto-antibodies and/or hypergammaglobulinemia, was present in 66% of these patients.

In the Fiel and the Khettry studies, the outcome of patients with plasma-cell rich AIH like features was poor, more than 60% dying from graft failure and portal hypertension.

Ward et al. compared the outcome of 40 HCV-positive liver transplant recipients with plasma cell hepatitis (PCH) and that of a control group of HCV recipients who did not develop PCH ($n = 80$) [64]. Both groups were matched for their year of transplantation and the availability of biopsy material. PCH patients were more likely to be female compared to controls (ratio male/female in the PCH cases 24:16 vs 71:9 in controls). In addition, PCH patients had worse outcomes than controls (65% vs 40%; $p < 0.01$), including increased mortality (50% vs. 30%, $p < 0.05$). Kaplan–Meier survival analysis showed significantly worse survival for PCH patients from 4 to 10 years post LT ($p < 0.05$). Explants from 40% of PCH patients had a score of 3 (plasma cells composing >30% of the infiltrate) compared to 18% of control patients [64]. Interestingly, in the study by Khettry et al. [63], plasmacytic periseptitis on the explant was also more frequently observed in patients with post-transplant AI-like hepatitis (89% of the AIH compared to only 31% that either developed typical recurrent HCV or showed no evidence of HCV recurrence). These data suggest that HCV recipients with significant plasma cell infiltrates in their native livers may have an immunological predisposition to also develop AIH like features in the allograft.

An AI-like hepatitis has also been reported in liver transplant recipients treated with PEG and RBV for recurrent hepatitis C [56,58,65]. In general, these patients have no history of AI disease, and HCV RNA is undetectable at the time of the secondary rise in liver enzymes. The latter renders the hypothesis that the liver allograft damage in these treated patients is truly related to autoimmunity as opposed to HCV *per se*, more convincing. The clinical presentation, including the pattern of aminotransferase elevation, IgG rise, detectable smooth-muscle antibody, typical histological features of AIH, and response to therapy (steroids and azathioprine) is consistent with the diagnosis of post-transplantation immune mediated hepatitis. In fact, in most cases, the application of the International Diagnostic Criteria for Autoimmune Hepatitis gives scores consistent with probable or definite AIH. Interestingly, the AIH score was generally negative in these patients prior to antiviral therapy (Table 1).

Berardi et al. [65] reported the largest series of such patients to date, describing 9 of 44 HCV-positive liver allograft recipients who developed AI-like hepatitis following at least 6 months of treatment with PEG and RBV. These patients developed significant graft dysfunction and hepatitis despite clearance of HCV RNA in all but 1 case. Three patients developed other definite autoimmune disorders including overlapping anti-mitochondrial antibody-positive cholangitis, autoimmune thyroiditis and systemic lupus erythematosus, respectively. Withdrawal of antiviral treatment and introduction of steroids resulted in remission in 5 patients and graft failure and death in two others. The authors concluded that IFN therapy may have induced this AIH [65]. However, atypical rejection remains a potential cause since some of the patients had histological evidence of ductopenia suggestive of CR. Indeed IFN induced CR is a well recognized risk factor for graft failure (see above).

In the aforementioned study by Fiel, 14 patients (37%) were receiving IFN therapy at the time of the diagnosis of PCH with 4/14 having undetectable HCV RNA [62]. An important observation in this study was the lack of association between antiviral therapy for HCV recurrence and the development of the histological changes, its resolution, or clinical outcome.

HCV itself has been shown in the immune competent patient to be independently associated with a high incidence of autoimmune diseases, such as cryoglobulinemia, Sjogren like syndrome or immune mediated thyroidits, and auto-antibodies, such as ANA and LKM-1 are frequently detected in HCV-positive patients [7,9,13,23]. Isolated cases of HCV-associated mixed cryoglobulinemia have been reported in the liver transplant population. In one study, mixed cryoglobulinemia was found in approximately 20% of the HCV-positive liver transplant recipients compared to none in the HCV-negative group. Only half of the patients with detectable cryoglobulins in the serum had pathological manifestations of cryoglobulinemia [66]. IFN and ribavirin therapies have both been used in combination and as monotherapy to treat the exacerbation or reappearance of HCV-associated cryoglobulinemia after liver transplantation with variable results [67].

In the non-transplant HCV patients, recognition of AIH like features is based on the presence of significant plasma cells in the biopsy and aggressive interface activity. Furthermore, the AIH pattern in HCV patients has been associated with higher serum levels of gamma-globulin and immunoglobulin G, a higher frequency of human leukocyte antigen DR3 and high titers of anti-smooth muscle antibodies in serum which suggests that in some patients with a genetic susceptibility to autoimmune phenomena HCV infection triggers autoimmune processes in the liver that contribute to tissue damage. In addition, IFN and RBV exert a variety of immune modulatory effects that may further trigger autoimmune phenomena [68–71]. Thus, IFN inhibits T-suppressor-cell function, induces natural killer cells and cytotoxic T lymphocytes, stimulates major histocompatibility complex class 1 antigen expression, and polarizes the adaptive immune response to Th1, which is likely an important factor in IFN-induced autoimmunity. The combination of HCV infection and IFN therapy may have a synergistic effect in triggering autoimmunity. Since most cases occur once HCV RNA has become negative, one potential hypothesis is that a vigorous immune response promoting virus clearance also favors tissue damage with subsequent cryptic antigen release in a context of interferon-induced major histocomaptibilty complex (MHC) up regulation (Fig. 5).

None of the risk factors evaluated in the published reports, including gender, immunosuppression, the use of RBV, and/or the presence of auto-antibodies were found to be associated with the development of the AI phenomena during antiviral therapy. Interestingly, Lodato et al. reported a potential protective role of granulocyte colony stimulating factor (G-CSF) [72]. In this study, *de novo* AIH occurred in 9/45 of the non-GCSF group vs 0/23 in the GCSF group ($p < 0.03$). The immunomodulatory effect of G-CSF on human $CD4^+$ T cells, with skewing T-cell differentiation toward the Th2 phenotype, and subsequent suppression of T cell alloreactivity may, in part, explain this association [72]. However, this potentially beneficial GCSF effect needs to be confirmed by others and validated in well-designed prospective studies.

Although infrequently, there have been cases of AIH, including some with fulminant presentation [73], triggered by interferon-ribavirin treatment in the non-transplant setting [71].

Unresolved question

Apart from the many unresolved questions already mentioned above, the most challenging clinical problem, perhaps, is how to distinguish AIH from ACR, and both from recurrent HCV, in the presence and absence of IFN-based antiviral therapy. It has been suggested that ACR should be diagnosed when the immune response is directed primarily at an antigen unique to the allograft liver, while AIH in contrast should be diagnosed when tissue damage is mediated by memory cells in the recipients [74]. However in daily practice distinguishing the two diagnoses remains based on surrogate markers. The proportion of plasma cells in the infiltrate is currently used as an important marker together with the presence of bile duct damage and the severity of the interface activity. Rejection-related infiltrates usually contain less than 30% plasma cells; the majority of bile ducts exhibit lymphocytic damage with mild interface activity [51]. Interface activity is more severe in AIH with less bile duct damage with a higher proportion of plasma cells than in ACR [51]. These criteria need to be validated prospectively for their reproducibility.

Another unresolved issue is the significance of central perivenulitis (CPV) in HCV recipients. CPV described as zone 3 inflammation surrounding the hepatic vein with or without associated necrosis is a distinct immune mediated histopathologic process occurring in the liver allograft for which several etiologies including ACR, CR, AIH, or recurrence of chronic HCV have been postulated [75].

When occurring within the first weeks post liver transplantation, CPV presents characteristic features of perivenular inflammation in association with characteristic portal tract changes of acute rejection [51]. More frequently, features of isolated CPV are seen in patients presenting with graft dysfunction several months or more following transplantation [75]. In this 'late CPV' cases, hepatic venous endothelial inflammation is rarely present and portal tract inflammation is variable in severity and composition and often lacks the typical features seen in early ACR [75]. Late CPV is often associated with long term graft injury, including CR and *de novo* AIH [76]. Therefore, it may be warranted to consider CPV presenting at anytime point post liver transplantation as a form of cellular rejection [76]. Should this, indeed, hold true, treatment with increased immunosupression may be indicated even in the context of recurrent HCV, as it may prevent the morbidity due to late graft failure and progressive parenchymal injury leading to significant fibrosis (Fig. 3C). This clearly requires more data, ideally from prospective controlled trials.

In conclusion, both immune-mediated complications associated with IFN-based therapy in HCV-infected liver transplant recipients, including AIH-like hepatitis and acute or chronic rejection; tend to occur in the context of a strong anti-HCV immune response with relatively low or undetectable viremia. To differentiate these entities in clinical practice currently relies largely on histopathology and, to a lesser extent, on autoimmune serological markers. A better understanding of the underlying cellular pathomechanisms will be required to develop diagnostic markers with improved accuracy, as well as more specific strategies for prevention and treatment.

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Key Points

- Immune-mediated complications related to the use of interferon and ribavirin in HCV-infected liver transplant recipients include acute and chronic rejection as well as de novo "autoimmune" hepatitis.
- Acute and chronic rejections are infrequent complications of antiviral therapy often associated with concomitant low or negative serum HCV RNA.
- *De novo* autoimmune hepatitis also termed autoimmune hepatitis-like recurrence, graft dysfunction mimicking AIH or plasma cell hepatitis has been described in patients undergoing liver transplantation for reasons unrelated to autoimmunity. In HCV infected patients, it remains controversial whether these cases represent a true autoimmune (alloimmune) process, as opposed to an atypical manifestation of recurrent disease or of acute or chronic allograft rejection.
- Histologic findings are an essential part in the differential diagnosis between these entities. Any flare in liver enzymes in patients treated with antiviral, particularly in those with undetectable HCV RNA, should raise the suspicion of these complications and warrant the performance of a liver biopsy.

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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