

Medical Writers' Circle

a series of articles

written by medical
professionals about
the management
and treatment of

Hepatitis C

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Hepatitis C and Liver Transplantation

End-stage liver disease (cirrhosis) due to chronic hepatitis C viral (HCV) infection has become the leading indication for liver transplantation (LTx) in the United States. Unfortunately, LTx does not cure HCV, a common misconception. Instead, recurrent HCV infection of the new liver occurs in almost all instances and some form of liver damage is noted histologically (seen under the microscope in a liver biopsy specimen) in the vast majority of cases.

Furthermore, the natural history of recurrent HCV following LTx appears to be significantly accelerated compared to that in non-LTx cases. Rather than the 20% figure quoted for non-LTx cases who may develop cirrhosis after 20-30 years, anywhere from 10 to 30% of LTx recipients with recurrent HCV have advanced fibrosis (scarring) or full-blown cirrhosis within only 5 years. Another problem is that, once cirrhosis develops post-LTx, complications occur more rapidly than in non-LTx cases. If another LTx is required, the outcome is usually not as favorable and some liver transplant centers refuse to offer a second LTx on this account.

In some instances, a particularly aggressive form of recurrent HCV develops within only a few months post-LTx and this condition has been labelled "fibrosing cholestatic hepatitis" (FCH). It also occurs in some cases of

recurrent hepatitis B post-LTx where it was first described. FCH is characterized by progressive jaundice (yellowing of the skin and whites of the eyes) with a rapid decline in liver function leading to liver failure, most often associated with markedly elevated viral levels detected in the bloodstream (more than 20 times pre-LTx levels) and in the liver tissue as well. In these cases, the virus itself appears to be the major cause of liver damage (cytopathic), whereas in most other cases of recurrent HCV post-LTx (as discussed below) the liver damage is thought to be immunologically related, due to "innocent bystander" injury to the liver cells as the immune cells try to kill off the virus, albeit unsuccessfully. In FCH, loss of the new liver is common within 3-6 months post-LTx and retransplantation is invariably a failure. The aggressive nature of FCH suggests that these cases may be infected with a more virulent form of HCV which in some way contributes to the poor outcome, perhaps aggravated by the use of higher doses of immunosuppression early following LTx. Fortunately, this type of recurrent HCV is uncommon.

On the other hand, a sizeable number (30-50%) of patients with recurrent HCV post-LTx follow a more indolent course with moderately high viral levels (10-20 times pre-LTx levels) but minimal damage histologically despite a slow but significant progression to

cirrhosis after 10-15 years. The ability to predict how a given patient with recurrent HCV will do post-LTx remains an intense area of research since it might then differentiate between patients who need anti-HCV treatment versus those who do not, thereby reducing side effects and costs. Certain factors have been identified as being important. These include: viral levels in the bloodstream pre-LTx or early post-LTx, viral genotype, age of the liver donor, degree of immunosuppression post-LTx, timing of the HCV recurrence post-LTx, early histologic findings post-LTx, and failure to respond to interferon-based therapies prior to LTx. More often than not, however, these are too variable to help in predicting the outcome in a particular individual.

The events associated with HCV infection of the new liver post-LTx are now becoming clearer. One recent study assessed viral levels in the bloodstream (via serial sampling and mathematical time-plots called "kinetics") during and shortly after LTx. The investigators found that for a brief period after the old liver is removed, HCV is not detectable, and infection of the new liver occurs quite early, in fact at the time of reperfusion (restoration of blood flow by the surgeons) during the final stages of the LTx operation itself. In general, pre-LTx viral levels are reached within 4 days post-LTx and continue to rise until 1-4 months when they reach

10-20 times the pre-LTx levels. At that point, viral levels begin to fall somewhat (as discussed below) but they remain significantly higher than those prior to the LTx, except in cases of FCH where the levels continue to rise inexorably. In the majority of patients with recurrent HCV post-LTx who don't

In most cases of chronic hepatitis, liver enzymes (along with viral levels) remain stable although elevated during the ensuing months or even years, and serial liver biopsies show some degree of damage albeit mild. The risk of developing fibrosis and/or cirrhosis is unpredictable, but

the common practice of rapidly tapering and stopping corticosteroids soon after LTx in the hope that this will ameliorate viral replication and, indirectly, the liver damage thought to be triggered by it. The use of induction (prior to LTx) immune therapies to reduce the need for immunosuppression

have led to sustained virologic response (cure) rates of around 25% post-LTx compared to 40% in ideal non-cirrhotic pre-LTx patients. The recent introduction of the longer-acting pegylated interferons (PEG-IFN) and RBV should help improve sustained virologic response rates to 40% or more. Studies are currently underway to address this. Nevertheless, when best to intervene with anti-HCV treatment remains uncertain. Some experts treat "pre-emptively"—before significant HCV recurrence post-LTx. On the other hand, most authorities recommend waiting first for histologic damage to occur with evidence of chronic hepatitis and/or progression in fibrosis before committing the patient to potentially toxic anti-HCV treatment.

In summary, recurrent HCV post-LTx is becoming an all-to-common problem. Fortunately, most patients do reasonably well although 10-30% develop cirrhosis after 5 years or more. Very few have the more aggressive form of FCH related to markedly elevated viral levels. Intense research should soon shine a light upon the events that occur in the new liver during viral infection and the immune response to it, in order to develop more effective treatment protocols once recurrent infection has occurred and, ultimately, strategies to prevent reinfection of the new liver to begin with.

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The risk of developing fibrosis and/or cirrhosis is unpredictable, but tends to be infrequent (10-30%, depending on the transplant center).

develop FCH, liver enzymes remain close to normal or minimally elevated (unless rejection of the liver occurs, which must be confirmed by a liver biopsy and treated appropriately), despite relatively high sustained viral levels in the bloodstream and liver.

Then, around 1-4 months post-LTx, there is often a marked rise in liver enzymes during the phase of "acute" hepatitis, which is confirmed histologically (and usually distinct from acute rejection). Of note, viral levels in the bloodstream start to fall at this time. This is thought to be due to the body's immune response to the virus, although considerably blunted due to the immunosuppressants the patient is on in order to prevent rejection. If immunosuppression has been particularly strong (due to prior episodes of rejection), especially with single or repeated doses of corticosteroids or OKT3 (a potent immunomodulator), viral replication can be quite high (no counteracting effect of the immune system) and the patient is then at significant risk to develop FCH. Fortunately, in most other cases, viral levels fall at this point as do liver enzymes, and the patient enters the phase of "chronic" hepatitis, usually starting around 6 months post-LTx and continuing indefinitely.

tends to be infrequent (10-30%, depending on the transplant center). Viral levels tend to fall steadily depending on the degree to which the immune response is restored in any given patient post-LTx, in conjunction with the common practice nowadays to taper and stop corticosteroids at this time (i.e., 6 months post-LTx). However, in a sizeable number of cases, the immune "reconstitution" associated with tapering immunosuppression may paradoxically worsen liver damage, leading instead to a more rapid progression to cirrhosis, as the immune cells try to rid the body of HCV but indirectly damage the liver cells as "innocent bystanders." The higher viral levels that persist post-LTx likely play a major role, as perhaps does the alloimmune (organ rejection) response. Certain genetic factors such as cytokine (intercellular mediator) response (e.g., TNF- α), liver steatosis (fat), and body mass index (as measure of excess total body fat) may also contribute.

Of interest, the degree of liver damage associated with recurrent HCV post-LTx appears to be worse now (since 1995 or 1996) than it was a decade or so ago. The reason(s) for this remain uncertain but may relate to the use of more potent immunosuppressants nowadays and also to

post-LTx may be beneficial although as yet unproven. In terms of specific immunosuppressants used post-LTx, tacrolimus and cyclosporine do not seem to differ appreciably in their effects on viral replication or post-LTx outcomes. Another newer immunosuppressant, mycophenylate mofetil, showed some promise as an anti-HCV agent itself in preliminary studies but this has not panned out. In fact, a recent study showed that when this drug was used in conjunction with induction therapy such as anti-interleukin-2 receptor antibody, it was found to be deleterious.

In terms of anti-HCV treatment, ideally it would be best to clear the body of HCV prior to the LTx in order to minimize the risk associated with recurrence. Unfortunately, it is usually quite difficult to treat patients awaiting LTx due to the low blood counts seen in these cases due to the large spleen (from congestion related to the liver cirrhosis) that affects these counts. Post-LTx, the situation is also not ideal since anti-HCV treatment is not well tolerated for a variety of reasons. The use of growth factors such as G-CSF (white cell booster) and epoietin (red blood cell booster) to increase cell counts is helpful. Overall, post-LTx, standard interferon (IFN) and ribavirin (RBV) together