

New therapies against HCV: Expected risks and challenges associated with their use in the liver transplant setting

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Current approaches to HCV therapy in the liver transplant setting

Current approaches to anti-viral therapy (AVT) in the setting of liver transplantation are based on the use of pegylated interferon in combination with ribavirin (PegIFN/RBV). Attempts to clear HCV pretransplant have been successful in about 15–20% of the patients with genotype 1 infection and about 20–35% with genotype 3 [1,2]. Such patients usually have relatively lower MELD scores (<18) than many other patients listed for transplant. Despite this AVT is associated with an increased risk of serious bacterial infections [3]. Sustained viral response (SVR) pretransplant is associated with lack of viral recurrence post-transplant [1,2]. Early post-transplant AVT is not thought to be useful due to lack of efficacy and poor tolerability [4,5]. The commencement of AVT is usually considered at about the 12-month mark based on protocol biopsies. Patients with either F2 or F1 with significant portal inflammation (stage \geq to 2) are usually considered for AVT6–8. SVRs in the range of 20–30% for patients with HCV genotype 1 (G1) and 40–50% for patients with HCV G3 are obtained [6–8]. SVR post-transplant has been linked to both donor and recipient *IL28* polymorphisms [9–11]. Achievement of SVR in the post-transplant setting is associated with improved survival compared to patients who do not achieve an SVR [6–8].

Given the importance of viral clearance in the pre and post-transplant setting, such results have been thought to be somewhat unsatisfactory and the liver transplant community has been eagerly awaiting new anti-HCV therapies.

A brief summary of the new HCV therapies

Perhaps it is best to consider the new AVTs as first, second, and third “wave” therapies (Table 1). These new AVTs include direct antiviral agents (DAAs). The first DAA wave consists of therapy with the NS3/4A protease inhibitors (P.Is) boceprevir or telaprevir added to pegylated interferon and ribavirin [12–15]. National registration bodies have recently approved these new agents. They are administered 3 times per day and are aimed against

HCV G1. Added toxicities are considerable [12–15]. SVRs are increased from 45–50% to 60–70% for treatment naïve patients.

The second wave consists of replacing boceprevir and telaprevir with second generation NS3/4A protease, HCV polymerase or NS5a inhibitors (summarized in [16]). These agents can be given daily, sometimes have additional genotype specificity but may also still have significant side effect profiles [17–33]. The next generation protease inhibitors in combination with PegIFN/RBV generally seem to have similar efficacy to the first wave new AVT [17,18,22,24,26,28] although results with polymerase and NS5a inhibitors (plus PegIFN/RBV) have increased SVRs up to 90% [19,21,23,25,26,29–31]. There is preliminary data that combinations of DAAs and PegIFN/RBV (so called quadruple therapy) may have very high SVRs (>95%) [20,27,28,32].

Despite some enthusiasm for the best of the second wave therapies, the third “wave” is likely to be the most significant and certainly the most exciting. This wave aims to replace interferon altogether. The regimes use DAAs in combination without interferon but sometimes with ribavirin e.g., a HCV NS5A polymerase inhibitor combined with second (or third generation) NS3/4 protease inhibitors or an NS5A inhibitor [31–36]. One exciting regime just used a nucleoside polymerase inhibitor plus ribavirin [33]. This resulted in SVRs of 90–100% in treatment naïve G2/3 patients requiring only 3 months of therapy with no recorded toxicity. However, the same regime applied to genotype 1 patients who were previously null responders to PegIFN/RBV, however, it seems disappointing with significant relapse rates [34]. An alternative regime of an NS5A inhibitor plus a polymerase inhibitor, given for only 3 months led to an SVR of 90% in patients with HCV G1b who had previously been null responders to interferon [35]. It is generally thought that G1b is more sensitive to the DAAs and is associated with an enhanced resistance barrier. It is unclear whether ribavirin will remain an important agent in these new treatment regimens [20,28,37].

In summary, these “third wave” regimes are aimed to be non-genotype specific, taken once per day, have limited toxicities and taken for a short duration (as short as 3 months). As mentioned, SVR is expected to be in 90% range. It should be noted, however, that many of these studies are at the proof of concept stage and have only been reported in small numbers of patients. Furthermore, these agents have not yet been used in patients with advanced liver disease and portal hypertension (see Table 2).

Currently, there is no data on any of these first, second or third “wave” AVT regimes in the setting of liver transplantation. Thus,

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Table 1. The three “waves” of direct antiviral agents for HCV infection.*

| Wave | Predicted dates in practice | Regimen | Genotype | Therapy duration (mo) | SVR (%) | Side effects |
|------|-----------------------------|---------------------------|----------|-----------------------|---------|--------------|
| 1st | 2011-2014 | B + P + R* | 1 | 6-12 | 65-70 | ++ |
| | | T + P + R ^o | 1 | 6-12 | 65-70 | ++ |
| 2nd | 2013-2015 | P.I + P + R | 1 | 6 | 65-80 | ± → + |
| | | Pol.I + P + R | pan | 6 | 60-90 | ± → + |
| | | P.I/Pol.I + NS5AI + P + R | pan | 6 | 90 | ± → + |
| 3rd | 2014- | Pol.I + R | pan | 3-6 | 90 | ± |
| | | Pol.I + P.I ± R | pan | 3-6 | 90 | ± |
| | | NS5AI + P.I + Pol.I | pan | 3-6 | 90 | ± |

*Treatment naïve patients.

^aRibavirin; B, boceprevir.

^oT, telaprevir.

Pi, protease inhibitors; Pol I, polymerase inhibitor; NS5AI, NS5A inhibitor.

Table 2. Some issues beyond “proof of concept studies for” interferon-free therapies.

| |
|--|
| • SVRs in non-G2/G3, non-1b patients |
| • Genotype specificity |
| • Duration of therapy in non-G2/G3, non-1b patients |
| • Duration of therapy in transplant patients (pre and post) |
| • Side effect profile in cirrhotic patients with portal hypertension |
| • SVRs in cirrhotic patients with portal hypertension |

the following discussion is largely speculative and deductive. It will be interesting to come back in the years ahead as new data arise. Hopefully the comments below will have some relevance but that cannot be guaranteed!

Use of the new therapies pretransplant (Table 3)

Triple therapy with either telaprevir or boceprevir

The first issue is that these agents are only aimed at HCV G1. The second issue is that many of these patients will already have failed PegIFN-based AVT. Thus, it will remain important (as now) to classify patients into those who have previously relapsed versus those who have been non-responders. Patients without cirrhosis who have relapsed may have up to an 85% SVR to these new regimens whilst non-responders may be as low as 30% [13,14]. However, previously interferon-treated patients with well-compensated cirrhosis and significant portal hypertension

are likely to have much lower SVRs. There is evidence that *IL28* polymorphism testing still has a role in treating patients with telaprevir or boceprevir [38]. Perhaps this will be even more important in treating patients with advanced disease in order to maximize SVRs.

The third issue is: what is the expected SVR in naïve subjects with cirrhosis and portal hypertension being treated with these agents? Although it is tempting to use these agents (given the increased SVR) it is not clear what that SVR will be. If we assume a 50% improvement on the current 15–20% SVR in patients with genotype 1 infection then the likely SVR will still only be in the vicinity of 20–30%. That assumes that the treatment withdrawal rate will be the same as the current standard of care therapies. However, that is unlikely.

The fourth issue is the likely increased side effect profile when treating such patients. A recent study in abstract form gives some data on the real time use (non-clinical trial) of these regimens in patients with cirrhosis who had failed previous interferon therapies [39]. Although there is no SVR data, safety data for both telaprevir and boceprevir were given for the first 16 weeks of therapy. In these patients, 19–28% had varices, 29–48% were relapsers, the mean serum albumin was about 40 g/dl, and the mean platelet count was 150,000. Thus although some of these may have been transplant candidates the vast majority were not. Despite this, 4 deaths occurred in 362 patients (1.3%) in the first 16 weeks, and 6–12% had therapy discontinued due to serious adverse events. Erythropoietin was used in about 50% of patients and blood transfusion was required in between 6–18% of patients.

This data does raise caution about the safety profile in much sicker patients. Concern with the skin rash in patients with portal hypertension is even greater than in non-cirrhotic patients. These

Table 3. Potential issues with 1st “wave” therapies in the transplant setting.

| | |
|-----------------|--|
| Pretransplant | <ul style="list-style-type: none"> • Only G1 patients • Overall SVR may only be 20-25% in G1 patients • Many patients previous non-responders to PegIFN/RBV, SVR even lower • Toxicity profile may be higher |
| Post-transplant | <ul style="list-style-type: none"> • Only G1 patients • Drug-drug interactions (tacrolimus, cyclosporin, TOR inhibitors ↑ 5x) • Overall SVR only 40% |

patients have significant defects in neutrophil function [40] and secondary skin infections (particularly *Staphylococcus*) could prove fatal.

The final issue is the emergence of anti-protease resistance strains of HCV in pretransplant patients [41]. This will be a particular issue in previous interferon non-responders where, if these new therapies are continued for any length of time, then resistant strains will be amplified. Thus stopping rules need to be strictly observed in these patients. The implication here in transplant patients will be the effect of access to future protease inhibitor-based therapies if significant resistance is detected. If significant resistance emerges, patients with mild disease can probably wait until better agents emerge (third wave). However, transplant candidates may require more urgent access to newer therapies but will almost certainly not be suitable for anti-protease-based therapies that have cross-resistance profiles with boceprevir and telaprevir.

I would conclude that the significant use of these first wave therapies in pretransplant waiting list patients will be problematic and perhaps not worth the effort or the risk. As now, such therapies will probably be confined to Child A patients with hepatocellular cancer. Already much discussion has been had on whether to “*by pass*” these agents in this patient group and head straight to second wave or third wave agents.

Triple/quadruple therapy with next generation AVT

If boceprevir and telaprevir are likely to have minimal impact then what about the next wave of AVT? As mentioned, the major difference between these agents and boceprevir or telaprevir is the ease of administration (daily) and less genotype specificity. Side effects still occur (although different) and the SVR seems about the same in next generation P.Is plus PegIFN/RBV. It would seem that the main advantage with these agents would be in patients infected with genotype 2/3 virus where the P.I. had expended genotype specificity. Currently, such patient's pretransplant may have an SVR of up to 35%. Extrapolating that these second wave agents would increase SVR by 50% then perhaps we could expect SVRs of about 45% or even 50% pretransplant. Thus it may be tempting to use them. However, the key once again will probably be tolerability. The widespread use in patients infected with genotype 1 HCV would seem to have similar caveats to the use of boceprevir and telaprevir. As mentioned, patients infected with genotype 1 HCV who failed these therapies would not be suitable/eligible for second wave protease inhibitor therapies with cross-resistance profiles.

As previously mentioned, polymerase inhibitors or NS5A inhibitors plus PegIFN/RBV, however, may have a significant impact re SVRs. Tolerability will mainly revolve around the PegIFN/RBV combination as now.

Non-interferon-based therapy

This seems to be most likely a breakthrough and a paradigm shift for patients awaiting liver transplantation. The goal of these approaches is fourfold. (1) To achieve 90% SVR, (2) to have minimal side effects, (3) to be pan genotypic, and (4) to be of short duration (maximum 6 months). All of these seem potentially achievable. 90–100% SVRs have already been reported in treatment naïve patients infected with genotype 2/3 HCV using just polymerase inhibitor and ribavirin for 3 months [33]. Although initially tested in patients with genotype 2/3 HCV, this regime

is thought to be pan genotypic. Use of an NS5A inhibitor + next generation protease inhibitor in patients with genotype 1b HCV (who were previously null responders to interferon) also resulted in a 90% SVR [35].

It is expected that an increasing number of combinations will emerge in the next 1–2 years and perhaps be in clinical practice within 5 years ([16], Table 1). If such predictions are true, then the whole landscape of human liver transplantation will change dramatically, perhaps in a similar fashion to the change in outcomes that occurred in patients with chronic hepatitis B infection awaiting transplantation in the mid to late 1990s, with the introduction of lamivudine and adefovir [42].

The first change would be that almost all patients awaiting liver transplantation would be rendered PCR negative and effectively cured of HCV. This would include patients with hepatocellular cancer and low MELD scores. These patients based on current paradigms could be treated for 3–6 months with AVT and proceed to transplant within 3–6 months with the likelihood of no HCV recurrence.

The second group would be those who have end stage decompensated liver disease. Currently, it seems very unlikely that such patients will be treated with boceprevir or telaprevir or even second wave approaches, as both require PegIFN/RBV. In the pretransplant context, however, I would dispute the automatic conclusion that obtaining an SVR in such decompensated patients will necessarily avoid liver transplantation in a similar fashion to that seen in HBV. Firstly, there are HBV patients who do not recover and die, despite successful control of HBV replication [43]. MELD scores of >25 characterize these patients. Secondly, decompensation in chronic HBV infection is often due to flair of HBV replication superimposed on cirrhosis. In other words, HBV patients usually do not just slip slowly into decompensation and overt liver failure. In contrast, that is exactly what patients with end stage HCV cirrhosis do, often precipitated by infection or bleeding. Although we would all hope that eliminating HCV at this stage would revert such patients to a compensated state, this remains to be established. It is worthy to note that data are lacking on significant improvement in MELD scores in patients currently on waiting lists undergoing SVR with current standard of care with PegIFN/RBV. At best, some of these patients stabilize and even if improvement is seen, it happens slowly (Xavier Forns, Barcelona; Greg Everson, Colorado personal communications). It could be argued that non-interferon-based regimes will not have the catabolic effects in these patients that is induced by interferon and hence improvement will be expected and happen over a shorter time frame. This remains an interesting point of discussion that the future will resolve. In addition to these issues is the recent provocative finding that patients with HCV infection still have increased liver-related morbidity and mortality compared to the general population, despite obtaining an SVR [44]. If this is true then liver transplantation for patients with decompensated HCV and an SVR may still be required.

To conclude, third wave therapies are likely to dramatically change the landscape. It is predicted that these therapies delivered pretransplant will prevent HCV recurrence post-transplant. Treatment duration may differ depending on genotype and previous responses to interferon. Patients with HCC and HCV will still require transplantation. It remains unclear, however, what percentage of patients with decompensated advanced liver failure and high MELD scores will be “rescued” thus avoiding transplant altogether. Watch this space...

Frontiers in Liver Transplantation

Could new therapies prevent HCV infection of the allograft at time of transplant?

New anti HCV monoclonal antibodies

Current approaches using such interventions have not been successful. However, a more recent study using a human monoclonal antibody against HCV E2 suppressed viral replication during the 7 days of therapy immediately post-transplant [44]. Thus, this approach may still have some merit.

What about blocking uptake at receptor level?

The identification of Claudin1, CD81, Occludin, and Scavenger receptor class B1 (SR-B1) as a network of receptors involved in HCV uptake does raise the possibility that blocking Mabs aimed at HCV binding sites could prevent HCV uptake into the liver at the time of transplantation [45–47]. Currently, however, no such *in vivo* data exist although a recent study in humanized mice has shown that novel monoclonal antibodies against SR-B1 are effective not only in preventing uptake but also cell – cell spread of HCV [48].

What about blocking uptake at the tyrosine kinase level?

Recent data indicate that the tyrosine kinase system feeding off the epidermal growth factor receptor is crucial in the complete uptake of HCV into hepatocytes [49].

Such inhibitors currently exist in oncological practice and could theoretically be applied intraoperatively and immediately post surgery to block uptake of HCV at the time of allograft implantation. The toxicity of such molecules administered for short periods of time may be minimal. Perhaps such agents could be used in combination with neutralizing mAbs and blocking mAbs aimed at HCV receptors. It is unclear what duration of therapy post-liver transplantation would be required but it seems likely it would be >1 week.

In conclusion, such approaches outlined in this section are intellectually appealing but currently it is not clear how practical they would be. They may be unnecessary if third wave DAAs are very successful.

Use of new therapies post-liver transplant (Table 4)

Triple therapies with either telaprevir/boceprevir

As mentioned, current treatments with PegIFN/RBV yield about a 20–30% SVR (G1) in the stable post-transplant setting. The use of telaprevir or boceprevir in these patients may increase SVR to about 40% (G1). Thus, there is currently great interest in introduc-

ing such therapies as soon as possible in this setting. Several confounding issues, however, exist.

Firstly, drug–drug interactions [50–52]. Boceprevir and telaprevir are metabolized via the cytochrome P450 3a system and compete with cyclosporine, tacrolimus, evolumus, and rapamycin for metabolism. Emerging data suggest that the *area under the curve* for these immunosuppressive agents is dramatically increased when given with telaprevir or boceprevir. Increases of up to 70-fold have been observed with tacrolimus and 5-fold with cyclosporine. This will make boceprevir or telaprevir difficult to use but not impossible. Dose adjustments of these immunosuppressive drugs in a similar fashion to those required with some HART regimes in HIV infected transplant patients will be required.

Secondly, the side effect profile in immunosuppressed patients may be exaggerated and thirdly, the issue of previous non-responsiveness to interferon and potential protease inhibitor resistance may significantly decrease efficacy. Lastly, optimal durations of therapy will need to be established.

Despite these concerns, there are now several reports in abstract form on the use of either of these two agents in the post-transplant period. [53–61]. These reports usually only include a small number of patients although when presented at various meetings the numbers have been greater. In essence, several themes have emerged (Table 4). Firstly, there is little or no SVR data, Secondly, drug interactions seemed to have been well managed although very high levels of tacrolimus have occasionally been seen. Thirdly, many users have converted their patients to cyclosporine-based immunosuppression before commencing AVT. Fourthly, side effects and dose reduction of ribavirin are common. In some studies, treating cholestatic hepatitis has not always been successful due to the introduction of triple therapy-based AVT at very late stages of disease. Mortality has been reported in such patients. A recent report, however, does show an SVR can be achieved in cholestatic hepatitis [62].

Triple/quadruple therapies with next generation P.Is/polymerase inhibitors

The issues here are similar to those raised with boceprevir and telaprevir although the ease of use and increased genotype susceptibility and increase SVR in non-protease-based therapies may encourage early introduction. Furthermore, some P.Is have been developed that are not metabolized via the cytochrome P450 system and thus may be easier to use with current immunosuppressive drugs [63].

Non-interferon-based therapies

As pretransplant, there is great hope for the future here. Apart from the potential for marked increased efficacy, the lack of toxicity

Table 4. Observations in initial assessment of triple therapy for HCV post-liver transplant [53–62].

- | |
|---|
| • Side effects, particularly significant anemia very common (needing erythropoietin and/or blood transfusion) |
| • Ribavirin dose reduction common |
| • Many patients switched to cyclosporine-based immunosuppression before AVT |
| • Drug-drug interactions seem to be manageable |
| • Mortality observed if patients treated at advanced stages of recurrence (particularly advanced cholestatic HCV) |

Table 5. Non-interferon-based therapies. (A) Potential benefits of 3rd non-interferon-based therapies in liver transplant. (B) Limitations regarding non-interferon-based therapies in liver transplant.

| A | |
|--|--|
| Pretransplant | <ul style="list-style-type: none"> • SVR pretransplant will abolish post-transplant HCV recurrence • SVR pretransplant will lead to significant improvement of MELD scores and remove the need for transplant in non-HCC patients with MELD <25 |
| Post-transplant | <ul style="list-style-type: none"> • Could be used early after transplant • SVR rates very high • Reversal of established disease including cholestatic HCV |
| B | |
| <ul style="list-style-type: none"> • HCC patients will still require transplant • SVR in patients with MELD <25 may not abolish need for transplant | |

and absence of significant drug-drug interactions may enable the best of these therapies to be introduced very early post-transplant in patients who remain viremic at transplant (in a similar fashion to HBV antivirals). This would result in viral control from the time of transplant. It should, however, be pointed out that if these third wave agents cure HCV pretransplant, then no AVT at all will be required post-transplant! (see Table 5).

It is known that HCV replication occurs at the time of allograft implantation but for the first month post-transplant this rarely results in allograft pathology [64,65]. Thus, if viral control during this time and elimination within 3 months are achieved, it is likely that these type of agents could very well eliminate HCV related allograft pathology. This would be the holy grail of using such therapies if required early post-transplant. It would be presumed that very early use post-transplant would be better tolerated in ribavirin-free regimens. A challenge here would be the question concerning the duration of therapies post-transplant setting. If 3-month duration emerges as sufficient in the non-transplant setting, the post-transplant situation may require longer duration in the setting of immunosuppression. This will need to be studied. Even if early viral control and or elimination does not become the optimal strategy, it is likely that the use of these regimens will achieve a 90% SVR at later stages of infection, once again duration of therapy in the post later post-transplant will need to be clarified. Using such approaches should completely eliminate cholestatic HCV and even if such cases do occur, it would be hoped that the severe allograft dysfunction associated with a form of HCV infection could be reversed (although that cannot be totally assured).

Predictions of the (near) future

It seems likely that the new age of AVT will radically improve outcomes for patients with HCV infection in the setting of liver transplantation. Currently, this is a hope as there is no data to support this claim. It is a strong intellectual prediction based on non-transplant data. It may be only the introduction of the third wave of non-interferon-based therapies that will achieve this routinely in the pre and post-transplant setting. Whether immediate uptake of the first and second wave therapies is warranted remains debatable and whether neutralization of the virus at the time of transplant is worth studying may depend on how successful the third wave of HCV therapeutics is in the transplant setting. In the long-run, successful use of the third wave will abolish HCV infection even in advanced disease well before transplant is required. This will leave only HCC patients and patients

with advanced liver failure that slip through the net and present late requiring transplantation. Furthermore, such patients will not require post-transplant AVT or, if they do, it will likely be for short periods of time.

Whatever the exact outcomes, exciting, and challenging times lie ahead.

As examples of questions that will be answered quite soon, the reader is invited to answer yes or no to the following, and revisit your answers in 3–5 years from now:

1. The introduction of boceprevir or telaprevir will significantly alter outcomes for patients on the transplant waiting list? (? No)
2. New second generation protease inhibitors will significantly alter outcomes for patients on the waiting list? (? Maybe)
3. Blocking HCV uptake at the time of transplant will become part of future anti HCV strategies? (? No)
4. Non-interferon-based therapies will lead to reversal of hepatic decompensation in the pre transplant setting? (? Maybe)
5. Non-interferon regimens will be used pretransplantation with subsequent elimination of HCV post-transplant in virtually all patients? (? Yes+++)
6. Non-interferon regimens will only be required for <6 months in the post-transplant setting? (? Maybe)
7. In 10 years time, the only HCV patients requiring transplantation will be those with HCC? (? Yes)

Conflicts of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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