

TITLE: Protease Inhibitor Use for Chronic Hepatitis C infection in Prior Null Responders and Recurrent Hepatitis C Infection Post Liver Transplant: A Review of the Clinical Evidence

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CONTEXT AND POLICY ISSUES

Chronic hepatitis C (CHC) remains a significant medical and economic burden in Canada, affecting nearly 1% of the population.¹ In 2007, it was estimated that 242,000 Canadians had chronic HCV infection and about 7,000 new infections occurred.² Of those with chronic infection, 15% to 25% will develop progressive liver disease, end stage liver disease, hepatocellular carcinoma or will require liver transplant.^{3,4} Hepatitis C is the principal cause of death from liver disease and the leading indication for liver transplantation.^{1,5,6} Recurrence of HCV occurs in more than 95% of patients after liver transplantation.⁷ Modelling data suggest that the incidence of more advanced HCV-related sequelae (e.g, decompensated liver disease, hepatocellular carcinoma [HCC] and liver transplantations) are expected to rise for at least another decade.¹ Fibrosis progression may be accelerated in patients with recurrent HCV infection post-liver transplantation, with 6% to 23% of patients developing cirrhosis after a median of 3.4 years.⁴ However, the indications for treatment, the optimal timing, dose and duration of treatment for patients with recurrent HCV infection post-transplantation are not clear.⁴ Therapy may be initiated preemptively, before the development of recurrent hepatitis, or may be started once recurrent clinical disease is evident.⁴ Analyses of studies examining the efficacy of treatment for recurrent HCV infection are hampered by the enrollment of small numbers of patients at single centers and the use of different immunosuppressive regimens, which may play a role in the accelerated liver disease following liver transplantation.⁸ One of the most important objectives of the treatment of HCV infection is to achieve the sustained viral response (SVR), which is defined as having undetectable plasma HCV RNA level 24 weeks after the last planned dose of study medication. It has been reported that standard peginterferon/ribavirin (PR) therapy results in a SVR of up to 30% in patients with histological HCV recurrence after liver transplantation.⁸

Boceprevir (BOC) and telaprevir (TP) are two NS3 protease inhibitors (PI) indicated for the treatment of CHC genotype 1 infection. They have shown statistically significant improvement of the SVR rate in patients with CHC who are treatment naïve^{9,10} or failed to respond to prior standard PR therapy.^{11,12} However, the comparative effectiveness and safety of triple therapy of BOC or TP plus PR compared with standard PR therapy alone in patients who are prior null responder (defined as less than 2 log₁₀ HCV RNA reduction after 12 weeks of PR therapy)¹³ or patients who have recurrent HCV after liver transplantation were not well established.^{1,4} The addition of PI to the established PR regimen may provide another opportunity for patients who have had a null response to prior PR therapy.¹² It is therefore important to ascertain the efficacy of PI-PR triple therapy in this population. The use of BOC or TP in the post-transplant setting in

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patients with genotype 1 HCV disease has been limited.^{7,14} It has been indicated that drug–drug (PI and immunosuppressive agents) interactions remain a significant clinical issue. The aim of this review is to evaluate the effective and safety evidence of BOC or TP-containing triple therapy regimens in the treatment of the above special populations.

RESEARCH QUESTIONS

1. What is the clinical evidence on sustained virological response rates with the protease inhibitors in patients who are classified as null responders on prior PR therapy?
2. What is the clinical evidence on sustained virological response rates with the protease inhibitors for patients who have undergone a liver transplant?

KEY FINDINGS

Patients with chronic hepatitis C (CHC) who are null responders to previous peginterferon/ribavirin (PR) therapy may benefit from telaprevir-PR triple therapy. There is no RCT data on this population for boceprevir (BOC)-PR triple therapy. At present, there is no evidence to determine the clinical benefit (in terms of sustained viral response) and harm of adding BOC or TP to PR therapy in patients with recurrent hepatitis C virus who have undergone a liver transplant.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Medline, Embase, PubMed, The Cochrane Library (2013, Issue 4), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies and conference abstracts. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and April 30, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to the selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1: Patients with chronic hepatitis C infection who are classified as null responders on prior PR therapy Q2: Patients with chronic hepatitis C infection who have undergone a liver transplantation
Intervention	PR plus protease inhibitor (boceprevir or telaprevir)
Comparator	PR alone or no comparator in a single arm study

Outcomes	Clinical benefit: SVR, AE, morbidity, mortality
Study Designs	Health technology assessments, systematic reviews and meta-analyses, randomized controlled trials, non-randomized studies, Emerging evidence (e.g. conference abstracts)

Exclusion Criteria

Studies not meeting the inclusion criteria, duplicate data reporting, and conference abstracts older than 2 years were excluded.

Critical Appraisal of Individual Studies

Randomized controlled trials (RCT) and non-RCTs were assessed with Scottish Intercollegiate Guidelines Network, Methodology checklist 2 (SIGN 50 Checklist 2).¹⁵ Critical appraisal of emerging evidence (i.e, abstract) was not performed due to the limited study information available for this type of evidence.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 513 citations. Upon screening titles and abstracts, 484 citations were excluded and 29 potentially relevant articles were retrieved for further review. Of the 29 potentially relevant reports, three studies^{12,16,17} including one conference abstract¹⁷ are included in this review. Twenty six articles were excluded due to unmet the inclusion criteria, duplicate data report or abstracts presented at greater than two years ago. The study selection process is outlined in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart (Appendix 1). No systematic reviews were identified for inclusion in this report.

One RCT (REALIZE)¹² and one uncontrolled, single treatment arm study¹⁶ were identified that studied the effectiveness (SVR) of triple therapy of TP combined with PR in the prior null responders to PR dual therapy. There is no evidence of BOC in prior null responders. No studies were found that reported the SVR and harms of triple therapy of BOC or TP with PR in patients with recurrent HCV who have undergone a liver transplant.

Emerging evidence

There was one open label, single treatment arm study (PROVIDE, Poordad et al.)¹⁷ that was identified relating to BOC treatment of prior null responders to PR; In this study, Poordad et al.¹⁷ reported that SVR result in patients who were prior null responder to PR therapy in previous BOC trials (SPRINT-2⁹ and RESPOND-2¹¹).

Summary of Study Characteristics

Details of the characteristics of the included studies are provided in Appendix 2.

1. What is the clinical evidence on sustained virological response rates with the protease inhibitors in patients who are classified as null responders on prior PR therapy?

The RCT (REALIZE)¹² was a multicentre study sponsored by the manufacturer of TP, which studied the comparative effectiveness and harms of TP plus PR in patients with CHC who failed previous PR therapy including 184 prior null responders. Null response was defined as less than 2 log₁₀ HCV RNA reduction at 12 weeks of PR therapy. The primary outcome was SVR, defined as maintenance of undetectable viral load 24 weeks after completion of therapy. Patients in the two TP groups received TP for 12 weeks. However, one of the two groups began the first four weeks of the study on placebo-PR before switching to TP-PR for the next 12 weeks ('delayed start'), while the other group began treatment with TP-PR. TP was administered orally at a dose of 750 mg every 8 hours; peginterferon alpha-2a was administered subcutaneously at a dose of 180 µg per week; and ribavirin was administered orally at a dose of 1000 to 1200 mg per day, based on weight.

In the open-label uncontrolled study, Muir et al.¹⁶ evaluated the efficacy and safety of TP-based triple therapy (TP/PR) in patients who were null responders to PR treatment (defined as less than a 1 log₁₀ decrease in HCV RNA at week 4 or less than a 2 log₁₀ decrease in HCV RNA at week 12). Patients were enrolled from the control arms of the three previous phase II PROVE studies (PROVE1,¹⁸ PROVE-2¹⁹ and PROVE-3²⁰). The treatment was 12 weeks of TP/PR followed by an additional 12 weeks or 36 of PR alone. TP was administered orally at a dose of 750 mg every 8 hours. Peginterferon alpha-2a was administered at a dose of 180 µg weekly, subcutaneously. Ribavirin was administered twice daily at a dose of 1,000 mg/day for patients weighing less than 75 kg and a dose of 1,200 mg/day for patients weighing 75 kg or more. Outcomes were SVR and adverse events. However, no adverse events were reported for the null responder's subgroup.

Emerging evidence

In an open-label uncontrolled single arm study (PROVIDE), Poordad et al.¹⁷ evaluated the SVR of triple therapy of BOC plus PR in the patients who were null responders to prior PR therapy (defined as <2 log₁₀ decline in HCV RNA at treatment week 12). Included patients were from PR control arms in previous registered two BOC trials, i.e. SPRINT-2⁹ and RESPOND-2.¹¹ BOC (800 mg, three times per day with food) given with peginterferon 1.5 µg/kg/week subcutaneously and weight-based ribavirin (600 to 1,400 mg/day) twice daily for up to 44 weeks.

2. What is the clinical evidence on sustained virological response rates with the protease inhibitors for patients who have undergone a liver transplant?

No evidence were identified that reported the SVR and harms of BOC or TP in patients with recurrent HCV who have undergone a liver transplant.

Summary of Critical Appraisal

A summary of the strengths and limitations of individual included studies is provided in Appendix 3.

1. What is the clinical evidence on sustained virological response rates with the protease inhibitors in patients who are classified as null responders on prior PR therapy?

The REALIZE¹² trial was randomized and double-blinded. The randomization was stratified based on the previous response (i.e. null response, partial response and relapse). Randomization appeared to be centralized, and measures were taken to maintain adequate allocation concealment. Overall, the loss to follow-up rate was small and intention to treat (ITT) analysis was employed.

The study by Muir¹⁶ was an open label, single treatment arm study; therefore it was neither blinded nor randomized. The methodological quality of this study was considered low because of the heterogeneity of the population and intervention. In terms of the population, two definitions of null response were applied (i.e. less than a 1 log₁₀ decrease in HCV RNA at week 4 or less than a 2 log₁₀ decrease in HCV RNA at week 12). Previous PR treatment history also varied, such as some of the patients (from study PROVE 3)²⁰ failed more than one course of prior PR therapies). In terms of intervention, the duration of additional PR treatment following TP/PR 12 weeks was either 24 weeks or 48 weeks because of a protocol amendment during the trial.

Summary of Findings

The main findings of the included studies are described in Appendix 4.

1. What is the clinical evidence on sustained virological response rates with the protease inhibitors in patients who are classified as null responders on prior PR therapy?

In the REALIZE study, 184 patients who were prior null responders were included. SVR rates were lower in patients who were prior null responders compared to the overall study population. For example, in the group that received 12 weeks TP/48 weeks PR, SVR rates were 29% in the subgroup identified as null responders versus 64% in overall population. SVR rates among prior null responders were, however, still statistically higher with TP-PR than with placebo-PR (29% versus 5%). Similar results (33%) were seen in the TP group that had a 'delayed start' of TP. Adverse events and other outcomes were not reported for prior null responder's subgroup.

In the open label, uncontrolled single treatment arm study, 51 prior null responders were included. Muir et al.¹⁶ found that the SVR rates were 17% and 56% in TP 12 / PR24 weeks and TP 12 weeks/PR 48 weeks respectively. The pooled overall SVR rate in the null responder subgroup was 37% (19/51). No adverse events reported for subgroup of null responders. However, it was reported that the adverse events were similar to those in previous registered TP trials. The author concluded that their findings demonstrated the benefit of retreatment with a TP-based triple therapy (T12/PR48) for patients who was prior null responder to standard PR therapy.

Emerging evidence

In the study by Poordad, et al. (PROVIDE),¹⁷ 48 patients met the criteria for a null response (<2 log₁₀ decrease in HCV RNA by week 12). It was reported that 38% (16/42) achieved SVR (27% of black patients, 42% of non-black patients and 41% genotype 1a) with BOC/PR. No adverse events and other outcomes were reported.

2. What is the clinical evidence on sustained virological response rates with the protease inhibitors for patients who have undergone a liver transplant?

No studies were identified that reported SVR of triple therapy of BOC or TP in combination with PR therapy in the treatment of recurrent HCV after liver transplantation.

Emerging evidence

An ongoing phase III RCT (REPLACE study)²¹ that evaluated the efficacy and safety of triple therapy of TP with PR in patients with genotype 1 hepatitis C infection after liver transplantation was identified. The primary outcome is SVR12 defined as having plasma HCV RNA level less than 25 IU/mL 12 weeks after the last planned dose of study medication. However, no results had been reported at the time of the present review.

Two full text articles^{22,23} and 12 conference abstracts²⁴⁻³⁵ were identified that reported the early treatment experience of triple therapy of TP^{22,24-27,30-35} or BOC^{23,28,29} in combination with PR therapy in the treatment of recurrent HCV after liver transplantation. The study designs were either small uncontrolled single arm studies or case series reports. The outcomes were focused on early virological response. No SVR were reported. The main characteristics and key findings were summarized in Appendix 5.

Limitations

The comparative evidence of triple therapy with TP (TP/PR) versus PR alone in prior null responders is limited to a relatively small sample size trial. No trials of BOC were identified that reported the comparative efficacy and safety of triple therapy with BOC (BOC/PR) compared with PR alone in previous null responders to PR. Only emerging (i.e., non-peer reviewed, abstract only) evidence from a single arm study was available for this agent.

A limitation of the identified studies is that they were not designed to detect differences in hard clinical outcomes such as morbidity and mortality, relying instead on SVR rates as the key measure of efficacy.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Although SVR rates are significantly lower in prior null responders to PR than those seen in the general CHC population, there is a statistically significant treatment effect of triple therapy of TP-PR over PR alone in this population. There is no comparative SVR data for BOC in the null responder population. However, a single arm treatment study with a small sample size (n = 48, presented in abstract form only) reported that 38% of prior null responders to PR achieved SVR with the treatment of BOC plus PR. No comparative efficacy and safety evidence on the use of triple therapy (TP or BOC plus PR) were identified in recurrent HCV infection post transplantation recipients, although preliminary early virological response were presented in abstracts and based on small single arm uncontrolled studies or case series. Further well-designed randomized controlled trials are warranted to determine the comparative clinical efficacy and safety profile of BOC or TP in treatment of CHC patients who are prior null responders to PR therapy or recurrent HCV infection who have undergone a liver transplant.

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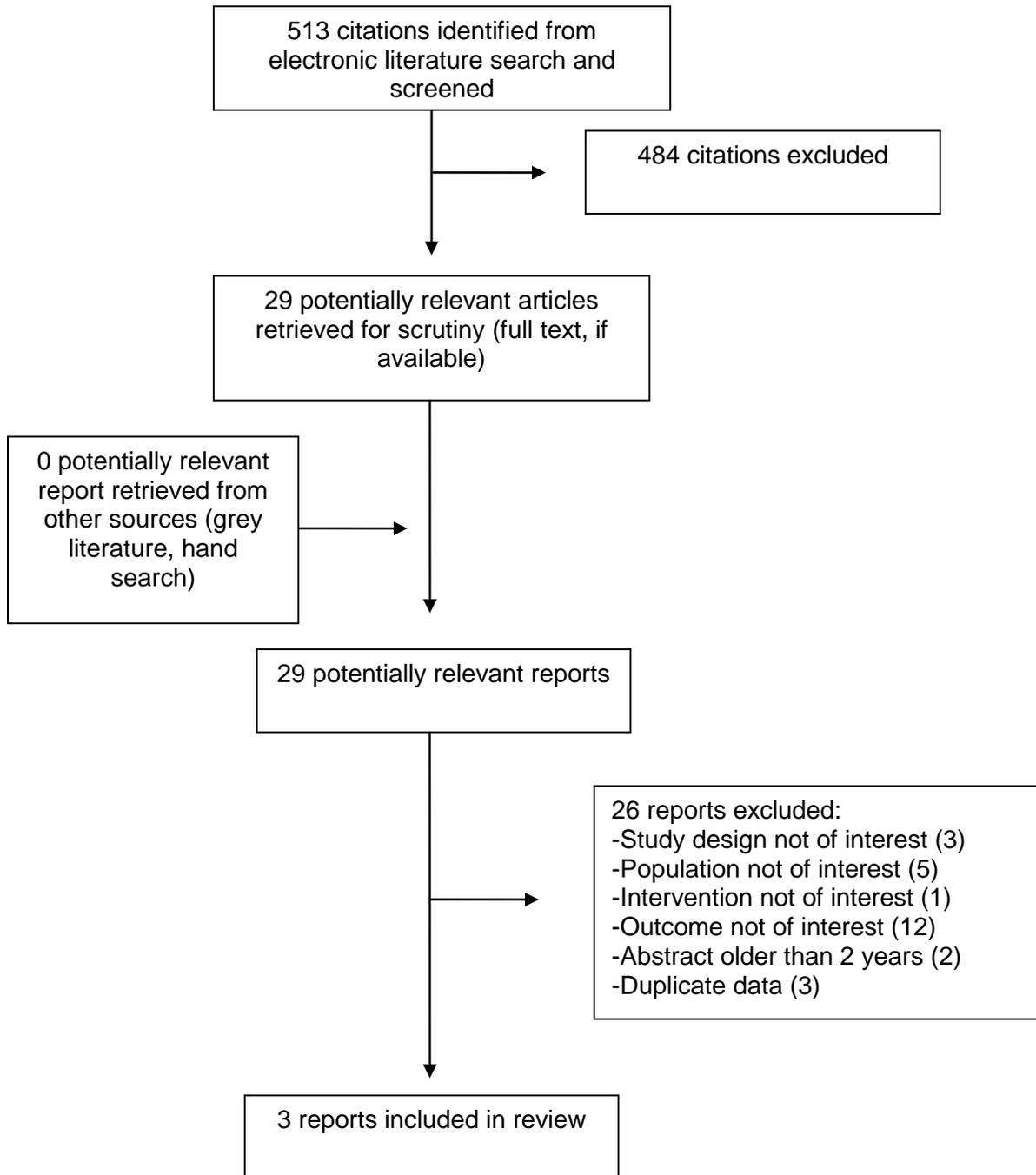
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Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Randomized and Non-Randomized Controlled Trials*

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention/Comparator(s)	Key Outcomes
Zeuzem 2011 ¹² (REALIZE study) Multi-countries (USA, Canada, etc.)	Double blind RCT Multicentre	<ul style="list-style-type: none"> • CHC genotype 1 with HCV RNA level ≥ 1000 IU/mL, treatment failure (including null responder**) with at least one prior course of PR therapy • Null responder subgroup N=184 	<ul style="list-style-type: none"> • TP + PR for 12 weeks then PL + PR for 4 weeks then PR for 32 weeks (n=72) • PL + PR for 4 weeks then TP + PR for 12 weeks then PR for 32 weeks (n=75) <p><u>Comparator(s)</u></p> <ul style="list-style-type: none"> • PL + PR for 16 weeks then PR for 32 weeks (n=37) 	SVR
Muir, 2011 ¹⁶ 28 sites in 7 countries (USA, Canada, etc.)	Open-label, non-RCT, rollover, no control arm (single arm)	CHC genotype 1 with HCV RNA level ≥ 1000 IU/mL, Prior no response (null) to PR-treatment*** in PR-control arms in three phase II PROVE studies ¹⁸⁻²⁰ (TP trials) n=51	<ul style="list-style-type: none"> • TP + PR for 12 weeks then PR for 12 or 36 weeks (T12PR24 or T12PR48) • No comparator 	SVR
Poordad, 2012 ¹⁷ (PROVIDE study) (USA, Canada, etc.)	Open-label, non-RCT, rollover, no control arm (single arm)	CHC genotype 1 with HCV RNA level ≥ 1000 IU/mL, Prior null response to PR-treatment** (in PR-control arms) in two phase III RCTs (SPRINT-2 ⁹ and RESPOND-2 ¹¹ (BOC trials) n=48	<ul style="list-style-type: none"> • BOC + PR for up to 44 weeks • No comparator 	SVR
BOC=boceprevir; CHC=chronic hepatitis C; HCV=hepatitis C virus; PL=placebo; PR=peginterferon plus ribavirin; RCT=randomized controlled trial; SVR=sustained virologic response; TP=telaprevir;				

*Only prior null response-subgroup data was extracted in this review

** Null response (no response) defined as less than a 2 log₁₀ decrease in HCV RNA at week 12 in the REALIZE Study.

***Null response defined as less than a 1 log₁₀ decrease in HCV RNA at week 4 or less than a 2 log₁₀ decrease in HCV RNA at week 12 in parent studies(PROVE1, PROVE2 and PROVE3);

Appendix 3: Summary of Study Strengths and Limitations

First Author, Publication Year	Strengths	Limitations
Zeuzem 2011 ¹² (REALIZE study)	<ul style="list-style-type: none"> • Research question was clearly defined • Randomization was stratified based on the previous response to PR. • Double blinding process was clearly described • Only difference between groups is treatment under investigation • Outcome was standard, valid and reliable • Intention to treat analysis was well reported 	<ul style="list-style-type: none"> • Key patient characteristics of the null-response subgroup at baseline are not reported. • Follow up too short to assess clinical outcomes such as mortality/morbidity
Muir, 2011 ¹⁶	<ul style="list-style-type: none"> • Null response population was clearly defined • No drop outs 	<ul style="list-style-type: none"> • No control arm • Two definitions of null response were applied (less than a 1 log₁₀ decrease in HCV RNA at week 4 or less than a 2 log₁₀ decrease in HCV RNA at week 12) • Follow up too short to assess clinical outcomes such as mortality/morbidity
Poordad, 2012 ¹⁷ (PROVIDE study)	<ul style="list-style-type: none"> • This was a single arm, non-controlled study. Data reported in abstract. Not appraisable. 	

Appendix 4: Summary of Main Study Findings and Author Conclusions

First author, publication year	Main findings	Author conclusions
<i>Randomized controlled trial on telaprevir</i>		
Zeuzem 2011 ¹² (REALIZE study)	SVR: <u>Overall (T12PR48 plus T12(DS)/PR48): 31% (46/147)</u> T12PR48 : 29% (21/72) T12(DS) PR48: 33% (25/75) <u>PR48: 2/37 (5%)</u> AE : NR for null responder subgroup	On page 2417: "Telaprevir combined with peginterferon plus ribavirin significantly improved rates of SVR in patients with previously treated HCV infection, regardless of whether there was a lead-in phase."
<i>Non-RCT on telaprevir</i>		
Muir, 2011 ¹⁶	SVR: <u>Overall : T12PR24-48: 37% (9/51)</u> <u>T12PR24: 17% (4/24)</u> <u>T12PR48: 56% (5/27)</u> AE: NR for null responder subgroup However, it was reported that the safety profile was similar to that observed in the earlier phase II studies	On page 1538: "This study demonstrated the benefit of retreatment with a telaprevir-based regimen for patients with well-characterized nonresponse (null and partial) or relapse to a prior course of PR treatment."
<i>Non-RCT on boceprevir</i>		
Poordad, 2012 ¹⁷ (PROVIDE study)	SVR: BOC/PR : 16/42 (38%) AE : NR	On page 166: "When retreated with BOC/PR 38% of prior PR null responders achieved SVR, which compares to SVR rate (33%) observed in poorly IFN responsive patients treated in the SPRINT-2 and RESPOND-2 studies." ¹⁷
AE=adverse event; BOC=boceprevir; HCV=hepatitis C virus; DS=delayed start; IFN=interferon; NR=not report; PEG=pegylated; PR=peginterferon plus ribavirin; RCT=randomized controlled trial; SVR=sustained virological response; TP=telaprevir;		

Appendix 5: Summary of Findings and Author Conclusions in Uncontrolled Studies on Recurrent HCV Post-Liver Transplant

First author, publication year	Study Characteristics	Main findings	Author conclusions
Telaprevir			
Nair, 2012 ²⁴	P: 12 pts with recurrent hepatitis C post LT I: TP12PR48 wks; (ISA: TAC) C: none O: HCV virologic response	All patients who received 12 wks of therapy with TP were RNA undetectable at week 12; -No adverse event related to TAC was noted	"Telaprevir based regimens can be used in post-transplantation patients with reduced dosing of tacrolimus. Once a week dosing of tacrolimus is sufficient to keep the level in therapeutic range and avoid toxicity. Early virological response indicates effectiveness in these difficult to treat patients. As anticipated, pancytopenia is a major concern in these patients and requires intense monitoring."
Kwo, 2012 ²⁵	P: seven adult pts with recurrent HCV post LT with null response to PR for 12 wks (< 2 log ₁₀ reduction) I: Four week lead-in PR followed by adding TP. (IS: CYA) C: none O: virologic response	No virological response data extractable	"Conversion to CYA followed by four week PR lead-in with addition of telaprevir can lead to significant clearance rates at week 24 in null responders with advanced fibrosis though high rates of anemia/RBV dose reduction, growth factor, and transfusion requirements were noted. Dose reduction of RBV to 200 mg was associated with treatment failure. CYA Interactions were easily managed by CYA dose adjustment. EOT results will be available for 3/4 individuals who are HCV RNA undetected at week 24 by 11/2012."
Mantry, 2012 ²⁶	P: 17 pts with recurrent hepatitis C post LT I: TP12PR24 or 48 wks (IS: TAC) C: none O: HCV virologic response	Of the 17 patients, 6 had rapid virological response and extended (e)RVR; additionally 6 patients became aviremic at 32,33,40,55,62 84 and 90 days and had complete early virologic response.	"We report the first experience of treating HCV recurrence in post liver transplant recipients with telaprevir based triple therapy in setting of TAC based immunosuppression. We observed robust virologic responses in a majority of patients and TAC/Telaprevir interactions and side effects were manageable. Our preliminary data show that this treatment shows promising virologic responses in patients and merits prospective evaluation."
O'Leary, 2012 ²⁷	P: 12 pts with recurrent hepatitis C post LT I: TP plus PR (duration: NR) (IS: RAP or TAC or CYA) C: none O: HCV virologic response	7/12 (58%) patients had undetectable viral loads at wk 4 of triple therapy, 5/12 patients had <43 IU/mL. All 9/9 patients treated for 12 weeks had no detectable virus (cEVR). 5/5 patients treated for 24 weeks are	"Triple therapy with telaprevir after a Peg-RBV lead-in was safe and achieved 100% cEVR in LT recipients on rapamune, tacrolimus, or cyclosporine. However, drug interactions necessitate close monitoring and use only in highly compliant patients with good renal function."

First author, publication year	Study Characteristics	Main findings	Author conclusions
		virus negative.	
Pungpapong, 2012 ³⁰	P: seven pts with recurrent hepatitis C post LT I:TP plus PR (duration: NR) (IS: CYA) C: none O: HCV virologic response	At last visits, 4 patients (57%) had undetectable HCV RNA (first at wk1, 5, 9, 12).	"In our initial experience utilizing telaprevir+PR to treat HCV genotype 1 after LT, 1/6 patients (17%) achieved undetectable HCV RNA by wk4 (RVR) and 3/3 patients (100%) achieved undetectable HCV RNA by wk12 (cEVR). Adjustment of CYA dose and interval was required. Cytopenias were common. Ongoing follow-up would provide additional insights into the safety and efficacy of Telaprevir+PR to treat HCV genotype 1 in LT recipients."
Burton, 2012 ³¹	P: 12 pts with recurrent hepatitis C post LT I:TP12/PR48 wks; (IS: CYA or MMF) C: none O: HCV virologic response	Mean HCV RNA (IU/ml) prior to starting TP was 2.4x10 ⁶ (55-15x10 ⁶ IU/ml). Mean 1 week HCV RNA was 1895 IU/ml (0-19,400 IU/ml). By week 4, 11/12 had HCV RNA <43 IU/ml.	"CsA-based immunosuppression and C2 monitoring effectively maintains immunosuppression and prevents rejection during TT for recurrent HCV. Rates of early virologic response with TT exceed those previously published using PR alone. Anemia is a significant problem, but rash events are rare. Telaprevir-based TT is manageable and may enhance virologic responses in liver recipients."
Shin, 2012 ³²	P: five pts with rHCV post LT I:TP plus PR(duration NR); (IS: TAC or EVE) C: none O: HCV virologic response	Two patients achieved 2-log (3,330 from 1,000,000 IU/ml) and 3-log (734 from 1,010,000 IU/ml) viral reductions in the 1st week follow-up. Two other patients successfully obtained "SVR" after 5 weeks of therapy (from 2,790,000 and from 167,000 IU/ml, respectively). One patient has persisted "SVR" after 12 week course of therapy. (SVR was not defined in the abstract)	"Triple combination therapy has shown potent effect on HCV reduction on patients who tolerated therapy. This new therapy might have a role in improving both graft and patient survival. As drug tolerance is pivotal to completing this therapy course, it is necessary to determine the timing of onset of therapy and the management of the adverse effects. Further study with more patients is ongoing."
McCashland, 2012 ³³	P: 10 pts with rHCV post LT I:TP plus PR(duration 1-24 wks); (IS: CYA) C: none O: HCV virologic response	2 out of 9 patients achieved RVR; 3/3 patients who have completed 12 weeks of TT have non-detectable HCV RNA; 1 patient is HCV RNA	"RVR was achieved in 22% of patients on TT after LT . TT does not have a negative impact in achieving CSA target levels. Hematological AE are common while on TT after L."

First author, publication year	Study Characteristics	Main findings	Author conclusions
		negative at week 24.	
Werner,2012 ²²	P: nine pts with rHCV post LT I:TP plus PR(duration 12 wks); (IS: CYA, TAC) C: none O: HCV virologic response	7 completed the 12 weeks of triple therapy. At week 4, 4 of the patients were found to be HCV RNA-negative, and importantly, 8 were found to be negative at week 12.	"In conclusion, this pilot study provides evidence showing that TVR-based triple therapy is effective within the first 4 to 12 weeks in LT patients suffering from HCV genotype 1 recurrence, and it also provides evidence showing that drug-drug interactions between TVR and immunosuppressants can be handled appropriately through the close monitoring of trough levels and adequate dosage adjustments."
Pereira, 2012 ³⁴	P: Six pts with rHCV post LT I:TP plus PR(duration 12 wks); (IS: TAC) C: none O: HCV virologic response	One patient had to stop the therapy due to skin rash and headache after one week; Two patients achieved 3 log 10 HCV reduction after 1-2 week therapy; Two patients achieved "SVR" after 5 weeks therapy. (SVR not defined)	"Triple combination therapy has shown a potent effect on HCV reduction in patients who tolerated therapy. This new therapy may have a role in improving both graft and patient survival. As drug tolerance is pivotal to completing this therapy course, it is necessary to determine the optimal time of therapy and the management of adverse effects, Further study is ongoing"
Rogers, 2012 ³⁵	P: two pts with rHCV post LT I:TP plus PR(duration 12 wks); (IS: TAC) C: none O: HCV virologic response	Patient one achieved undetectable HCV and remained after 10 weeks of therapy. Virologic response for patient two: not reported	"TP can safely be administered post-transplant with careful monitoring and tacrolimus dose adjustment. The tacrolimus target was increased by 30% to minimize the risk of rejection and IFN induced immune mediated graft injury while on TP. Longer follow-up is needed to determine if TP use post-transplant is beneficial."
BOC			
Aqel,2012 ²⁸	P: 23 pts with recurrent hepatitis C post LT I:BOC plus PR (duration: 24wks) (IS: CYA) C: none O: HCV virologic response	Ten patients (43%) achieved complete early virologic response; four of them continue to be negative at week 24.	"Boceprevir based triple therapy can be used post LT but requires close clinical monitoring. Antiviral efficacy of this regimen is better than standard therapy in difficult to treat population. Patients should be closely monitored for adverse events. Ongoing follow up will provide additional data regarding safety and efficacy of this regimen."
Schilsky,2012 ²⁹	P: three pts with recurrent hepatitis C post LT I: BOC plus PR (duration: NR) (IS: CYA) C: none	Patient one achieved undetectable HCV viral load by day 19 of BOC. Patient two experienced greater than a 2 log	"Our experience demonstrates that triple therapy with BOC offers promising early results in the treatment of severe recurrent genotype 1 HCV in LTRs."

First author, publication year	Study Characteristics	Main findings	Author conclusions
	O: HCV virologic response	decrease in HCV viral load by day 19 of BOC; patient three had a delayed biochemical response but showed improved histology.	
Coilly, 2012 ²³	P: Five pts with recurrent hepatitis C post LT I: BOC plus PR (duration: NR) (IS: CYA, TAC, EVE) C: none O: HCV virologic response	A virological response was observed in all patients (mean HCV viral load [HVL] decrease at week 12, 6.64 +/- 0.35 log(10) IU/ml).	On page 5728: "A virological response was observed in all patients (mean HCV viral load [HVL] decrease at week 12, 6.64 +/- 0.35 log(10) IU/ml). These preliminary results in liver transplant patients with HCV recurrence demonstrate the feasibility and safety of coadministration of boceprevir and IT"
<p>AE=adverse event; BOC=boceprevir; C=comparator; C2=2 hr post-dose CSA level; CSA= cyclosporine; cEVR=complete early virological response; CYA=cyclosporine; EOT=end of treatment; EVE=everolimus; HCV=hepatitis C virus; I=intervention; IFN=interferon; ISA=immunosuppression agent; IT=immunosuppressive therapy; LT=liver transplantation; LTRs=liver transplant recipients; MMF=mycophenolate mofetil; NR=not report; O=outcome; P=population; PEG=pegylated; PR=peginterferon plus ribavirin; RAP=rapamune; rHCV=recurrent HCV; RVR=rapid viral response; RBV=ribavirin; RCT=randomized controlled trial; SIR=sirilimus; TAC=Tacrolimus; TP=telaprevir; wks=weeks. TT= triple therapy.</p>			