

TITLE: Retreatment, Switching and Extended Therapy with Boceprevir and Telaprevir for Chronic Hepatitis C Infection: A Review of the Clinical Effectiveness and Safety

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CONTEXT AND POLICY ISSUES

Two new protease inhibitors, boceprevir and telaprevir, were recently approved by Health Canada for treatment of chronic hepatitis C infection, genotype 1. By their current indications, these agents are to be added to peginterferon-ribavirin (PR) therapy.

Although within the same drug class, the two new protease inhibitors were studied in different clinical trial programs, and it is not entirely clear what differences exist between the two agents. The fact that both agents have been approved by Health Canada within months of each other has not allowed time for clinicians to establish where each should be positioned with respect to the other. It may be important to know, for example, whether patients who fail on one protease inhibitor can still be considered candidates for a trial of the other protease inhibitor. Similarly, if a patient has a poor response to or is not tolerating one protease inhibitor, is there evidence that they can safely and effectively be switched to the other? Evidence relating to prolongation of protease inhibitor therapy beyond the duration approved in the product monographs may also be of interest for patients experiencing inadequate response to therapy.

There is also a dilemma as to where to position these new protease inhibitors with respect to existing PR therapy, particularly in treatment-naïve patients. Should treatment-naïve patients be initiated on triple therapy (i.e., aggressively treat the virus from the outset with the best possible regimen) or, for economic and perhaps tolerability reasons, should triple therapy be reserved for patients who fail or are responding poorly to a PR regimen? It may therefore be important to understand the efficacy and safety of adding a protease inhibitor after initiation of a PR regimen.

The information in this review is intended to support jurisdictions across Canada in their listing decisions on the protease inhibitors for hepatitis C. This report was reviewed by a clinical expert in hepatology.

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RESEARCH QUESTIONS

1. What is the clinical evidence for retreating a patient with chronic hepatitis C infection with a protease inhibitor?
2. What is the clinical evidence for switching a patient with chronic hepatitis C infection to the other protease inhibitor midway through completion of the original PR-protease inhibitor therapy?
3. What is the clinical evidence for adding boceprevir or telaprevir treatment for patients with chronic hepatitis C infection who are currently undergoing treatment with only PR?
4. What is the clinical evidence regarding longer courses of treatment (of either PI-PR or PR alone) than approved in product monographs for patients with poor virological response on PI-PR or PR alone?

KEY MESSAGE

There is currently no available evidence for retreatment of patients with CHC infection with protease inhibitors.

There is currently no available evidence for switching a patient with CHC infection from one protease inhibitor to the other midway through completion of the original PR-protease inhibitor therapy.

There is evidence that initiating boceprevir after a 4-week lead-in period with PR leads to a higher response rate than continuing on PR alone. There is also evidence that in treatment-experienced patients, initiating telaprevir 4 weeks into a PR regimen is as efficacious and safe as starting patients on telaprevir-PR. There is no evidence for initiating a protease inhibitor after four weeks of PR therapy. There is also no evidence comparing the addition of a PI to PR at 4 weeks with continuation of PR alone in patients who achieve rapid virological response (undetectable HCV at 4 weeks); such patients demonstrate high SVR rates with 24 weeks of PR alone, therefore the benefit of PI-PR therapy is uncertain.

There is evidence that extending treatment duration with PR from 48 to 72 weeks leads to a statistically significant increase in the rate of sustained virologic response (SVR). However, given the availability of the protease inhibitors, it is perhaps unlikely that PR regimens longer than 48 weeks would be considered for most patients exhibiting slow virological response.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including MEDLINE, PubMed, EMBASE, The Cochrane Library (2011, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated list of major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents. The search was not limited by publication date. The search was run on January 4, 2012. A supplemental limited literature

search was performed on January 13, 2012 in MEDLINE and PubMed for publications addressing longer courses of treatment for peginterferon-ribavirin therapy.

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: Adult patients with chronic hepatitis C genotype 1 infection, previously treated with PI-PR Q2, Q3: Adult patients with chronic hepatitis C genotype 1 infection, currently being treated with PI-PR Q4: Adult patients with chronic hepatitis C genotype 1 infection demonstrating poor virologic response on PI-PR or PR alone
Intervention	Q1, Q3: PI-PR Q2: PI-PR (group switched to new PI) Q4: PI-PR or PR alone, standard 48 week regimen
Comparator	Q1, Q3: PR alone Q2: PR alone, or PI-PR (group continuing on original PI) Q4: PI-PR or PR alone, extended regimen
Outcomes	Sustained virologic response (SVR), morbidity, mortality, harms
Study Designs	Health technology assessments, systematic reviews and meta-analyses, randomized controlled trials, non-randomized trials Emerging evidence (e.g. conference abstracts)

Exclusion Criteria

Health technology assessments, systematic reviews and meta-analyses published prior to 2010 were excluded, as were duplicate publications of the same study. Studies that were included in selected systematic reviews were also excluded.

Critical Appraisal of Individual Studies

The quality of the included systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.¹ The adequacy of randomization, allocation concealment, blinding (of patients, clinicians or health care providers, data collectors and outcome assessors), loss to follow-up, early stopping of trial, and description of intention-to-treat analysis were considered in the critical appraisal of the included randomized controlled trials (RCTs).

SUMMARY OF EVIDENCE

Quantity of Research Available

The main literature search and supplemental search yielded 1081 citations. Upon screening titles and abstracts, 1046 citations were excluded and 35 potentially relevant articles were retrieved for full-text review. Of the 35 potentially relevant reports, 24 did not meet the inclusion criteria. Eleven reports are included in this review. The study selection process is outlined in a

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Appendix 1).

Five systematic reviews were identified focusing on PR treatment extension.²⁻⁶ One of the five reviews did not explicitly state that it focused on trials of patients who were slow/poor responders, thus this review was excluded.⁶

Four RCTs were identified for inclusion.⁷⁻¹⁰ Of these, three⁷⁻⁹ examined addition of protease inhibitors to PR therapy and one¹⁰ focused on PR treatment extension. Three non-randomized trials on treatment extension were also identified.¹¹⁻¹³

No studies were identified examining retreatment of patients with chronic hepatitis C with a protease inhibitor, or switching from one protease inhibitor to another.

Summary of Study Characteristics

The characteristics of the included systematic reviews are summarized in Appendix 2. The characteristics of the included RCTs and non-randomized studies are provided in Appendix 3 and Appendix 4, respectively.

What is the clinical evidence for retreating a patient with chronic hepatitis C infection with a protease inhibitor?

No literature identified.

What is the clinical evidence for switching a patient with chronic hepatitis C infection to the other protease inhibitor midway through completion of the original PR-protease inhibitor therapy?

No literature identified.

What is the clinical evidence for adding boceprevir or telaprevir treatment for patients with chronic hepatitis C infection who are currently undergoing treatment with only PR?

The phase 3 studies of boceprevir (SPRINT-2, RESPOND-2, Study 5685) featured a 4 week lead-in period, where all patients received PR, before adding either boceprevir or placebo to the regimen.^{7,8} Unless the patients were in the response guided therapy group, they received boceprevir-PR for the remainder of the 48 week regimen. For telaprevir, only one of the groups in one of the phase 3 studies (REALIZE) featured a ‘delayed start’ regimen, where patients randomized to triple therapy started with 4 weeks of PR before adding telaprevir.⁹ There was no evidence available regarding addition of a protease inhibitor after four weeks of PR therapy.

SPRINT-2 randomized 1099 patients 1:1:1 to boceprevir-PR, boceprevir-PR response guided therapy (RGT) or placebo, all on a background of peginterferon alpha 2b plus ribavirin (PR). Patients in SPRINT-2 were treatment-naïve, and had to have a minimum HCV RNA level of 10000 IU/ml. RESPOND-2 randomized 404 patients 2:2:1 to boceprevir-PR, boceprevir-PR RGT or placebo-PR, respectively, all on a PR background. RESPOND-2 and study 5685 randomized patients who were non-responders (decrease in HCV RNA but not to undetectable levels) or relapsers (undetectable HCV RNA at end of treatment but detectable during follow up). Prior null responders (< 2 log₁₀ decline in HCV RNA at Week 12 of prior therapy) were excluded from RESPOND-2. Patients in SPRINT-2 were slightly younger than patients in RESPOND-2 and study 5685 (50 versus 53 years). The majority of patients (≥60%) in all three

trials were male, and most patients (>80%) were Caucasian. The majority of patients in SPRINT-2 (65%), RESPOND-2 (59%) and study 5685 (56%) were HCV genotype 1a.

SPRINT-2 and RESPOND-2 featured a background of peginterferon alfa-2b and ribavirin (PR) plus either boceprevir or placebo. Study 5685 used peginterferon alfa-2a as part of the background with ribavirin. Each study featured a lead-in period of 4 weeks where patients received PR. In SPRINT-2, the boceprevir-PR group and placebo-PR groups were treated for an additional 44 weeks. Additionally, there was a third group that employed response guided therapy (RGT), in which the boceprevir-PR RGT group received boceprevir-PR for 24 weeks (weeks 5 to 28). If HCV RNA was undetectable in weeks 8-24 then treatment was deemed complete, otherwise PR was continued with placebo from weeks 28 through 48.

In REALIZE, 662 treatment-experienced patients were randomized 2:2:1 to either telaprevir-PR, delayed-start telaprevir with PR, or placebo-PR. The primary outcome was sustained virologic response. Patients were typically about 50 years of age on average, and the majority were male. Approximately half of all patients had previously experienced a relapse on PR therapy, approximately one-quarter were null responders, and about 20% were partial responders. About one-quarter of patients in REALIZE had cirrhosis at baseline. Patients in the two telaprevir groups received telaprevir for 12 weeks. However, one of the two groups began the first four weeks of the study on placebo-PR before switching to telaprevir-PR for the next 12 weeks ('delayed start'), while the other group began treatment with telaprevir-PR. The total duration of PR therapy in all arms was 48 weeks.

What is the clinical evidence regarding longer courses of treatment (of either PI-PR or PR alone) than approved in product monographs for patients with poor virological response on PI-PR or PR alone?

Systematic reviews

Five systematic reviews published in either 2010 (N=1) or 2011 (N=4) were identified.²⁻⁶ Each of these focused on studies that extended therapy of PR from 48 to 72 weeks. One of the five reviews did not explicitly state that it focused on trials of patients who were slow/poor responders, thus this review was excluded.⁶ All of the systematic reviews shared the same objective, to determine the effect of extended therapy with PR in patients with slow virologic response. The primary endpoint used to determine efficacy in all systematic reviews was the sustained virologic response (SVR), defined as maintenance of undetectable virus 24 weeks after end of treatment. In all cases, therapy was extended from the standard 48 weeks of PR to 72 weeks of PR. Patients in the included studies for all of the systematic reviews had to have been treatment naïve, although not all studies restricted to genotype 1. The reviews typically included the same studies, although there were some differences. In one case, this might have been due to timing of publication (two studies were published in 2010)^{14,15} while in the other case it is not clear why one study¹⁶ was not included in one review⁵ but was in the others.

Randomized controlled trials

One partially randomized open label RCT was identified (Nagaki 2009) that was not included in the systematic reviews.¹⁰ This study compared a 48 week regimen of PR to both a 72 week and a 96 week extended regimen of PR. The study was multicentre but entirely located in Japan. The sample size was also small (N=35 across 3 groups).

Non-randomized controlled trials

Three non-RCTs were identified.¹¹⁻¹³ Akuta compared the efficacy of 72 weeks PR (N=65) versus 48 weeks PR (N=130).¹³ These patients were primarily late virologic responders (HCV RNA positive at 12 weeks and negative at 24 weeks after start of treatment. Consecutive patients were recruited from a single Japanese centre. All participants received subcutaneous PEG-IFN-alpha 2b (median dose of 1.4 µg/kg) in combination with oral ribavirin (median dose of 11.1 mg/kg). Patients completing either 48 or 72 weeks therapy were enrolled into this study. A total of 318 patients were originally included in the 72-week cohort, but that number was reduced to 130 patients who were matched for age, sex, and time from start of treatment to the initial point of HCV RNA negativity.

Ikeda enrolled 82 consecutive Japanese patients with HCV genotype 1b infection, who were treated with PR.¹¹ Treatment duration was determined by the rapidity of viral response. Patients with undetectable virus at week 4 had 48 weeks PR, and duration of PR gradually extended for those with viral clearance at week 8 (52 weeks), week 12 (56 or 60 weeks), or weeks 16-24 (72 weeks).

Oze 2011 was a retrospective multicentre trial that enrolled 213 patients who had an LVR and completed therapy with an undetectable HCV RNA.¹² For patients with LVR, combination therapy continued for 48 or 72 weeks based on the decision of the investigator or clinical centre.

No studies relating to extension of PI-PR regimens were identified.

Summary of Critical Appraisal

A summary of the strengths and limitations of individual included studies is provided in Appendix 5.

What is the clinical evidence for retreating a patient with chronic hepatitis C infection with a protease inhibitor?

No literature identified.

What is the clinical evidence for switching a patient with chronic hepatitis C infection to the other protease inhibitor midway through completion of the original PR-protease inhibitor therapy?

No literature identified.

What is the clinical evidence for adding boceprevir or telaprevir treatment for patients with chronic hepatitis C infection who are currently undergoing treatment with only PR?

SPRINT-2, RESPOND-2, and REALIZE were all double-blinded, and randomization was carried out using a centralized process, which would be expected to contribute to maintenance of allocation concealment. Loss to follow-up rates were small and ITT analysis was employed in all studies.

What is the clinical evidence regarding longer courses of treatment (of either PI-PR or PR alone) than approved in product monographs for patients with poor virological response on PI-PR or PR alone?

Systematic reviews

The systematic reviews each identified an objective, and defined inclusion criteria *a priori*. Results between reviews were all consistent, and this is not surprising as there were a number of studies that were common to all reviews. Details of individual studies were not reported in all reviews. Sample sizes were small (<100 patients/group) in each of the studies where details were reported.

Randomized controlled trials

The single RCT included for this research question had a number of critical appraisal issues, including the fact that it was not blinded, was described as ‘partially randomized’ (although the reason for the description of ‘partial’ randomization was not given), and had a small sample size.

Non-randomized controlled trials

The non-RCTs provided evidence of limited quality, as lack of randomization and blinding leads to considerable potential for bias.

Summary of Findings

The main findings of the individual included studies are provided in Appendix 6.

What is the clinical evidence for retreating a patient with chronic hepatitis C infection with a protease inhibitor?

No literature identified.

What is the clinical evidence for switching a patient with chronic hepatitis C infection to the other protease inhibitor midway through completion of the original PR-protease inhibitor therapy?

No literature identified.

What is the clinical evidence for adding boceprevir or telaprevir treatment for patients with chronic hepatitis C infection who are currently undergoing treatment with only PR?

With boceprevir, all patients went through a 4 week lead-in period, therefore there are no comparisons available of patients that initiated boceprevir with PR versus patients who began boceprevir 4 weeks into PR therapy. Patients in the boceprevir-PR groups had higher SVR rates than those treated with placebo-PR in both the treatment-naïve (66% versus 38%, $P < 0.001$) and treatment-experienced populations (66% versus 21%, $P < 0.001$). Responses were similar in patients undergoing response-guided therapy, and in study 5685.

With respect to telaprevir, SVR responses in the delayed start group of REALIZE were similar to those in patients who were initiated on triple therapy (64% versus 66%, respectively), and both were statistically better than with placebo-PR (16%, $P < 0.001$).

For both agents, the incidence of serious adverse events, adverse events, and withdrawals due to adverse events also did not differ between delayed start and immediate start.

What is the clinical evidence regarding longer courses of treatment (of either PI-PR or PR alone) than approved in product monographs for patients with poor virological response on PI-PR or PR alone?

Systematic reviews

In each of the systematic reviews, extending treatment with PR from 48 to 72 weeks improved SVR rates, and in each review the improvement was statistically significant. Relative risks (SVR at 72 weeks versus 48 weeks) were highly consistent between studies, ranging between 1.40 and 1.44. Not all studies reported absolute SVR responses, but in Di Martino, 39% of patients achieved SVR in the group receiving 72 weeks of PR, while 30% achieved SVR with 48 weeks of PR.³

Alavian et al reported adverse events between the two treatment durations.² There were no adverse events that occurred more frequently with normal or extended duration therapy. Extended duration therapy was associated with an increased risk of drug discontinuation (Relative risk [RR] 2.70, 95% confidence interval [CI] 1.60 to 4.56) and discontinuation due to safety reasons (RR 1.54, 95% CI 1.11 to 2.14).

Randomized controlled trials

Nagaki was underpowered to detect differences between 48, 72 and 96 week regimens of PR. SVR rates increased with increasing duration of therapy, from 48 weeks (38% of patients), to 72 weeks (58% of patients) to 96 weeks (89% of patients).¹⁰ Multivariate analysis identified treatment for 96 weeks as a statistically significant independent factor associated with SVR compared with shorter treatment periods. However it should be noted that the sample sizes of these groups were small (between 9 and 13 patients per group).

Non-randomized controlled trials

In Akuta, SVR was achieved by 61.5% and 32.3% of patients in the 72-week and 48-week regimens, respectively, and this difference was statistically significant ($P < 0.001$).¹³ No further relevant outcome data were presented.

In Ikeda, 40% of patients with late virological response achieved SVR, while 80% of patients with early virological response achieved SVR, and all 8 patients who had rapid viral response achieved SVR.¹¹

In Oze, the SVR rate was higher with 72 weeks treatment versus 48 weeks (59% versus 37%, $P = 0.002$).¹²

Limitations

Chronic hepatitis C is a slowly progressive condition that does not inevitably lead to serious complications such as cirrhosis and/or hepatocellular carcinoma.^{17,18} The studies included in this assessment did not report on liver-related mortality or morbidity, relying instead on SVR rates to compare the efficacy of various treatment strategies.



CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

There is currently no evidence available to guide whether patients can be successfully retreated with a protease inhibitor-PR regimen, or whether switching from one protease inhibitor to another during the course of a PR regimen is a potential strategy for addressing poor response or tolerability issues.

With respect to adding a protease inhibitor to ongoing PR therapy, the only available evidence consists of boceprevir trials that employed a 4 week lead-in period where patients took PR before adding boceprevir or one group of one telaprevir trial, which featured a 'delayed start' of the protease inhibitor four weeks after PR had been initiated. No evidence is available for adding a protease inhibitor more than four weeks after initiation of PR therapy. In both treatment-experienced and treatment-naïve patients, addition of boceprevir to an ongoing PR regimen at four weeks demonstrated higher SVR rates than PR therapy alone. There were no data comparing addition of boceprevir at four weeks with initiation of triple therapy without a lead-in period. For telaprevir, the REALIZE study in treatment-experienced patients demonstrated that telaprevir added 4 weeks into PR resulted in similar SVR rates as initiation of triple therapy, and higher SVR rates than PR alone. An important question that has yet to be studied is whether there is an advantage to the addition of a protease inhibitor to patients who achieve rapid virological response (RVR), i.e., HCV undetectability at four weeks. The benefits of PI in this population are uncertain since most patients with RVR are able to achieve SVR with only 24 weeks of PR therapy.¹⁹

No conclusions can be drawn about extending triple therapy with protease inhibitors, as there are no studies that have examined this. Data from several intermediate sized studies suggest that extending PR therapy from 48 weeks to 72 weeks can improve SVR rates in patients who are slow responders to therapy. Given the availability of protease inhibitor-based therapy, and in light of the significant adverse effect profile of PR therapy, it is perhaps unlikely that PR regimens longer than 48 weeks would be considered for most patients exhibiting slow virological response.

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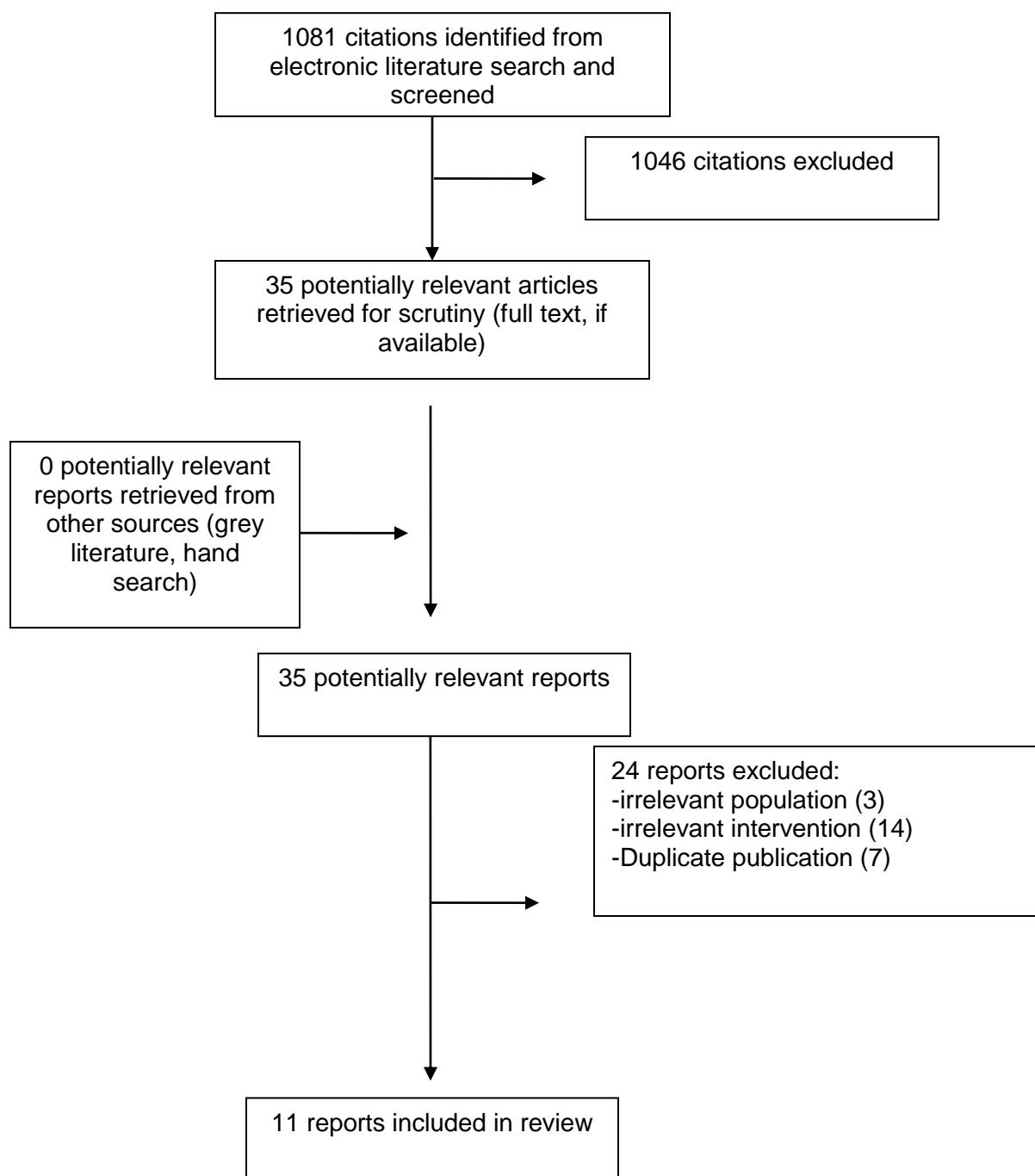
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REFERENCES

1. Shea BJ, Bouter LM, Peterson J, Boers M, Andersson N, Ortiz Z, et al. External validation of a measurement tool to assess systematic reviews (AMSTAR). PLoS ONE [Internet]. 2007 [cited 2012 Feb 8];2(12):e1350. Available from: <http://dx.plos.org/10.1371/journal.pone.0001350>
2. Alavian SM, Tabatabaei SV, Behnava B, Mahboobi N. Optimal duration of treatment for HCV genotype 1 infection in slow responders: a meta-analysis. Hepat Mon [Internet]. 2011 Aug 1 [cited 2012 Feb 15];11(8):612-9. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3227488>
3. Di Martino V, Richou C, Cervoni JP, Sanchez-Tapias JM, Jensen DM, Mangia A, et al. Response-guided peg-interferon plus ribavirin treatment duration in chronic hepatitis C: meta-analyses of randomized, controlled trials and implications for the future. Hepatology. 2011 Sep 2;54(3):789-800.
4. Farnik H, Lange CM, Sarrazin C, Kronenberger B, Zeuzem S, Herrmann E. Meta-analysis shows extended therapy improves response of patients with chronic hepatitis C virus genotype 1 infection. Clin Gastroenterol Hepatol. 2010 Oct;8(10):884-90.
5. Parikh M, Singh A, Sood G. Extended treatment duration for treatment naive chronic hepatitis C genotype 1 late viral responders: a meta-analysis comparing 48 weeks vs 72 weeks of pegylated interferon and ribavirin. J Viral Hepat. 2011 Apr;18(4):e99-103.
6. Gevers TJ, Slavenburg S, van Oijen MG, Drenth JP. Treatment extension benefits HCV genotype 1 patients without rapid virological response: a systematic review. Neth J Med. 2011 May;69(5):216-21.
7. Poordad F, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1195-206.
8. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1207-17.
9. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011 Jun 23;364(25):2417-28.
10. Nagaki M, Shimizu M, Sugihara JI, Tomita E, Sano C, Naiki T, et al. Clinical trial: extended treatment duration of peginterferon-alpha2b plus ribavirin for 72 and 96 weeks in hepatitis C genotype 1-infected late responders. Aliment Pharmacol Ther. 2009 Aug 15;30(4):343-51.
11. Ikeda H, Suzuki M, Okuse C, Yamada N, Okamoto M, Kobayashi M, et al. Short-term prolongation of pegylated interferon and ribavirin therapy for genotype 1b chronic hepatitis C patients with early viral response. Hepatol Res. 2009 Aug;39(8):753-9.
12. Oze T, Hiramatsu N, Yakushijin T, Mochizuki K, Imanaka K, Yamada A, et al. The efficacy of extended treatment with pegylated interferon plus ribavirin in patients with HCV genotype 1 and slow virologic response in Japan. J Gastroenterol. 2011 Jul;46(7):944-52.

13. Akuta N, Suzuki F, Hirakawa M, Kawamura Y, Yatsuji H, Sezaki H, et al. A matched case-controlled study of 48 and 72 weeks of peginterferon plus ribavirin combination therapy in patients infected with HCV genotype 1b in Japan: amino acid substitutions in HCV core region as predictor of sustained virological response. *J Med Virol.* 2009 Mar;81(3):452-8.
14. Ferenci P, Laferl H, Scherzer TM, Maierov A, Hofer H, Stauber R, et al. Peginterferon alfa-2a/ribavirin for 48 or 72 weeks in hepatitis C genotypes 1 and 4 patients with slow virologic response. *Gastroenterology.* 2010 Feb;138(2):503-12.
15. Miyase S, Ogata K, Haraoka K, Morishita Y, Fujiyama S. The efficacy of prolonging treatment with peginterferon alfa-2b and ribavirin to 72 weeks in chronic hepatitis C genotype 1 patients HCV RNA positive at week 8 but negative at week 12. *Acta Hepato Jpn.* 2010;51(1):48-50.
16. Sanchez-Tapias JM, Diago M, Escartin P, Enriquez J, Romero-Gomez M, Barcena R, et al. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterology.* 2006 Aug;131(2):451-60.
17. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology.* 2008 Aug;48(2):418-31.
18. Ghany MG, Strader DB, Thomas DL, Seeff LB, American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology.* 2009 Apr;49(4):1335-74.
19. Jensen DM, Morgan TR, Marcellin P, Pockros PJ, Reddy KR, Hadziyannis SJ, et al. Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. *Hepatology.* 2006 May;43(5):954-60.

Appendix 1: Selection of Included Studies

Appendix 2: Characteristics of Included Systematic Reviews

First author, country, publication year	Eligibility criteria	Included study designs	Included studies
Di Martino 2011 ³ Europe	<p>Population: Naïve patients with CHC genotype 1, experiencing a slow virologic response (detectable HCV RNA at week 12 despite a >2 log drop in viral load from baseline and undetectable HCV RNA at week 24)</p> <p>Intervention: PEG-IFN plus RIBA weight based (4 trials) or RIBA 800mg/d (2 trials) for either 48 weeks or 72 weeks (extended duration)</p> <p>Outcome: SVR</p>	RCTs (English publication)	6 RCTs Berg 2006, Sanchez-Tapias 2006, Ferenci 2010, Pearlman 2007, Buti 2009, Mangla 2008
Alavian 2011 ² Iran	<p>Population: Patients with CHC genotype 1, experiencing a slow virologic response (Detectable HCV-RNA at treatment week 4 Achieved at least 2 log decrease in HCV-RNA from baseline to 12 weeks or undetectable HCV-RNA at 24 weeks Genotype 1)</p> <p>Intervention: PEG-IFN alpha-2a 180 µg/kg/week or PEG-IFN alpha-2b 1.5 µg/kg/week plus weight based RIBA using standard (48 weeks) or extended (72 weeks) therapy</p> <p>Outcome: SVR</p>	RCTs	7 RCTs (N=1206 patients) Berg 2006, Sanchez-Tapias 2006, Ferenci 2010, Pearlman 2007, Buti 2009, Mangla 2008, Miyase 2010
Parikh 2011 ⁵ USA	<p>Population: treatment-naïve patients with CHC, experiencing a slow virologic response (>50IU/mL or ≥2 log decrease but detectable HCV RNA at week 12 and undetectable HCV RNA at week 24)</p> <p>Intervention: PEG-IFN 2a or 2b plus RIBA 800-1400mg for standard (48 weeks) or extended (72 weeks) course</p> <p>Outcomes: SVR, EOT response, relapse</p>	RCTs	5 RCTs Berg 2006, Ferenci 2010, Pearlman 2007, Buti 2009, Mangia 2008
Farnik 2010 ⁴ Germany	<p>Population: Patients with CHC Genotype 1, experiencing a slow virologic response (≥2 log10 decrease but detectable HCV RNA at week 12 followed by undetectable HCV RNA at week 24)</p> <p>Intervention: PEG-IFN-alpha plus RIBA for either 48 weeks or 72 weeks (extended therapy)</p> <p>Outcome: SVR</p>	RCTs	6 RCTs (N=1252) Berg 2006, Sanchez-Tapias 2006, Ferenci 2010, Pearlman 2007, Buti 2009, Manga 2008

HCV=hepatitis C virus; IFN=interferon; PEG=pegylated; RIBA=ribavirin; RCT=randomized controlled trial; SVR=sustained virologic response

Appendix 3: Characteristics of Included RCTs

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)
Zeuzem 2011 ⁹ REALIZE Multi-country	DBRCT Multicentre	CHC genotype 1 with HCV RNA level \geq 1000 IU/mL, failed at least one prior course of PR therapy n=662	TP + PR for 12 weeks then PL + PR for 4 weeks then PR for 32 weeks PL + PR for 4 weeks then TP + PR for 12 weeks then PR for 32 weeks	PL + PR for 16 weeks then PR for 32 weeks
Poordad 2011 ⁷ SPRINT-2 Multi-country	DBRCT Multicentre	Chronic infection with HCV genotype 1 Plasma HCV RNA level of 10,000 IU per milliliter or greater No previous treatment for HCV infection N=1099	Boceprevir 800 mg TID x 44 weeks (N=367) Boceprevir 800 mg TID x 24 weeks (RGt) (N=368) Peginterferon alfa-2B SC 1.5 μ g/kg once weekly; and weight-based oral ribavirin 600 to 1400 mg per day in divided doses	Placebo X 44 weeks (N=364) Peginterferon alfa-2B SC 1.5 μ g/kg once weekly; and weight-based oral ribavirin 600 to 1400 mg per day in divided doses
Bacon 2011 ⁸ RESPOND-2 Multi-country	DBRCT Multicentre	Chronic infection with HCV genotype 1, and either Non-response or Relapse on prior PR therapy (minimum duration 12 weeks): -Non-response (decrease in the HCV RNA level of at least 2 log ₁₀ IU/mL by week 12 but	Boceprevir 800 mg TID x 44 weeks (N=162) Boceprevir 800 mg TID x 32 weeks (RGt) (N=162) Peginterferon alfa-2B SC 1.5 μ g/kg once weekly; and weight-based oral ribavirin 600 to 1400 mg per day in divided doses	Placebo X 44 weeks (N=80) Peginterferon alfa-2B SC 1.5 μ g/kg once weekly; and weight-based oral ribavirin 600 to 1400 mg per day in divided doses

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)
		detectable HCV RNA during the therapy period) -Relapse (i.e., undetectable HCV RNA level at the end of treatment, without subsequent attainment of sustained virologic response during follow up period).N=404		
Nagaki 2009 ¹⁰ Japan	Partially randomized open label 48, 72, or 96 weeks treatment followed by assessment for SVR	HCV genotype 1 Treatment naïve or retreated Late responders were defined as HCV RNA first undetectable at week 12-48. (N=35)	48 weeks: PEG-IFN alpha-2b + RIBA (weight based)	72 weeks: as with 48 week regimen, then 24 weeks of PEG-IFN alpha-2b+low dose RIBA (200mg/d) 96 weeks: 48 week regimen then 48 weeks low dose PEG-IFN alpha-2b (0.75 µg/kg/week) plus RIBA 200 mg/d (doses were tapered with longer duration regimens to improve tolerability)

HCV=hepatitis C virus; **IFN**=interferon; **IU**=international units; **PEG**=pegylated;
RIBA=ribavirin; **SC**=subcutaneous; **SVR**=sustained virologic response; **TID**=three times daily

Appendix 4: Characteristics of Included Non-randomized Trials

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)
Oze 2011 ¹² Japan	Retrospective study	CHC genotype 1	48 week treatment group: Treated for 46-52 weeks	72 week treatment group: Treated for 68-78 weeks
Akuta 2009 ¹³ Japan	Case control Single centre	Adult Japanese patients with HCV genotype 1b (N=195)	48 weeks: PEG-IFN-alpha 2b at a median dose of 1.4 µg/kg subcutaneously plus oral ribavirin at a median dose of 11.1 mg/kg	72 weeks: PEG-IFN-alpha 2b at a median dose of 1.4 µg/kg subcutaneously plus oral ribavirin at a median dose of 11.1 mg/kg
Ikeda 2009 ¹¹ Japan	non-RCT	HCV positive with high viral load (>100 KIU/mL) (N=82)	Individualized (RVR): PEG-IFN alpha-2b (1.5 µg/kg/week) and weight-based ribavirin 600-1000mg	EVR, LVR

BOC=boceprevir; **DS**=delayed start; **EVR**=early virologic response; **HCV**=hepatitis C virus; **LVR**=late virologic response; **PR**=peginterferon/ribavirin; **RD**=risk difference; **RGT**=response guided therapy; **RR**=relative risk; **RVR**=rapid virologic response; **SAE**=serious adverse events; **SVR**=sustained virologic response

Appendix 5: Summary of Study Strengths and Limitations

First author, publication year	Strengths	Limitations
Di Martino 2011 ³	<ul style="list-style-type: none"> • Research question/inclusion criteria identified • Triplicate study selection • At least two databases searched • Conference abstracts included • Data provided for individual studies • Appropriate statistics performed • Conflict of interest declared 	<ul style="list-style-type: none"> • English language only • List of excluded studies not provided • No assessment of study quality provided • Publication bias not assessed
Alavian 2011 ²	<ul style="list-style-type: none"> • Research question/inclusion criteria identified • Duplicate study selection • At least two databases searched • All languages included • Data provided for individual studies • Assessment of study quality was performed and commented upon in conclusions • Appropriate statistics performed • Publication bias assessed • Conflict of interest reported as none 	<ul style="list-style-type: none"> • List of excluded studies not provided
Parikh 2011 ⁵	<ul style="list-style-type: none"> • Research question/inclusion criteria identified • At least two databases searched • Triplicate study selection • Data provided for individual studies • Appropriate statistics performed • Assessment of study quality appears to have been performed • Conflict of interest reported as none 	<ul style="list-style-type: none"> • List of excluded studies not provided • Publication bias reported as assessed but not described
Farnik 2010 ⁴	<ul style="list-style-type: none"> • Research question/inclusion criteria identified • At least two databases searched 	<ul style="list-style-type: none"> • English language only • List of excluded studies not provided

First author, publication year	Strengths	Limitations
	<ul style="list-style-type: none"> Duplicate study selection Abstracts included Data provided for individual studies Appropriate statistics performed Assessment of study quality was performed and commented upon in conclusions Conflict of interest declared 	
Randomized controlled trials		
Zeuzem 2011 ⁹ REALIZE	<ul style="list-style-type: none"> Centralized randomization Double blind design 	<ul style="list-style-type: none"> Follow up too short to assess clinical outcomes such as mortality/morbidity
Poordad 2011 ⁷ SPRINT-2	<ul style="list-style-type: none"> Central randomization Double blind design 	<ul style="list-style-type: none"> Follow up too short to assess clinical outcomes such as mortality/morbidity
Bacon 2011 ⁸ RESPOND-2	<ul style="list-style-type: none"> Central randomization Double blind design 	<ul style="list-style-type: none"> Follow up too short to assess clinical outcomes such as mortality/morbidity
Nagaki 2009 ¹⁰		<ul style="list-style-type: none"> Open label design Partial randomization Inadequate power
Non-Randomized controlled trials		
Oze 2011 ¹²		<ul style="list-style-type: none"> Non-randomized Non-blinded
Akuta 2009 ¹³		<ul style="list-style-type: none"> Non-randomized Non-blinded
Ikeda 2009 ¹¹		<ul style="list-style-type: none"> Non-randomized Non-blinded

Appendix 6: Summary of Main Study Findings and Author Conclusions

First author, publication year	Main findings	Author conclusions
<i>Systematic reviews</i>		
Di Martino 2011 ³	SVR, 72 versus 48 weeks: RR 1.40 [95% CI 1.11 to 1.77], P = 0.003	“Long durations of P/R therapy improve SVR, regardless of genotype. This effect is nonetheless negligible in rapid responders, with the most favorable conditions for SVR (G2, G1 with low viral load, and G3 with weight-adjusted ribavirin regimen).” (p. 789)
Alavian 2011 ²	SVR, 72 versus 48 weeks: RR 1.44 [95% CI 1.2 to 1.74]	“72 weeks of PR is significantly superior to the standard 48 week therapy for slow responders with genotype 1 infection” (p. 612)
Parikh 2011 ⁵	SVR, 72 versus 48 weeks: OR 1.67 [95% CI 1.16 to 2.40], P = 0.006 Relapses: OR 0.39 [95% CI 0.25 to 0.51], P < 0.0001	“Therapy extension in genotype 1 late viral responders may be a consideration to improve treatment response; however the proportion of patients with late viral response that might benefit from 72 week therapy appears to be small.” (p. e99)
Farnik 2010 ⁴	SVR, 72 versus 48 weeks: RD 12.6% [95% CI 5.7% to 19.5%], P = 0.0004	“Extending the duration of treatment with pegIFN-alfa-2a/b and ribavirin in patients with HCV genotype 1 and a slow response to therapy improves the rate of SVR” (p. 884)
<i>Randomized controlled trials</i>		
Zeuzem 2011 ⁹ REALIZE	SVR: T12PR48: 64% T12(DS)PR48: 66% PR48: 17% Relapses: T12PR48: 27% T12(DS)PR48: 25% PR48: 60% SAE: Pooled Telaprevir: 12% PR48: 5%	“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.” (p. 2417)
Poordad 2011 ⁷ SPRINT-2	SVR: BOC-PR48: 66% BOC-PR-RGT: 63% PR48 (control): 38% Relapses: BOC-PR48: 9% BOC-PR-RGT: 9% PR48 (control): 22% SAE: BOC-PR48: 12%	“The addition of boceprevir to standard therapy with PR, as compared with standard therapy alone, significantly increased the rates of sustained virologic response in previously untreated adults with chronic HCV genotype 1 infection. The rates were similar with 24 weeks and 44 weeks of boceprevir.” (p. 1195)

First author, publication year	Main findings	Author conclusions
	BOC-PR-RGT: 11% PR48 (control): 9%	
Bacon 2011 ⁸ RESPOND-2	SVR: BOC-PR48: 66% BOC-PR-RGT: 59% PR48 (control): 21% Relapses: BOC-PR48: 12% BOC-PR-RGT: 15% PR48 (control): 32% SAE: BOC-PR48: 14% BOC-PR-RGT: 10% PR48 (control): 5%	“The addition of boceprevir to peginterferon-ribavirin resulted in significantly higher rates of sustained virologic response in previously treated patients with chronic HCV genotype 1 infection, as compared with peginterferon-ribavirin alone.” (p. 1207)
Nagaki 2009 ¹⁰	SVR: 48 weeks: 5/13 (38%) 72 weeks: 7/12 (58%) 96 weeks: 8/9 (89%) Relapse: 48 weeks: 8/13 (62%) 72 weeks: 5/12 (42%) 96 weeks: 1/9 (11%)	“Extending the treatment duration from 48 weeks to 96 weeks improves SVR rates in genotype 1-infected patients with late virological response to peginterferon-alpha-2b and ribavirin.” (p. 343)
<i>Non-Randomized controlled trials</i>		
Oze 2011 ¹²	SVR: 48 weeks: 39/106 (37%) 72 weeks: 63/107 (59%)	“An earlier response predicts a higher SVR rate in patients with an LVR given 72-week treatment. Extended treatment with Peg-IFN plus ribavirin for patients with an LVR improved the treatment efficacy, even for aged patients.” (p. 944)
Akuta 2009 ¹³	SVR (overall) 48 weeks: 42/130 (32%) 72 weeks: 40/65 (62%)	“We conclude that 72-week PEG-IFN/RBV improves SVR rate for LVR, especially those with Arg70 and/or Leu91 of core region or wild-type of ISDR. Substitution of aa 70 and 91 is also a useful pretreatment predictor of response to 72-week PEG-IFN/RBV” (p. 452)
Ikeda 2009 ¹¹	SVR RVR: 8/8 (100%) EVR: 33/41 (80%) LVR: 6/15 (40%)	“Short treatment extension of PEG IFN plus RBV treatment protocols in EVR patients can improve overall SVR rates” (p. 753)

BOC=boceprevir; **CI**=confidence interval; **DS**=delayed start; **EVR**=early virologic response; **HCV**=hepatitis C virus; **VR**=late virologic response; **PR**=peginterferon/ribavirin; **RD**=risk difference; **RGT**=response guided therapy; **RR**=relative risk; **RVR**=rapid virologic response; **SAE**=serious adverse events; **SVR**=sustained virologic response