Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2013-B-048 Sofosbuvir

Stand: Juli 2013

I. Zweckmäßige Vergleichstherapie: Kriterien der VerfO

Sofosbuvir (2013-B-048)

Zur Behandlung der chronischen Hepatitis C (Genotyp 1 bis 6)

Kriterien gemäß 5. Kapitel § 6 Absatz 3 Satz 2 VerfO		
1. Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	- Ribaverin - Interferon alfa 2a - Peginterferon alfa 2a - Interferon alfa 2a - Peginterferon alfa 2a - Boceprevir (Genotyp 1) - Telaprevir (Genotyp 1)	
2. Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Nicht medikamentöse Maßnahmen kommen nicht in Betracht	
3. Als Vergleichstherapie sollen bevorzugt Arzneimittel-anwendungen oder nicht-medikamentöse Behandlungen herangezogen werden, deren patientenrelevanter Nutzen durch den Gemeinsamen Bundesausschuss bereits festgestellt ist.	- - Boceprevir (Beschluss nach § 35a SGB V vom 01.03.2012) - - Telaprevir (Beschluss nach § 35a SGB V vom 29.03.2012)	
4. Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	⇨ *siehe Evidenzrecherche*	
5. Bei mehreren Alternativen ist die wirtschaftlichere Therapie zu wählen, vorzugsweise eine Therapie, für die ein Festbetrag gilt.	Nicht angezeigt	
6. […] vorzugsweise eine Therapie, […] die sich in der praktischen Anwendung bewährt hat.	Nicht angezeigt	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff ATC-Code Handelsname	**Anwendungsgebiet** (Text aus Fachinformation/SmPC)
Sofosbuvir ATC-Code und Handelsname liegen nicht vor	In Kombination mit anderen Wirkstoffen zur Behandlung der chronischen Hepatitis C bei Erwachsenen.
Systemische Therapie	
Ribaverin Copegus® (J05AB04)	Copegus ist indiziert zur Behandlung der chronischen Hepatitis C und darf nur als Teil einer Kombinationstherapie mit Peginterferon alfa-2a oder mit Interferon alfa-2a angewendet werden. Copegus darf nicht als Monotherapie angewendet werden. Die Kombination von Copegus mit Peginterferon alfa-2a oder Interferon alfa-2a ist indiziert bei *erwachsenen Patienten,* die Serum-HCV-positiv sind, einschließlich Patienten mit kompensierter Zirrhose. Die Kombination mit Peginterferon alfa-2a ist auch indiziert bei Patienten mit einer klinisch stabilen HIV-Begleitinfektion, einschließlich Patienten mit kompensierter Zirrhose. Die Kombination von Copegus und Peginterferon alfa-2a ist indiziert bei unvorbehandelten Patienten und bei Patienten, bei denen eine vorhergehende Therapie mit Interferon alfa (pegyliert oder nicht pegyliert) alleine oder in der Kombinationstherapie mit Ribavirin versagt hat. Bitte beachten Sie die Fachinformation von Peginterferon alfa-2a oder Interferon alfa-2a für Informationen zur Anwendung des jeweiligen Arzneimittels.
Peginterferon alfa 2a Pegasys® (L03AB11)	Pegasys ist indiziert zur Behandlung *erwachsener Patienten* mit chronischer Hepatitis C, deren Serum HCV-RNA-positiv ist, einschließlich Patienten mit kompensierter Zirrhose und/oder mit einer klinisch stabilen HIV-Begleitinfektion. Pegasys wird bei Patienten mit chronischer Hepatitis C am besten in Kombination mit Ribavirin angewendet. Die Kombination von Pegasys und Ribavirin ist indiziert bei unvorbehandelten Patienten und bei Patienten, bei denen eine vorhergehende Therapie mit Interferon alfa (pegyliert oder nicht pegyliert) alleine oder in der Kombinationstherapie mit Ribavirin versagt hat. Die Monotherapie ist hauptsachlich bei einer Intoleranz oder Kontraindikationen gegen Ribavirin indiziert..
Interferon alfa 2a Roferon® (L03AB04)	– Histologisch nachgewiesene chronische Hepatitis C bei *erwachsenen Patienten*, bei denen HCV-Antikörper oder HCVRNA und erhöhte Serumspiegel der Alaninaminotransferase (ALT) ohne Leberdekompensation vorliegen.
	– Die Wirksamkeit von Interferon alfa-2a bei der Behandlung der Hepatitis C wird durch die Kombination mit Ribavirin erhöht. Roferon-A sollte als Monotherapie nur bei Intoleranz oder Kontraindikationen gegen Ribavirin angewendet werden.

Ribaverin Rebetol® (J05AB04)	**3-fach-Kombinationstherapie:** Rebetol ist, in Kombination mit Boceprevir und Peginterferon alfa-2b, bestimmt zur Behandlung der chronischen Hepatitis- C(CHC)-Infektion vom Genotyp 1 bei erwachsenen Patienten (18 Jahre und älter) mit kompensierter Lebererkrankung, die nicht vorbehandelt sind oder die nicht auf eine vorangegangene Therapie angesprochen bzw. einen Rückfall erlitten haben. Bitte beachten Sie die Fachinformationen zu Peginterferon alfa-2b und Boceprevir, wenn Rebetol in Kombination mit diesen Arzneimitteln angewendet wird. **Therapie mit zwei Arzneimitteln (Duale Therapie):** Rebetol ist bestimmt zur Behandlung der chronischen Hepatitis-C-Virusinfektion bei Erwachsenen, Kindern ab dem Alter von 3 Jahren und Jugendlichen und darf nur als Teil eines Kombinations-Dosierungsschemas mit Peginterferon alfa-2b oder Interferon alfa-2b angewendet werden. Eine Rebetol Monotherapie darf nicht angewendet werden. Bitte beachten Sie die Fachinformationen zu Interferon alfa-2b und Peginterferon alfa-2b, wenn Rebetol in Kombination mit diesen Arzneimitteln angewendet wird. Es liegen keine Informationen zur Sicherheit oder Wirksamkeit für die Anwendung von Rebetol mit anderen Formen von Interferon (d. h. kein alfa-2b) vor. **<u>Naive Patienten</u>** ***Erwachsene*** Patienten (18 Jahre und älter): Rebetol ist bestimmt für die · **3-fach-Kombinationstherapie** – in Kombination mit Peginterferon alfa-2b und Boceprevir zur Behandlung von erwachsenen Patienten mit chronischer Hepatitis- C-Infektion vom Genotyp 1 mit kompensierter Lebererkrankung. · **Duale Therapie** – in Kombination mit Interferon alfa-2b oder Peginterferon alfa-2b zur Behandlung von erwachsenen Patientenmit chronischer Hepatitis C, die nicht vorbehandelt sind, ohne Leberdekompensation sind, erhöhte Alanin-Aminotransferase- Werte (ALT-Werte) haben und die Hepatitis-C-Virus-Ribonukleinsäure(HCV-RNA)-positiv sind. ·**Duale Therapie** – in Kombination mit Peginterferon alfa-2b zur Behandlung einer CHC-Infektion bei Patienten mit kompensierter Zirrhose und/oder klinisch stabilerHIV-Co-Infektion (siehe Abschnitt4.4). **<u>Vorbehandelte Patienten</u>** ***Erwachsene*** Patienten: Rebetol ist bestimmt für die · **3-fach-Kombinationstherapie** – in Kombination mit Peginterferon alfa-2b und Boceprevir zur Behandlung von erwachsenen Patienten mit CHC-Infektion vom Genotyp 1 mit kompensierter Lebererkrankung. · **Duale Therapie** – in Kombination mit Peginterferon alfa-2b zur Behandlung von Patienten mit chronischer Hepatitis C, die auf eine vorangegangene Therapie mit Interferon alfa (pegyliert oder nicht-pegyliert) alleinoder inKombination mit Ribavirin nicht angesprochen bzw. einen Rückfall erlitten haben (siehe Abschnitt 5.1).

	· **Duale Therapie** – in Kombination mit Interferon alfa-2b zur Behandlung von Patienten mit chronischer Hepatitis C, die zunächst auf eine Interferon-alfa-Monotherapie angesprochen haben (mit Normalisierung der ALT-Werte am Ende der Behandlung), jedoch später einen Rückfall erlitten haben.
Peginterferon alfa 2b Pegintron® (L03AB10)	***Erwachsene (3-fach-Kombinationstherapie):*** PegIntron ist, in Kombination mit Ribavirin und Boceprevir (3-fach-Kombinationstherapie), indiziert zur Behandlung der chronischen Hepatitis-C(CHC)-Infektion vom Genotyp 1 bei erwachsenen Patienten (18 Jahre und älter) mit kompensierter Lebererkrankung, die nicht vorbehandelt sind oder die nicht auf eine vorangegangene Therapie angesprochen bzw. einen Rückfall erlitten haben. Bitte beachten Sie die Fachinformationen zu Ribavirin und Boceprevir, wenn Sie PegIntron in Kombination mit diesen Arzneimitteln anwenden. ***Erwachsene (Duale Therapie und Monotherapie):*** PegIntron ist indiziert zur Behandlung erwachsener Patienten (18 Jahre und älter) mit CHC, die Hepatitis-C-Virus-RNA(HCVRNA)-positiv sind, einschließlich Patienten mit kompensierter Zirrhose und/oder Patienten, die klinisch stabilmit HIV co-infiziert sind. PegIntron in Kombination mit Ribavirin (Duale Therapie) ist indiziert zur Behandlung der CHC-Infektion bei nicht vorbehandelten erwachsenen Patienten, einschließlich Patienten, die klinisch stabil mit HIV co-infiziert sind, und bei erwachsenen Patienten, die nicht auf eine vorangegangene Kombinationstherapie mit Interferon alfa (pegyliert oder nicht-pegyliert) und Ribavirin oder auf eine Interferon alfa-Monotherapie angesprochen bzw. einen Rückfall erlitten haben. Die Interferon-Monotherapie, einschließlich PegIntron, ist hauptsächlich indiziert im Fall einer Intoleranz oder einer Gegenanzeige gegenüber Ribavirin. Bitte beachten Sie die Fachinformation zu Ribavirin, wenn PegIntron in Kombinationmit Ribavirin angewendet wird.
Interferon alfa 2b IntronA® (L03AB05)	Vor Behandlungsbeginn mit IntronA sollten die Ergebnisse von klinischen Studien zum Vergleich von IntronA mit pegyliertem Interferon berücksichtigt werden ***Erwachsene*** IntronA ist indiziert zur Behandlung von erwachsenen Patienten mit chronischer Hepatitis C, die erhöhte Transaminasenwerte ohne Leberdekompensation haben und die Hepatitis C-Virus-RNA (HCV-RNA)-positiv sind. Die beste Art, IntronA bei dieser Indikation anzuwenden, ist die Kombination mit Ribavirin ***Kinder im Alter ab 3 Jahren und Jugendliche*** IntronA ist, in Kombination mit Ribavirin, bestimmt zur Behandlung von Kindern im Alter von 3 Jahren und älter und Jugendlichen mit chronischer Hepatitis C-Infektion, die nicht vorbehandelt sind, keine Leberdekompensation zeigen und die HCV-RNA-positiv sind. Bei der Entscheidung, eine Therapie nicht bis zum Erwachsenenalter zu verschieben, ist unbedingt zu berücksichtigen, dass die Kombinationstherapie eine Hemmung des Wachstums induziert. Es ist unklar, ob diese Wachstumshemmung reversibel ist. Die

	Entscheidung über eine Behandlung sollte von Fall zu Fall abgewogen werden.
Ribaverin Ribaverin-ratiopharm® (J05AB04)	Ribavirin-ratiopharm ® ist indiziert zur Behandlung der chronischen Hepatitis-CVirusinfektion (HCV-Infektion) bei Erwachsenen und darf nur als Teil eines Kombinations- Dosierungsschemas mit Peginterferon alfa-2b oder Interferon alfa-2b angewendet werden. Eine Ribavirin-ratiopharm ®-Monotherapie darf nicht angewendet werden. Es liegen keine Informationen zur Unbedenklichkeit oder Wirksamkeit für die Anwendung von Ribavirin-ratiopharm ® mit anderen Formen von Interferon (d.h. kein alfa-2b) vor. **Vorbehandelte Patienten** **Erwachsene** Ribavirin-ratiopharm ® ist in Kombination mit Interferon alfa-2b indiziert zur Behandlung von erwachsenen Patienten mit chronischer Hepatitis C, die zunächst auf eine Interferon-alfa-Monotherapie angesprochen haben (mit Normalisierung der ALT-Werte am Ende der Behandlung), jedoch später einen Rückfall erlitten haben. Ribavirin-ratiopharm® ist indiziert in Kombination mit Peginterferon alfa-2b zur Behandlung von erwachsenen Patienten mit chronischer Hepatitis C, die auf eine vorangegangene Therapie mit Interferon alfa (pegyliert oder nicht-pegyliert) allein oder in Kombination mit Ribavirin nicht angesprochen, bzw. einen Rückfall erlitten haben
Boceprevir Victrelis® (J05AE12)	Victrelis ist indiziert zur Behandlung der chronischen Hepatitis C (CHC)-Infektion vom Genotyp 1 in Kombination mit Peginterferon alfa und Ribavirin bei erwachsenen Patienten mit kompensierter Lebererkrankung, die nicht vorbehandelt sind oder die nicht auf eine vorangegangene Therapie angesprochen bzw. einen Rückfall erlitten haben
Telaprevir Incivo® (J05AE11)	INCIVOist in Kombination mit Peginterferon alfa und Ribavirin zur Behandlung der chronischen Hepatitis C vom Genotyp 1 bei erwachsenen Patienten mit kompensierter Lebererkrankung (einschließlich Zirrhose) indiziert: - die nicht vorbehandelt sind; - die entweder mit Interferon alfa (pegyliert oder nicht-pegyliert) allein oder in Kombination mit Ribavirin vorbehandelt wurden, einschließlich Patienten, die einen Rückfall (Relaps) erlitten haben, Patienten mit partiellem Ansprechen oder Patienten mit fehlendem Ansprechen (Null-Responder)

Quellen: Fachinformationen; Angaben in der Lauer-Taxe

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Indikation für die Recherche:

In Kombination mit anderen Wirkstoffen zur Behandlung der chronischen Hepatitis C bei Erwachsenen.

Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassenen Arzneimittel, s. Unterlage zur Beratung in AG: „Übersicht zVT, Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet".

Die Proteaseinhibitoren Telaprevir und Boceprevir sind für Patienten mit einer HIV – Koinfektion nicht zugelassen.

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenzbasierten systematischen Leitlinien zur Indikation „chronische Hepatitis C " durchgeführt. In die Rechercheergebnisse sind die Treffer des Auftrags 2012-B-031 und 2013-B-032, chronische Hepatitis C, Genotype 1 mit eingeflossen. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 04.06.2013 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AdkÄ, AWMF, GIN, NGC, TRIP, NICE, DAHTA, NIHR HSC. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Es wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab insgesamt 394 Treffer, welche anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Die erste Durchsicht ergab 209 eingeschlossene Quellen, die anschließend im Volltext überprüft wurden. Daraus konnten 51 Referenzen, in die synoptische Evidenz-Übersicht aufgenommen werden.

Abkürzungen:

BOC: Boceprevir
BW: Body weight
CI: Confidence interval
HCV: Hepatitis C virus
HIV: Human immunodeficiency virus
IFN: Interferon
OR: Odds ratio
PegIFN: Peginterferon
PI: Protease Inhibitor
RBV: Ribavirin
RR: Relative risk
SVR: Sustained response rate
TVR: Telaprevir

G-BA	
Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a des Fünften Buches Sozialgesetzbuch (SGB V) Telaprevir. Berlin (Ger): G-BA; 2012.[14] Stand: **29.03.2012**	**Telaprevir** ***Zugelassenes Anwendungsgebiet:*** Incivo® ist in Kombination mit Peginterferon alfa und Ribavirin zur Behandlung der **chronischen Hepatitis C vom Genotyp 1** bei erwachsenen Patienten mit kompensierter Lebererkrankung (einschließlich Zirrhose) indiziert: – die nicht vorbehandelt sind; – die entweder mit Interferon alfa (pegyliert oder nicht-pegyliert) allein oder in Kombination mit Ribavirin vorbehandelt wurden, einschließlich Patienten, die einen Rückfall (Relaps) erlitten haben, Patienten mit partiellem Ansprechen oder Patienten mit fehlendem Ansprechen (Null-Responder). 1. ***Zusatznutzen*** des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie a) In Kombination mit Peginterferon + Ribavirin gegenüber Peginterferon + Ribavirin bei therapienaiven Patienten mit chronischer Hepatitis-C-Virus (cHCV) Infektion (Genotyp 1) *Zweckmäßige Vergleichstherapie:* Peginterferon plus Ribavirin Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Peginterferon plus Ribavirin: Hinweis auf einen Zusatznutzen von Telaprevir, Ausmaß nicht quantifizierbar. b) In Kombination mit Peginterferon + Ribavirin gegenüber Peginterferon + Ribavirin bei therapieerfahrenen Patienten mit chronischer HCV-Infektion (Genotyp 1) *Zweckmäßige Vergleichstherapie:* Peginterferon plus Ribavirin Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Peginterferon plus Ribavirin: Hinweis auf einen Zusatznutzen von Telaprevir, Ausmaß nicht quantifizierbar.
Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a des Fünften Buches Sozialgesetzbuch (SGB V) Boceprevir. [15] Stand: **01.03.2012**	**Boceprevir** ***Zugelassenes Anwendungsgebiet:*** VictrelisR ist indiziert zur Behandlung der **chronischen Hepatitis C (CHC)-Infektion vom Genotyp 1** in Kombination mit Peginterferon alfa und Ribavirin bei erwachsenen Patienten mit kompensierter Lebererkrankung, die nicht vorbehandelt sind oder die nicht auf eine vorangegangene Therapie angesprochen bzw. einen Rückfall erlitten haben. 1. ***Zusatznutzen*** des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie a) In Kombination mit PegInterferon + Ribavirin gegenüber PegInterferon + Ribavirin bei therapienaiven Patienten mit chronischer Hepatitis-C-Virus (cHCV) Infektion (Genotyp 1) *Zweckmäßige Vergleichstherapie:* Peginterferon plus Ribavirin Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Peginterferon plus Ribavirin: Hinweis auf einen Zusatznutzen von Boceprevir, Ausmaß nicht quantifizierbar. b) In Kombination mit PegInterferon + Ribavirin gegenuber PegInterferon + Ribavirin bei therapieerfahrenen Patienten mit cHCV-Infektion (Genotyp 1) *Zweckmäßige Vergleichstherapie:* Peginterferon plus Ribavirin Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenuber Peginterferon plus Ribavirin: Hinweis auf einen Zusatznutzen von Boceprevir, Ausmaß nicht quantifizierbar.

Cochrane Reviews

Brok et al. 2009: Ribavirin monotherapy for chronic hepatitis C. **[7]**	Systematische Literaturrecherche bis März 2009. Der Anteil der Patienten mit **Hepatitis-C-Virus-Genotyp 1** wurde in 8 Studien (Median 73%; range 40 bis 97%) berichtet. Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung:** To assess the beneficial and harmful effects of ribavirin monotherapy for patients with chronic hepatitis C. **Population:** Patients with chronic hepatitis C **Patienten:** 657 Patienten **Vergleiche:** • ribavirin versus no intervention or placebo; • ribavirin versus interferon. **Endpunkte:** Primäre Endpunkte: Failure of serum (or plasma) sustained virological response, Liver-related morbidity plus all-cause mortality All adverse events Sekundäre Endpunkte: Failure of end of treatment virological response, Failure of sustained biochemical response, Failure of end of treatment biochemical response, Failure of histological response, Quality of life **Ergebnisse (basierend auf 14 eingeschlossenen RCTs):** **Compared with placebo or no intervention** • ribavirin had no significant effect on the sustained virological response (RD 0%, 95% CI -2% to 3%, five trials) or end of treatment virological response (RD 0% 95% CI -3% to 3%, ten trials). • Ribavirin had no significant effect on liver-related morbidity plus mortality (RD0%, 95%CI -2%to 3%, 11 trials). • Ribavirin significantly increased the risk of adverse reactions, including anaemia. • Ribavirin significantly improved end of treatment biochemical and histological response but not the sustained biochemical response. • Ribavirin was significantly inferior to interferon regarding virological and biochemical responses (five trials) **Ribavirin versus interferon** • Compared with ribavirin, interferon significantly increased the number of patients with an end of treatment virological response (RD 17%; 95% CI 7% to 27%, five trials), but not the number with sustained virological response (RD 13%; 95% CI -4% to 29%, two trials). • No liver-related morbidity or mortality was reported in any trial. • Compared with ribavirin, interferon increased the number with end of treatment and sustained biochemical responses. • no significant difference in adverse events or treatment discontinuations between ribavirin and interferon. • None of the trials reported histological response or quality of life. Fazit der Autoren: Ribavirin seems without beneficial effects on serum virological response and liver-related morbidity or mortality, and significantly increased the risk of adverse reactions. Ribavirin monotherapy seems significantly inferior to interferonmonotherapy. The total number of included patients is small, and more trials are perhaps needed. The use of ribavirin monotherapy for chronic hepatitis C cannot be recommended outside randomised trials.

	Anmerkungen FBMed: Der Anteil der Patienten mit Hepatitis-C-Virus vom Genotyp 1 wurde in acht Studien (Median 73%, von 40% auf 97%) berichtet.
Brok et al. 2010: Ribavirin plus interferon versus interferon for chronic hepatitis C. [6]	Systematische Literaturrecherche bis März 2009. Der Anteil der Patienten mit **Hepatitis-C-Virus-Genotyp 1** wurde in 72 Studien (Median 61%; range 0 bis 100%) 61%) berichtet. Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung:** To assess the beneficial and harmful effects of ribavirin and interferon combination therapy versus interferon monotherapy for chronic hepatitis C. **Population:** Patients with chronic hepatitis C. **Patienten:** 12,707 Patienten **Vergleiche:** Comparisons of any type, dose, or duration of ribavirin plus interferon alpha therapy versus interferon alpha monotherapy **Endpunkte:** Primäre Endpunkte: failure of serum (or plasma) sustained virological response (SVR); liver-related morbidity plus all-cause mortality; all adverse events Sekundäre Endpunkte: failure of end-of-treatment virological response; failure of histological response; quality of life. **Ergebnisse (basierend auf 83 eingeschlossenen RCTs):** **Failure of serum sustained virological response** • Combination therapy significantly reduced the number with failure of SVR when all patients were combined (RR 0.75, 95% CI 0.71 to 0.79; 67 trials) • Combination therapy had a significant effect on the response in subgroups of naive (RR 0.72, 95% CI 0.68 to 0.75; 25 trials, I2 = 34%), relapsers (RR 0.62, 95% CI 0.54 to 0.70; 14 trials, I2 = 57%), and non-responders (RR 0.89, 95% CI 0.84 to 0.93; 22 trials, I2 = 63%) • Sensitivity analyses of trials with genotype 1 (RR 0.67, 95% CI 0.56 to 0.80, 7 trials) gave the same overall results showing that adding ribavirin significantly reduced the number with failure of SVR. **Liver-related morbidity plus all-cause mortality** • Few patients developed cirrhosis, hepatocellular carcinoma, or died • On combination therapy the number of outcomes was 16 out of 7482 patients, and on monotherapy the number of outcomes was 29 out of 5225 patients. • Combination therapy significantly reduced morbidity plus mortality (Peto OR 0.43, 95% CI 0.23 to 0.79, I2 = 0%). • The results were not significant for naive alone (Peto OR 0.55, 95% CI 0.20 to 1.55), relapsers alone (Peto OR 0.13, 95% CI 0.00 to 6.78), or non-responders alone (Peto OR 0.56, 95% CI 0.17 to 1.19). **Adverse events and reactions** • The most frequent adverse reaction was anaemia, which occurred in 727 out of 4448 patients (16%) on combination therapy and 43 out of 2944 (1%) on monotherapy (RR 9.45, 95% CI 7.42 to 12.05; 35 trials). • Combination therapy significantly increased the risk of leukopenia (RR 3.42, 95% CI 1.38 to 8.49; 3 trials), but not neutropenia or thrombocytopenia. • Combination therapy increased the risk of several dermatological adverse reactions, eg,dermatitis (RR 1.67, 95% CI 1.21 to 2.30; 3 trials),

	pruritus (RR 1.62, 95% CI 1.29 to 2.02; 18 trials), and rash (RR 1.74, 95%CI 1.17 to 2.61; 12 trials). • Combination therapy also led to a significant increase in gastrointestinal adverse reactions (dyspepsia and anorexia or nausea), insomnia, and miscellaneous adverse events (cough, dyspnoea, and fatigue). **Failure of end-of-treatment virological response** • Combination therapy significantly reduced the number of patients with failure of virological response (RR0.72, 95%CI 0.69 to 0.77; 78 trials). • Combination therapy also had a significant effect on virological response of naive patients, relapsers, and non-responders individually. **Failure of histological response** • All post-treatment biopsies were performed between 3 to 12 months after the end of treatment. Combination therapy significantly reduced the number of patients with failure on both inflammation score (grading) (RR 0.84, 95% CI 0.77 to 0.91; 11 trials) and fibrosis score (staging) (RR 0.95, 95% CI 0.92 to 0.97;9 trials). • Combination therapy also had a significant effect on liver histology of naive patients, relapsers, and non-responders individually. **Quality of life** • Only one trial with 257 relapsers reported data on quality of life. • Combination therapy had a significant beneficial effect on some subscales. These included scales on general health (MD 7.00, 95% CI 0.67 to 13.33), social functioning (MD 6.00, 95% CI 1.22 to 10.78), and mental health (MD 5.00, 95% CI 1.53 to 8.47). **Anmerkungen FBMed:** Subgruppenanalysen für „Failure of serum sustained virological response“ für Patienten mit Genotyp 1 Patienten wurden durchgeführt.
Iorio et al. 2010: Antiviral treatment for chronic hepatitis C in patients with human immunodeficiency virus. [30]	Systematische Literaturrecherche bis Mai 2009. The mean proportion of patients with **hepatitis C genotype 1 ranged from 44% to 78%.** Patienten mit einer HIV/HCV-Koinfektion. **Fragestellung:** To assess the benefits and harms of antiviral treatment for **chronic hepatitis C in patients with HIV.** **Population:** Patients with chronic hepatitis C and stable HIV co-infection. **Patienten:** 2269 Patienten **Vergleiche:** • Randomised comparisons of peginterferon (any type, ie, alpha 2a or 2b) plus ribavirin versus peginterferon or interferon (any type, ie, alpha 2a or 2b) plus ribavirin • randomised comparisons of peginterferon plus ribavirin given for different doses or treatment durations **Endpunkte:** <u>Primäre Endpunkte:</u> Virologic response defined as loss of hepatitis C virus RNA: • at the end of treatment • at least six months after treatment (sustained virological response). <u>Sekundäre Endpunkte:</u> Mortality; Progression to acquired immunodeficiency syndrome (AIDS) related illness; Hospitalisation; Histological response; Biochemical response (normalisation of transaminases); Level of CD4-positive T-Lymphocytes; Level of HIV RNA; All adverse events; Withdrawals and dropouts

	Ergebnisse (basierend auf 14 eingeschlossenen RCTs): *Peginterferon plus ribavirin versus interferon plus ribavirin:* **Virologic response defined as loss of hepatitis C virus RNA from the blood** • Peginterferon plus ribavirin was more effective in achieving end of treatment and sustained virological response compared with interferon plus ribavirin (5 trials, 1340 patients). • the benefit of peginterferon plus ribavirin was seen irrespective of HCV genotype although patients with genotype 1 or 4 had lower response rates (27%) than patients with genotype 2 or 3 (56%). ➔ Peginterferon plus interferon increased the risk of achieving a sustained virological response for both subgroups (genotype 1 or 4 RR 3.36, 95% CI 2.33 to 4.86 and genotype 2 or 3 RR 1.70, 95% CI 1.36 to 2.12). **Mortality** • No significant difference was found between patients randomized to peginterferon plus ribavirin versus interferon plus ribavirin (RR 1.27, 95% CI 0.49 to 3.30; Chi2 statistic = 0.35). **Adverse events** • The most frequent adverse events were anaemia, flu-like symptoms, and depression • Fourteen per cent of patients randomised to peginterferon plus ribavirin developed anaemia and 64% flu-like symptoms. • Both anaemia and flu-like symptoms occurred significantly more frequently among patients randomized to peginterferon plus ribavirin (RR 1.57, 95%CI 1.16 to 2.14 and RR 1.16, 95% CI 1.07 to 1.26, respectively). • The risk of depression was not significantly different in the two treatment groups (RR 0.97, 95% 0.80 to 1.17). **Withdrawals and dropouts** • The proportion of patients who dropped out or were withdrawn for any reason was significantly lower among patients randomized to peginterferon plus ribavirin compared with interferon plus ribavirin (30% and 36%; RR 0.82, 95% CI 0.71 to 0.96). **Other secondary outcome measures** • No data were available allowing analysis of the outcomes progression to AIDS, hospitalisation, biochemical response, level ofCD4-positive lymphocytes, or levels of HIV RNA. *Peginterferon plus ribavirin versus peginterferon alone:* **Virologic response defined as loss of hepatitis C virus RNA from the blood** • Peginterferon plus ribavirin was more effective in achieving end of treatment and sustained virological response compared with peginterferon (2 trials, 714 patients). • The proportion of patients with a sustained virological response was highest among patients randomised to peginterferon plus ribavirin (131 of 359), versus peginterferon alone (64 of 355, RR 2.03, 95% CI 1.57 to 2.63). • The difference was seen for patients with genotype 1 or 4 (RR 1.71, 95% CI 1.24 to 2.38) **Mortality** • Five deaths were reported in the two treatment groups (RR 1.00, 95% CI 0.29 to 3.41) **Histological response** • The number of patients with improved histology and paired liver biopsies was 77 of 135 (57%) in the peginterferon plus ribavirin group and 52 of

	134 (39%) in the peginterferon group. **Adverse events, withdrawals, and dropouts** • In total, 113 patients randomised to peginterferon plus ribavirin and 129 patients randomised to peginterferon were lost to follow up (RR 0.86, 95% CI 0.71 to 1.05) • Six patients in both treatments groups became anaemic (RR 1.00, 95% CI 0.33 to 3.05). • No significant differences were seen in occurrence of flu-like symptoms (RR 2.40, 95% CI 0.35 to 16.58) or depression (RR 0.76, 95% CI 0.57 to 1.03). **Other secondary outcome measures** • No data were available for any of the remaining outcomes. <u>Fazit der Autoren:</u> Peginterferon plus ribavirin may be considered a treatment for patients with chronic hepatitis C and stable HIV who have not received treatment for hepatitis C as the intervention may clear the blood of HCV RNA. Supporting evidence comes mainly from the analysis of this non-validated surrogate outcome assessed in comparisons against other antiviral treatments. There is no evidence on treatment of patients who have relapsed or did not respond to previous therapy. Careful monitoring of adverse events is warranted. **Anmerkungen FBMed:** Subgruppenanalysen für die anhaltende virologische Ansprechrate der Patienten mit Genotyp 1 und 4 Patienten wurden durchgeführt.
Katz et al. 2012: Extended peginterferon plus ribavirin treatment for 72 weeks versus standard peginterferon plus ribavirin treatment for 48 weeks in chronic hepatitis C genotype 1 infected slowresponder adult patients. [31]	Systematische Literaturrecherche bis November 2011. The mean proportion of **genotype 1 was 79.9%** in the nine trials that reported the genotype. Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung:** To compare the therapeutic benefits and harms of different antiviral regimens in patients with hepatitis C re-infected grafts after liver transplantation. **Population:** Patients with hepatitis C viral re-infection of the liver graft irrespective of age, cadaveric or living donor transplant, indication for liver transplantation, first or retransplantation, and the immunosuppressive therapy used. **Patienten:** 1369 Patienten **Vergleiche:** Peginterferon (alfa-2a or alfa-2b) and ribavirin for 72 weeks versus peginterferon (alfa-2a or alfa-2b) and ribavirin for 48 weeks **Endpunkte:** <u>Primäre Endpunkte:</u> Overall mortality; HCV-related mortality; Liver-related morbidity <u>Sekundäre Endpunkte:</u> Number of participants with sustained virological response (SVR); Number of participants with end of treatment response (EOR); Number of participants who relapsed; Adherance to treatment; Reduction of treatment dose; Occurrence of adverse events **Ergebnisse (basierend auf 7 eingeschlossenen RCTs):** • None of the included trials mentioned primary outcomes.

	Sustained virological response • extension of the treatment period to 72 weeks increased the sustained virological response according to both definitions (71/217 (32.7%) versus 52/194 (26.8%); risk ratio (RR) 1.43, 95% CI 1.07 to 1.92, P = 0.02, I2 = 8%; and 265/499 (53.1%) versus 207/496 (41.7%); RR 1.27, 95% CI 1.07 to 1.50, P = 0.006, I2 = 38%), with a risk difference of 0.11 and calculated number needed to treat of nine. **End of treatment response and number of participants who experienced virological relapse after treatment** • The end of treatment response was not significantly different between the two treatment groups. • The number of participants who relapsed virologically was found to be lower in the groups that had been treated for 72 weeks using both definitions (27/84 (32.1%) versus 46/91 (50.5%); RR 0.59, 95% CI 0.40 to 0.86, P = 0.007, I2 = 18%, 3 trials; and 85/350 (24.3%) versus 146/353 (41.4%); RR 0.59, 95% CI 0.47, 0.73, P < 0.000001, I2 = 0%, 3 trials). **Adherence to treatment, reduction of treatment dose, and adverse events** • The length of treatment did not significantly affect the adherence (247/279 (88.5%) versus 252/274 (92.0%); RR 0.95, 95% CI 0.84 to 1.07, P = 0.42, I2 = 69%, 3 trials). • In the single trial that reported adverse events, no significant difference was seen between the two treatment groups. <u>Fazit der Autoren:</u> This review demonstrates higher a proportion of sustained virological response after extension of treatment from 48 weeks to 72 weeks in HCV genotype 1 infected patients in whom HCV RNA was still detectable but decreased by ≥ 2 log after 12 weeks and became negative after 24 weeks of treatment, and in patients with detectable HCV RNA after four weeks of treatment with peginterferon plus ribavirin. The observed intervention effects can be caused by both systematic error (bias) and random errors (play of chance). There was no reporting on mortality and the reporting of clinical outcomes and adverse events was insufficient.More data are needed in order to recommend or reject the policy of extending the treatment period for slow responders.
Koretz et al., 2013 Interferon for interferon nonresponding and relapsing patients with chronic hepatitis C [32]	**Fragestellung:** To assess the benefits and harms of interferon monotherapy retreatment in chronic hepatitis C patients who are nonresponders and relapsers to previous interferon therapy. **Systematische Literaturrecherche im Suchzeitraum bis 2012** **Vergleich:** interferon monotherapy with no treatment **Population:** Patients with chronic Hep C, non-responder and relapsing **Endpunkte:** Mortality (all-cause and liver-related), Quality of life (however defined by authors), Adverse events **Ergebnisse (7 Studien)** • Based on all trials reporting the outcomes, no significant difference was observed in either all-cause mortality (78/843 (9.3%) versus 62/867 (7.2%); risk ratio (RR) 1.30, 95% confidence interval (CI) 0.95 to 1.79; 3 trials) or hepatic mortality (41/532 (7.7%) versus 40/552 (7.2%); RR 1.07, 95% CI 0.70 to 1.63; 2 trials);

	• When only the two trials at low risk of bias were combined, all-cause mortality was significantly higher in the recipients of the pegylated interferon (78/828 (9.4%) versus 57/848 (6.7%); RR 1.41, 95% CI 1.02 to 1.96) although trial sequential analysis could not exclude the possibility of random error. • There was less variceal bleeding in the recipients of the interferon (4/843 (0.5%) versus 18/867 (2.1%); RR 0.24, 95% CI 0.09 to 0.67; 3 trials), although again trial sequential analysis could not exclude the presence of a type I error and the effect could not be confirmed in a random-effects model meta-analysis. • No significant differences were seen with regard to the development of ascites, encephalopathy, hepatocellular carcinoma, or the need for liver transplantation. • The recipients of interferon had significantly more sustained viral responses (20/557 (3.6%) versus 1/579 (0.2%); RR 15.38, 95% CI 2.93 to 80.71; 4 trials) and a type I error was excluded by trial sequential analysis. **Fazit der Autoren** The clinical data were limited to patients with histologic evidence of severe fibrosis who were retreated with pegylated interferon. In this scenario, retreatment with interferon did not appear to provide significant clinical benefit and, when only the trials at low risk of bias were considered, retreatment for several years may even have increased all-cause mortality. Such treatment also produced adverse events. On the other hand, the treatment did result in improvement in some surrogate outcomes, namely sustained viral responses and histologic evidence of inflammation. Interferon monotherapy retreatment cannot be recommended for these patients. No clinical data are available for patients with less severe fibrosis. The sustained viral response cannot be used as a surrogate marker for hepatitis C treatment in this clinical setting with low sustained viral response rates and needs to be validated in others in which higher sustained viral response rates are reported.

Systematische Reviews / HTA

Hinweis: Behandlung der chronischen Hepatitis C vom Genotyp 1

Alavian et al. 2011: Optimal Duration of Treatment for HCV Genotype 1 Infection in Slow Responders: A Meta-Analysis. [2]	*Systematischer Review mit einer Metaanalyse zum Vergleich einer 72-Wochen vs. 48-Wochen anti-HCV Therapie mit Peg-Interferon und Ribavirin.* Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung:** Zusammenfassen der Ergebnisse von Studien, welche die optimale Behandlungsdauer für HCV-Patienten vom Genotyp 1-Infektion bei „slow responders“ beinhalten. ***Suchzeitraum:*** *k.A.* ***Endpunkte:*** *SVR-Rate* ***Patienten:*** *1206 Patienten* ***Ergebnisse*** *(basierend auf 7 Studien (alles RCTs):* • Slow virological responders, welche die 72-wöchige Therapie erhielten, hatten eine signifikant höhere Wahrscheinlichkeit für das Erreichen SVR als Patienten, die die 48-wöchige Therapie erhielten [RR = 1.44 (95% CI, 1.20–1.73)] *<u>Fazit der Autoren:</u> Die Meta-Analyse zeigte, dass die 72-wöchige Therapie mit Peginterferon und Ribavirin deutlich besser ist, als die Standard-48-wöchige Therapie in „slow responders“ mit HCV vom Genotyp 1-Infektion.*
Canadian Agency for Drugs and Technologies in Health 2012: Boceprevir and Telaprevir for Chronic Hepatitis C Infection. [10]	Health Canada recently approved boceprevir (Victrelis) and telaprevir (Incivek) for **treatment of chronic hepatitis C, genotype 1 infection**: • *for previously treated patients, adding a protease inhibitor (PI) to standard therapy with peginterferon alfa and ribavirin (PR) can triple the likelihood of treatment success* • *there are no head-to-head trials to provide guidance on where each drug should be positioned with respect to the other* *Das Expertenkomitee empfiehlt die Ergänzung der Standardtherapie (Ribavirin plus Peginterferon) mit Boceprevir oder Telaprevir, wenn folgende Kriterien gelten:* • *reduzierter Preis* • *nachweisbare Viruslast (level of Hep. C Virus detectable) in den letzten 6 Monaten* • *ein mittels Biopsie nachgewiesenes Fibrosestadium von F2, F3 oder F4* • *keine HIV- Ko-Infektion* • *nur eine Therapieoption (entweder 12 Wochen Telaprevir oder bis zu 44 Wochen Boceprevir)* *Bisher liegen lediglich umfassende Studien zum Endpunkt dauerhaftes virologisches Ansprechen (SVR) vor (vgl. siehe Abbildung).*

	For boceprevir:[1] **Trial** / **SVR for Patients Treated with Boceprevir plus PR** / **SVR for Patients Treated with Placebo plus PR** SPRINT-2: Treatment-naive patients — 63% to 66% — 38% RESPOND-2: Patients with a history of non-response or relapse on PR — 59% to 66% — 21% Study 5685: Patients with a history of non-response or relapse on PR — 64% — 21% *PR = peginterferon alfa and ribavirin; SVR = sustained virologic response.* For telaprevir:[2] **Trial** / **SVR for Patients Treated with Telaprevir plus PR** / **SVR for Patients Treated with Placebo plus PR** ADVANCE: Treatment-naive patients — 75% — 44% REALIZE: Treatment-experienced patients — 64% to 66% — 16% *PR = peginterferon alfa and ribavirin; SVR = sustained virologic response.*
Chou et al. 2013: Comparative Effectiveness of Antiviral Treatment for Hepatitis C Virus Infection in Adults: A Systematic Review. [13]	Systematischer Review mit Metaanalyse zum Vergleich der 2 Fach-Therapie und 3 Fach-Therapie. **Alle Genotypen.** The proportion of patients with HCV genotype-1 ranged from 44% to 78% **Fragestellung:** To compare benefits and harms of antiviral regimens for chronic HCV infection in treatment-naive adults. **Suchzeitraum:** 1947 bis August 2012 ***Endpunkte:*** *SVR-Rate* ***Anzahl der Patienten:*** *k.A.* **Anzahl der Studien:** 90 Studien **Ergebnisse:** • Dual therapy with pegylated interferon alfa-2b plus ribavirin was associated with a lower likelihood of SVR than was pegylated interferon alfa-2a plus ribavirin (absolute difference, 8 percentage points [95% CI, 3 to 14 percentage points]) on the basis of 7 poor- to fair-quality trials. • For genotype 1 infection, fair-quality trials found that triple therapy with pegylated interferon, ribavirin, and either boceprevir (2 trials) or telaprevir (4 trials) was associated with a higher likelihood of SVR than was dual therapy (absolute difference, 22 to 31 percentage points). • Compared with dual therapy, boceprevir triple therapy increased risk for hematologic adverse events and telaprevir triple therapy increased risk for anemia and rash. A large well-designed cohort study and 18 smaller cohort studies found that an SVR after antiviral therapy was associated with lower risk for all-cause mortality than was no SVR. Fazit der Autoren: SVR rates for genotype 1 infection are higher with triple therapy that includes a protease inhibitor than with standard dual therapy. Die SVR-Rate nach einer antiviralen Therapie scheint mit verbesserten klinischen Ergebnissen assoziiert.
Cooper et al. 2012: Boceprevir and telaprevir for the treatment of chronic hepatitis C genotype 1	*Systematischer Review mit Metaanalyse zur Wirksamkeit und Sicherheit von Boceprivir und Telaprevir in Kombination mit pegiliertem Interferon Alpha und Ribavirin. Keine Angaben zu Patienten mit einer HIV/HCV-Koinfektion zu entnehmen.* **Fragestellung**: Das Ziel dieser Studie war es, die relative Wirksamkeit

infection: an indirect comparison meta-analysis. Therapeutics and Clinical Risk Management 2012; 8:105-130. [15]	und Sicherheit von Boceprevir und Telaprevir in einem indirekten Vergleich / Meta-Analyse zu untersuchen, wenn sie in Kombination mit pegyliertem Interferon alpha und Ribavirin verwendet werden. **Suchzeitraum:** von Beginn der jeweiligen DB bis Oktober 2011 **Endpunkte:** Primäre Endpunkte: dauerhaftes virologisches Ansprechen, Rezidive und Therapieabbruch; Sekundäre Endpunkte: unerwünschte Ereignisse wie Anämie, Neutropenie, Ausschlag und Juckreiz **Anzahl der Patienten:** 5072 Patienten **Anzahl der Studien**: 10 Studien **Ergebnisse** (basierend auf 10 ***Phase II- und III- Studien*** *(alles RCTs), davon 4 zu BOC und 6 zu TVR):* • *Im indirekten Vergleich ergaben sich weder für therapie-naive noch für vorbehandelte Patienten signifikante Unterschiede in Bezug auf die primären Endpunkte* • *Im direkten Vergleich ergaben sich signifikante Unterschiede für die Dreifachtherapie sowohl mit BOC als auch mit TVR versus Placebo+Ribavirin+PegIFN Alpha für therapie-naive als auch für vorbehandelte Patienten* ▪ ***SVR** naive Patienten: RR 1,91 [95%KI 1,65-2,21]* ▪ ***SVR** vorbehandelte Patienten: RR 3,09 [95%KI 2,24-4,28]* ▪ ***Relapse** naive Patienten: RR 0,24 [95%KI 0,06-1,0]* ▪ ***Relapse** vorbehandelte Patienten: RR 0,36 [95%KI 0,2-0,62]* ▪ ***Therapieabbruch** naive Patienten: RR 0,65 [95%KI 0,47-0,89]* ▪ ***Therapieabbruch** vorbehandelte Patienten: RR 0,54 [95%KI 0,45-0,65]* • *TVR war häufiger assoziiert mit Ausschlag und Juckreiz; bei therapie-naiven Patienten traten unter BOC häufiger Neutropenien auf (RR 1,46 (95%KI 1,09-1,95)* Fazit der Autoren: Boceprevir und Telaprevir erscheinen vergleichbar in Bezug auf die anhaltende virologische Ansprechrate, Rückfall, oder Behandlungsabbruch für Patienten, welche mit der Standard-Dosis-Therapie und „response-guided“ Behandlungsdauer behandelt wurden.
Cure et al. 2012: Efficacy of telaprevir and boceprevir in treatment-naı¨ve and treatment-experienced genotype 1 chronic hepatitis C patients: an indirect comparison using Bayesian network meta-analysis.[16]	Systematischer Review zu Boceprevir und Telaprevir (ohne Meta-Analyse). Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung**: The objective of this study was to indirectly compare the efficacy of telaprevir and boceprevir combined with PR in achieving SVR in both treatment-naı¨ve and experienced patients infected with G1 chronic HCV, using a Bayesian network meta-analysis framework. **Suchzeitraum:** Januar 2000 bis Juli 2011 **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 11 Studien **Endpunkte:** SVR- Rate (defined as undetectable HCV RNA level 24 weeks after the end of therapy) **Anzahl der Patienten**: 5318 Patienten

	Ergebnisse (basierend auf 11 Studien): *Treatment-naive patients:* • for telaprevir (12 weeks+response guided treatment [RGT] 24/48 weeks PR) and boceprevir (24 weeks+RGT 28/48 weeks PR) versus PR were respectively 3.80 (2.78–5.22) and 2.99 (2.23–4.01). • The OR for telaprevir versus boceprevir was 1.42 (0.89–2.25), with a probability for telaprevir being more effective (P[OR41]) of 0.93. *Treatment-experienced patients:* • OR of telaprevir (12 weeksþ48 weeks PR) and boceprevir (32 weeksþRGT 36/48 weeks PR) versus PR were respectively 13.11 (7.30–24.43) and 5.36 (2.90–10.30). • The OR for telaprevir versus boceprevir was 2.45 (1.02–5.80), with telaprevir having a probability of 0.98 of being more effective. Fazit der Autoren: In the absence of direct comparative head-to-head studies between telaprevir and boceprevir for the treatment of chronic HCV genotype 1 patients, an indirect comparison based on Bayesian network meta-analysis suggests better efficacy for telaprevir than boceprevir in both treatment-naive and treatmentexperienced patients.
Dang et al. 2012: Telaprevir for Chronic Hepatitis C with Genotype 1: A Meta-Analysis. [17]	Systematischer Review zu Telaprevir (ohne Meta-Analyse). Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung**: We assessed its antiviral efficiency in untreated patients and in patients who did not have an SVR to previous therapy in order to identify an optimal regimen for each type of patient. **Suchzeitraum:** Bis September 2010 **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 5 Studien **Endpunkte:** Primäre Endpunkte: SVR-Rate, end of treatment response (ETR); Sekundäre Endpunkte: Unerwünschte Ereignisse und Behandlungsabbruch ***Ergebnisse*** *(basierend auf 5 Studien)**:*** • Overall analysis revealed a significant effect of telaprevir in both naive patients (RR, 1.32; 95% CI, 1.08-1.60) and previously failed treated patients (p<0.0001). • Monotherapy and double therapy seemed to show no effect in naive patients. • Triple therapy followed with PegIFN-2a plus ribavirin seemed to be effective in both naive patients and previously failed treated patients. • Telaprevir was associated with a significantly higher incidence of serious adverse events (RR, 1.45; 95% CI, 1.00-2.10) and with discontinuation (RR, 2.23; 95% CI, 1.40-3.55) because of adverse events. • In naive patients, relapsers and non-responders, the regimen of telaprevir/PegIFN-2a/ribavirin for 12 weeks followed by PegIFN-2a/ribavirin for 12 weeks (T12PR24) was the optimal regimen regarding to efficiency and duration. Fazit der Autoren: Telaprevir combined with PegIFN-2a plus ribavirin may improve sustained response in genotype 1 chronic hepatitis C. Regimen T12PR24 may be the best regimen in this respect. New randomized controlled trials are required to confirm this meta-analysis.

Gevers et al. 2011: Treatment extension benefits HCV genotype 1 patients without rapid virological response: a systematic review. [22]	Systematischer Review ohne Meta-Analyse zur Behandlungsdauer. Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung**: The purpose of this systematic review is to evaluate different treatment duration regimes on achieving SVR and to make an evidence-based recommendation on the optimal length of treatment for HCV genotype 1 patients. **Anzahl der Patienten:** 1267 Patienten **Suchzeitraum:** 2000 bis März 2010 **Anzahl der Studien:** 5 Studien **Endpunkte:** Primäre Endpunkte: SVR-Rate, (ETR); Sekundäre Endpunkte: end of treatment response (EOT) **Ergebnisse** (basierend auf 5 Studien)**:** • In the RCT that randomised at absence of rapid virological response **(**RVR), SVR was significantly higher in the extended treatment arm (57 *vs* 42%, p=0.02) with an RR of 1.35 (95% CI 1.04 to 1.75). • This tendency was also observed in the studies that randomised at slow response (44 *vs* 35%), although no longer statistically significantly different. Fazit der Autoren: Prolonged 72-week treatment should be considered in HCV genotype 1 patients without RVR at week 4, as this increased SVR.
Gu et al. 2012: Telaprevir for genotype 1 chronic hepatitis C: a systematic review and meta-analysis. [26]	Systematischer Review mit Meta-Analyse zu Telaprevir**.** Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung**: To assess the beneficial and harmful effects of telaprevir for patients with genotype 1 chronic hepatitis C. **Suchzeitraum:** 1980 bis Mai 2012 **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 6 Studien **Endpunkte:** Primäre Endpunkte: SVR-Rate, virologic response at the end of treatment; Sekundäre Endpunkte: relapse rate**,** severe adverse events, treatment discontinuations, commonly reported adverse events, including anemia, neutropenia, rash and pruritus. **Ergebnisse (basierend auf 5 Studien):** • Telaprevir in combination with peginterferon alfa and ribavirin seemed to show a significant effect on sustained virologic response, virologic response at the end of treatment and relapse rate in naive patients and previously unsuccessfully treated patients, except T12PR12 which seemed without beneficial effect on: o Sustained virologic response: OR=1.41; 95% CI 0.83 to 2.40) o relapse rate (Odds Ratio OR=1.55; 95% CI 0.71 to 3.36) in naive patients. • It also was associated with a significantly higher incidence of severe: o adverse events OR=2.15, 95% CI1.29 to 3.58) o treatment discontinuation OR=4.79, 95% CI1.72 to 13.37) because of adverse events in previously unsuccessfully treated patients, but not in naive patients. Fazit der Autoren: Telaprevir in combination with peginterferon alfa and ribavirin has been recommended as option for the treatment of genotype 1 chronic hepatitis C. It has been considered as effective to improve viral

	response and reduce relapse rate in patient who suffer genotype 1 chronic hepatitis C. However, the treatment should be monitored carefully as it may cause some severe adverse events. For further confirmation of its treatment effect and clarify its possible adverse events, more randomized clinical trials need to be carried out.
Hartwell et al. 2011: Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. [27]	Systematischer Review ohne Meta-Analyse zu Telaprevir**.** Patienten mit einer HIV/HCV-Koinfektion. **Fragestellung**: To assess the clinical effectiveness and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C virus (HCV) in three specific patient subgroups affected by recent licence changes: those eligible for shortened treatment courses [i.e. those with low viral load (LVL) and who attained a rapid virological response (RVR) at 4 weeks of treatment], those eligible for re-treatment following previous nonresponse or relapse, and those co-infected with human immunodeficiency virus (HIV). **Suchzeitraum:** Bis Oktober 2009 **Endpunkte:** sustained virological response (SVR), relapse rate and adverse events **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 4 Studien **Ergebnisse** (basierend auf 6 RCTs): • All six included RCTs were in patients who were eligible for shortened treatment duration. • No RCTs comparing peginterferon alfa with or without ribavirin with BSC were identified for the HCV/HIV co-infection or re-treatment patient groups. • In the subgroup of patients who achieved an RVR and had LVL at baseline, SVR rates were comparable (i.e. no statistically significant differences) between groups who received the standard duration of treatment and those who received shortened courses, for both genotype 1 and genotypes 2 and 3. This implies that this patient group can receive shortened courses of peginterferon combination therapy without compromising SVR rates. • For both genotype 1 and genotype 2 and 3 patients, there were no statistically significant differences in rates of RVR between treatment groups who received the standard duration of treatment and those who received shortened courses. Rates of RVR in genotype 2/3 patients were observed to be generally higher than in genotype 1 patients. • Relapse rates in the subgroup of patients with LVL and RVR (one trial) were low and not significantly different between those treated for 24 versus 48 weeks. • Treatment for 24 weeks resulted in a significantly lower biochemical response rate (reduction of ALT to normal levels) and histological response rate than 48 weeks of treatment in one trial of genotype 1 patients. Shortening the treatment duration had no effect on biochemical response in one trial of genotype 2/3 patients. Rates of biochemical and histological response should be treated with caution, as the results relate only to those patients with available data and rates were not reported in the subgroup of patients with LVL and RVR. • Adverse events were presented for treatment groups as a whole and the reporting of statistical tests varied. However, the most frequently occurring adverse events were similar across all the trials and included flu-like symptoms, insomnia, anorexia, dermatological symptoms and

	alopecia. • There was a trend for a lower incidence of adverse events in patients who were treated for a shorter duration (three trials), although statistically they were comparable between treatment arms. The incidence of dose discontinuations was significantly lower in those receiving a shortened treatment regimen in one trial. Fazit der Autoren: The clinical trial evidence indicates that patients may be successfully treated with a shorter course of peginterferon combination therapy without compromising the likelihood of achieving an SVR.
Parikh et al. 2011: 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**; 18 (4): e99-103.[40]	Systematischer Review mit Meta-Analyse zum Vergleich einer 48-Wochen vs. 72-Wochen Therapie mit Peg-Interferon+Ribavirin. 5 RCTs in die Analyse eingeschlossen. Keine Angaben zu Patienten mit einer HIV/HCV-Koinfektion zu entnehmen. **Fragestellung**: In this study, we undertook a systematic review of the literature and performed a metaanalysis to compare 72 weeks of treatment to the standard duration of 48 weeks in HCV genotype I patients with LVR. **Suchzeitraum:** 2004 bis 2010 **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 5 Studien **Endpunkte:** End of Treatment Response, sustained virological response (SVR), Rückfallraten **Patienten:** k.A**.** **Ergebnisse** (basierend auf 5 Studien)**:** • End of Treatment Response [Response bei Behandlungsende]: kein stat. sign. Unterschied • SVR: 25% für 48 Wochen vs. 32% für 72 Wochen mit einem OR 1,67 (1,16–2,40) und p=0,006, I^2=0%. • Rückfallraten: 55% für 48 Wochen vs. 35% für 72 Wochen mit einem OR 0,39 (0,25-0,61) und p<0,0001, I^2=0%. Fazit der Autoren: „Extending the treatment duration from 48 to 72 weeks in genotype 1 infected patients with late virological response improves SVR. Thus, therapy extension in genotype 1 late viral responders (LVR) may be a consideration to improve treatment response; however, the proportion of patients with LVR that might benefit from 72-week therapy appears to be small.”
Singal et al. 2010: Meta-analysis: re-treatment of genotype I hepatitis C nonresponders and relapsers after failing interferon and ribavirin combination therapy. Aliment Pharmacol Ther **2010**; 32 (8): 969-83.[43]	Systematischer Review mit Meta-Analyse zur Retherapie der Non-responder und Rückfälle nach Peg-Interferon+Ribavirin. 18 RCTs in die Analyse eingeschlossen. Keine Angaben zu Patienten mit einer HIV/HCV-Koinfektion zu entnehmen. **Fragestellung:** To quantify sustained virological response (SVR) rates with different re-treatment regimens through meta-analysis of randomized controlled trials (RCTs). **Suchzeitraum:** 1997 bis September 2008 **Endpunkte:** SVR-Rate **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 10 Studien **Ergebnisse** (basierend auf 10 Studien)**:** • Bei Non-Respondern: Verbesserung des SVR mit RR 1,49 (95% KI: 1,09–2,04) durch hochdosierte Re-therapie mit Peg-Interferon im Vergleich zur Standard Peg-Interferon Therapie. SVR in den meisten

	Studien unter 18 %. • Bei Rückfällen: Verbesserung des SVR mit RR 1,57 (95% KI: 1,16–2,14) durch hochdosierte Retherapie mit Peg-Interferon oder verlängerte CIFN-Therapie im Vergleich zur Standard Peg-Interferon Therapie. SVR bei 43-69%. Fazit der Autoren: "In genotype 1 HCV treatment failure patients who received combination therapy, re-treatment with high-dose PEG-IFN combination therapy is superior to re-treatment with standard combination therapy, although SVR rates are variable for nonresponders (≤18%) and relapsers (43–69%). Re-treatment may be appropriate for selected patients, especially relapsers and individuals with bridging fibrosis or compensated cirrhosis."
Singal et al. 2011: Peginterferon alfa-2a is superior to peginterferon alfa-2b in the treatment of naive patients with hepatitis C virus infection: meta-analysis of randomized controlled trials. Dig Dis Sci 2011; 56 (8): 2221-6. [44]	Systematischer Review mit Meta-Analyse zum Vergleich von Peg-Interferon Alpha-2a vs. Alpha-2b. 9 RCTs eingeschlossen. Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung:** To quantify sustained virological response (SVR) rates with different re-treatment regimens through meta-analysis of randomized controlled trials (RCTs). **Suchzeitraum:** k.A. **Endpunkte:** SVR rates **Patienten:** 3,546 Patienten **Ergebnisse** (basierend auf 9 Studien)**:** • SVR stat. sign. höher bei Peg-Interferon Alpha-2a mit OR 1,36 (1,07–1,73), p = 0,01. Fazit der Autoren: "PEGIFN alfa-2a has superior efficacy with higher SVR as compared to PEGIFN alfa-2b in treatment naive HCV-infected patients. The safety profile of the two types of PEGIFN was similar." **Anmerkungen FBMed:** Analyse auf Studien beschränkt, die nur therapienaive Patienten enthalten. "Because the response rate in patients who are previous non-responders to HCV treatment and those with human immunodeficiency virus (HIV) co-infection are substantially different compared to treatment-naive patients we restricted our analysis to studies that included only patients who were naı¨ve to HCV treatment."
Sitole et al. 2013: Telaprevir Versus Boceprevir in Chronic Hepatitis C: A Meta-Analysis of Data From Phase II and III Trials. [45]	Systematischer Review mit Meta-Analyse zu Teleprevir. Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung:** This meta-analysis compared 24- and 48- week sustained viral responses (SVR) and drug-related adverse events (AEs) between telaprevir and boceprevir triple-therapy regimens in the treatment of chronic HCV infection. **Suchzeitraum:** 1995 bis Oktober 2012 **Endpunkte:** SVR-Rate, AEs ((anemia, diarrhea, nausea, pruritis, and rash), discontinuations, **Patienten:** k.A. **Ergebnisse** (basierend auf 8 Studien)**:**

	• With telaprevir, the ORs (95% CI) for SVR at 24 weeks in treatment-naive and treatment-experienced patients were 3.31 (2.27– 4.82; *P* < 0.0001) and 4.21 (1.83–9.72; *P*<0.001), respectively. • Telaprevir triple therapy did not result in more drug related discontinuations but did cause additional rash, pruritis, and anemia. • With boceprevir, the ORs (95% CI) were improved in both treatment-naive and treatment experienced patients (3.55 [2.66-4.56; *P*< 0.0001] and 7.34 [3.92–13.9; *P* <0.0001]), but with more treatment-related anemia and dysgeusia. Fazit der Autoren: Based on the findings from this metaanalysis, telaprevir or boceprevir combined with Peg-IFN _ RBV had favorable short-term data on SVR while resulting in more drug-related AEs. Extended follow-up is required to determine whether these agents offer a reduction in the risk for chronic hepatitis C genotype 1–related mortality and/or hospitalization.
Smith et al. Telaprevir: an NS3/4A protease inhibitor for the treatment of chronic hepatitis C. Ann Pharmacother **2011;** 45 (5): 639-48 [47]	Review zu Telaprevir. Einzelne deskriptive Darstellung der verfügbaren Studien der Phasen I bis III. Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung:** To review the use of telaprevir for the treatment of chronic hepatitis C. **Suchzeitraum:** 1966 bis Januar 2011 **Endpunkte:** SVR rates **Patienten:** k.A. **Ergebnisse:** • Telaprevir has activity against HCV genotype 1 infection in vitro and in vivo, but monotherapy results in rapid viral resistance. • In 3 Phase 2 and 3 Phase 3 randomized placebo-controlled trials, 12 weeks of telaprevir, along with varying durations of ribavirin treatment, induced higher sustained virologic response (SVR) compared with ribavirin alone. • SVR was approximately 70% in treatment-naïve patients, 50-60% for patients in whom • SVR had not occurred with prior ribavirin treatment, and 40-45% of those who received ribavirin alone. • There was a high incidence of maculopapular rash (52% in 1 trial) and anemia (27% in 1 trial) in telaprevir-treated patients. • The average dropout rate in Phase 3 trials as a result of adverse effects was 13%. Fazit der Autoren: “Twelve weeks of telaprevir with concomitant ribavirin treatment increases SVR for treatment-naïve and non-naïve patients with genotype 1 chronic HCV compared to 48 weeks of ribavirin treatment. Telaprevir may shorten the length of ribavirin therapy for some patients with extended rapid viral response, but viral mutations, adverse effects, and a high dropout rate may reduce the SVR see in clinical practice.”
Wilby et al. 2012: Review of boceprevir and telaprevir for the treatment of chronic hepatitis C. Can J	Systematischer Review zu Boceprevir und Telaprevir (ohne Meta-Analyse). All HCV genotypes and patient populations were included. **Fragestellung:** To summarize and evaluate the published literature pertaining to boceprevir and telaprevir, and to provide clinicians with suggestions for use in patients with chronic hepatitis C infection.

Gastroenterol 2012; 26 (4): 205-10.[49]	**Suchzeitraum:** bis September 2011 **Patienten:** k.A. **Ergebnisse** Der Review enthält eine deskriptive Beschreibung von 4 Phase III Studien (je 2 RCTs für Boceprevir (SPRINT-2, RESPOND-2) und 2 für Telaprevir (ADVANCE, REALIZE), die bereits im Rahmen der frühen Nutzenbewertung bewertet wurden. Fazit der Autoren: Boceprevir and telaprevir will revolutionize the management of hepatitis C genotype 1 patients and will most likely decrease the burden of end-stage disease worldwide. However, current clinical limitations include establishing appropriate and cost-effective treatment durations, and use in special populations such as transplant patients and patients coinfected with HIV. Future research will need to clarify these clinical obstacles to clearly define the role of these agents in hepatitis C management.

Systematische Reviews

Hinweis: Behandlung der chronischen Hepatitis C vom Genotyp 4 (je nach Darstellung Studienergebnisse auch andere Genotypen mit extrahiert)

Bota et al. 2011: Response to Standard of Care Antiviral Treatment in Patients with HCV Liver Cirrhosis – a Systematic Review. [5]	Systematischer Review zu Pegylated Interferon alpha 2a, Pegylated Interferon alpha 2b und Ribavirin. Keine Angaben zu Patienten mit einer HIV/HCV-Koinfektion zu entnehmen. **Fragestellung:** The aim of this study was to establish the sustained virological response (SVR) rates in HCV patients with liver cirrhosis treated with standard of care therapy (Pegylated Interferon and Ribavirin for 48 weeks in genotypes 1 and 4 and 24 weeks in genotypes 2 and 3). ***Suchzeitraum:*** *Bis Februar 2011* ***Endpunkte:*** *SVR-Rate* ***Patienten:*** *1,149 Patienten* ***Ergebnisse*** *(basierend auf 11 Studien):* • The overall SVR rate was 33.3% (95%CI-confidence interval=30.6-36.2%). • SVR was significantly higher in patients with genotypes 2 and 3 (422 patients) as compared to those with genotypes 1 and 4 (692 patients): 55.4% (95%CI=50.7-60.1) versus 21.7% (95%CI=18.7-25), p<0.0001. Fazit der Autoren: The overall SVR rate in cirrhotic patients treated with standard of care therapy is 33.3%, but lower in cases affected by genotypes 1 and 4 (21.6%) which makes them a priority regarding the development of more potent drugs for effective treatment.
Chan et al. 2009: The utility of therapeutic drug monitoring for ribavirin in patients with chronic hepatitis C--a critical review **[11]**	Review der die Studien, die Ribavirin-Konzentration oder die Dosis und das Ansprechen auf die Behandlung gemessen haben wurden eingeschlossen. Patienten mit einer HIV/HCV-Koinfektion. **Fragestellung:** To evaluate the utility of therapeutic drug monitoring (TDM) for ribavirin in chronic hepatitis C. ***Suchzeitraum:*** *Beginn der jeweiligen DB bis Juni 2009* ***Endpunkte:*** *Rate of SVR achievement* ***Patienten:*** *k.A.* **Ergebnisse** (basierend auf 12 Studien für Hepatitis C–HIV Koinfektion) Patients with HCV infection who are co-infected with HIV: • The reported rate of SVR achievement with combination therapy in this patient group is 17–29% for genotypes 1 and 4. • In addition, these patients are also on concomitant antiretroviral therapy that may be involved in pharmacokinetic and pharmacodynamic drug interactions. As a result, it is paramount that HCV infection be adequately treated. • Attempts have been made to discern correlations between ribavirin and virologic response and toxicity in coinfected patients to help in optimizing treatment. • There is evidence that an opposite effect is seen in HCV–HIV coinfected patients. • Furthermore, although several trials showed a dose–response relationship, one study demonstrated no correlation between ribavirin dose and virologic response.

<table>
<tr><td></td><td>Fazit der Autoren: There is conflicting evidence about the existence of a correlation between ribavirin concentrations and virologic response or development of toxicity. This inconsistent evidence, coupled with the currently employed effective strategies that maximize sustained virologic response and minimize development of anemia, precludes the utility of TDM for ribavirin.</td></tr>
<tr><td>Gluud et al. 2009: Peginterferon Plus Ribavirin for Chronic Hepatitis C in Patients With Human Immunodefi ciency Virus. [25]</td><td>Systematischer Review zu Peginterferon plus Ribavirin bei Patienten mit chronischer Hepatitis C und HIV-Koinfektion. The mean proportion of patients with hepatitis C genotype 1 ranged from 44 to 78 % .

Fragestellung: The aim of this study was to assess the effects of peginterferon plus ribavirin for chronic hepatitis C in patients with human immunodefi ciency virus (HIV).

Suchzeitraum: bis Juli 2008
Patienten: k.A.
Endpunkte: Primäre Endpunkte: virological response; Sekundäre Endpunkte: mortality (all cause), improvement in histology, losses to follow-up, and adverse events

Ergebnisse (basierend auf 7 Studien):
Patients with HCV infection who are co-infected with HIV:

• The patients included had chronic hepatitis C and stable HIV and were not previously treated with interferon or ribavirin (treatment naive).
• The treatment duration ranged from 24 to 48 weeks.
• Peginterferon plus ribavirin increased the proportion of patients with an end-of-treatment or sustained virological response compared with interferon plus ribavirin or peginterferon alone.
• In subgroup analyses of trials comparing peginterferon plus ribavirin with interferon plus ribavirin, the proportion with a sustained virological response was 26 % (109 of 423) for patients with genotype 1 or 4 and 57 %.
• Several adverse events occurred, including fatal lactic acidosis and liver failure, but there were no significant differences in mortality rates between treatment groups.

Subgroup meta-analyses of randomized trials on patients with HIV and hepatitis C genotype 1 or 4

<table>
<tr><td colspan="2">End-of-treatment virological response</td></tr>
<tr><td colspan="2">Peginterferon plus ribavirin vs. interferon plus ribavirin</td></tr>
<tr><td>Genotype 1 or 4</td><td>147 / 423 (35 %) vs. 37 / 419 (9 %); RR 3.92 (2.82 – 5.47); _ 2 = 0.27; I 2 = 23 %</td></tr>
<tr><td colspan="2">Peginterferon plus ribavirin vs. peginterferon</td></tr>
<tr><td>Genotype 1 or 4</td><td>73 / 213 (34 %) vs. 42 / 209 (20 %); RR 1.71 (1.24 – 2.38); _ 2 = 0.40; I 2 = 0 %</td></tr>
<tr><td colspan="2">Sustained virological response</td></tr>
<tr><td colspan="2">Peginterferon plus ribavirin vs. interferon plus ribavirin</td></tr>
<tr><td>Genotype 1 or 4</td><td>109 / 423 (26 %) vs. 32 / 419 (76 %); RR 3.36 (2.33 – 4.86); _ 2 = 0.78; I 2 = 0 %</td></tr>
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<tr><td colspan="2">Peginterferon plus ribavirin vs. peginterferon</td></tr>
<tr><td>Genotype 1 or 4</td><td>55 / 213 (26 %) vs. 27 / 209 (13 %); RR 2.01 (1.33 – 3.05); _ 2 = 0.47; / 2 = 0 %</td></tr>
</table>
<u>Fazit der Autoren:</u> Peginterferon plus ribavirin may be considered for treatment-naive patients with HIV and chronic hepatitis C. Adverse events should be monitored carefully.
</td></tr>
<tr><td>Marcellin et al. 2012:
Safety profile of standard- vs.
high-dose peginterferon alfa-2a plus standard-dose ribavirin in HCV genotype 1/4 patients: pooled analysis from 5 randomized studies. [35]</td><td>
Retrospective Analyse gepoolter Daten von 5 RCTs zur Behandlung von Patienten mit HCV vom Genotyp 1 und 4. Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen.

Fragestellung: This analysis examines the safety profile of standard- versus high-dose peginterferon alfa-2a.

Suchzeitraum: k.A.

Endpunkte: adverse events, treatment discontinuations
Patienten: 2,940 Patienten
Ergebnisse (basierend auf 5 RCTs):

In standard and high-dose groups, similar frequencies of serious adverse events (SAEs, 3.2 and 4.2%, respectively) and treatment discontinuations for safety reasons (2.8 and 2.9%) were reported.
More patients reported weight decrease as an adverse event (AE) in the 360 µg/week group (7.7 vs.3.3%).
Significant ($p < 0.05$) independent predictors for discontinuation due to safety were older age, male gender, lower albumin and low neutrophil count, but not the starting dose of peginterferon alfa-2a.
Although more laboratory abnormalities were reported in patients receiving high-dose peginterferon alfa-2a, this was not reflected in AEs or discontinuations, suggesting these are adequately managed by dose modification.

<u>Fazit der Autoren:</u> High-dose peginterferon alfa-2a for 12 weeks does not significantly increase the incidence of SAEs or discontinuations for safety reasons, beyond that of a standard dose regimen.
</td></tr>
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Hinweis: Behandlung der chronischen Hepatitis C vom Genotyp 2 und 3 (je nach Darstellung Studienergebnisse auch andere Genotypen mit extrahiert)

Andriulli , 2008 Meta-analysis: the outcome of anti-viral therapy in HCV genotype 2 and genotype 3 infected patients with chronic hepatitis [3]	**Fragestellung**: To report sustained virological response (SVR) rates for HCV-2 and HCV-3 infection. *Systematische Literaturrecherche im Suchzeitraum 2001-2007* ***Population*** *Pat mit Genotyp 2 und 3* *(Ko-infektionen mit HIV wurden ausgeschlossen)* ***Anzahl der Patienten:** 2275 Patienten* *Endpunkte: SVR* **Ergebnisse** SVR nach 24 Wochen Behandlung (8 Studien): • SVR rates were 74% and 68%, respectively, for HCV-2 and HCV-3 genotype patients. • Among high viraemics, SVR rate in HCV-2 infection (75%) differed from the 58% value in HCV-3 infection. • Among low viraemic patients, respective rates were 79% and 75%. SVT nach rapid virological response (RVR) (4 Studien) • In RVR patients treated for 12–16 or 24 weeks, SVR rates in HCV- 2 infection were 83% and 84%, respectively, and in HCV-3 infection 84% and 86%. • In patients without RVR treated for 24 weeks, SVR was higher in HCV-2, with a 17.8% weighted difference. ***Fazit der Autoren*** Twenty-four weeks of therapy should remain standard duration for HCV-2 and low viraemic HCV-3 patients. In RVR patients, HCV-3 patients respond to short-treatment as well as HCV-2 patients, irrespective of basal viraemia. Patients without RVR may need longer treatment than the recommended 24 weeks.
Hartwell, 2009 Pegylated and non-pegylated interferon-alfa and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and meta-analysis [28]	**Fragestellung:** The aim of this systematic review was to assess the clinical effectiveness of pegylated (PEG) and non-pegylated interferon (IFN) alfa and ribavirin (RBV) for the treatment of adults with histologically mild HCV. ***Systematische Literaturrecherche im Suchzeitraum bis 2007*** ***Vergleich*** Therapien: IFN (2a or 2b) + RBV vs PEG (2a or 2b) + RBV oder Monotherpie PEG, wenn RBV nicht möglich ist • Studies were included comparing the different drugs with placebo, each other, or best supportive care. ***Population*** *Patients with mild HCV* *(1 Studien mit Patienten mit HIV Ko-infektionen; Überwiegend wurden therapienaive Patienten eingeschlossen)*

	Anzahl der Patienten: *2,776* ***Anzahl der Studien:*** *10 Studien* ***Endpunkte:*** *SVR* **Ergebnisse (10 Studien)** • Treatment with PEG + RBV combination therapy resulted in significantly higher sustained virological response (SVR) rates than treatment with IFN + RBV combination therapy. • Treatment for 48 weeks with PEG + RBV was significantly more effective than the same treatment for 24 weeks. • Significantly higher SVR rates were seen with IFN + RBV compared with either IFN monotherapy or no treatment. • Five IFN trials reported significantly higher SVR rates with IFN + RBV (range, 33–69 percent) compared with either IFN monotherapy (range, 18–23 percent) or no treatment (zero response). • A total of 460 participants were enrolled in the four trials included in the meta-analysis comparing IFN + RBV with IFN monotherapy or IFN + placebo. The relative risk (RR) of not experiencing an SVR was 0.59 (95 percent CI, 0.51 – 0.69) and was statistically significant (p < .00001). Heterogeneity was not statistically significant (p = .29) and the I^2 value was 20.7 percent. **SVR by Genotype** • SVR rates according to genotype were reported by all the included studies with broadly similar results. It should be noted that reporting of genotype groups was not consistent across trials making comparisons difficult, and few trials reported within-group comparisons. • SVRs were higher for patients with the more favorable genotypes (i.e., genotypes 2 and 3, commonly labeled as “non-1”) compared with genotype 1, irrespective of treatment. • In two of the PEG trials, between-group comparisons showed that patients with genotype 1 treated for 48 weeks had significantly higher response rates than patients on the same therapy for 24 weeks. • Treatment duration did not have a significant effect on virologic response for patients with genotype 2 or 3 for either of these PEG trials. ***Fazit der Autoren*** Patients with histologically mild HCV can be successfully treated with both PEG and IFN combination therapy, and response rates are broadly comparable with those achieved in patients with advanced disease. Treating patients in the early milder stages of HCV is, therefore, a clinically effective option.
Slavenburg, 2009 Optimal length of antiviral therapy in patients with hepatitis C virus genotypes 2 and 3: a meta-	**Fragestellung:** The purpose of this study is to systematically analyse all randomized controlled trials (RCTs) that compare short (12-16 weeks) versus standard (24 weeks) duration in HCV genotypes 2 and 3, in order to assess the relative efficacy of each arm. ***Systematische Literaturrecherche im Suchzeitraum 2000-2008***

analysis [46]	***Population*** ***Pat. mit HepC Typ 2 + 3*** ***Anzahl der Patienten:*** *k.A.* ***Anzahl der Studien:*** *8 Studien* *Vergleich: standard pegylated interferon and ribavirin combination therapy in HCV genotypes 2 and 3 patients and compared short (12-16 weeks) with standard (24 weeks) treatment duration. (Pat. Mit HIV-Koinfektion wurden nicht eingeschlossen.)* ***Endpunkte: SVR*** **Ergebnisse (8 Studien, n=2786):** • Meta-analyses were carried out on SVR data from three studies randomized at baseline and five studies randomized at rapid virological response (RVR) to either 12-16 weeks or a 24-week course. • Pooled SVR data were higher in standard treatment in RCTs that randomized at baseline, with a relative risk (RR) of 0.88 (95% confidence interval [Cl] 76-1.01). • The pooled proportion of SVR rates of RCTs that randomized at RVR were similar in the short treatment group (82%) as in the standard treatment (83%), with the pooled effect given by a RR of 1.00 (95% Cl 0.92-1.09) ***Fazit der Autoren*** *In conclusion, this study shows that for HCV genotype 2 and 3 patients achieving RVR at week 4, the efficacy of a shorter (12-16 weeks) treatment with pegylated interferon and ribavirin is not different from 24 weeks. Patients who do not achieve RVR at week 4 should receive at least 24 weeks of treatment.*

Hinweis: Behandlung der chronischen Hepatitis C alle Genotypen (d.h. keine Differenzierung))

Awad et al., 2010 Peginterferon alpha-2a Is Associated with Higher Sustained Virological Response than Peginterferon alfa-2b in Chronic Hepatitis C: Systematic Review of Randomized Trials [4]	Systematischer Review zu Peginterferon alpha-2a im Vergleich zu Peginterferon alpha-2b **Fragestellung:** We conducted a Cochrane systematic review to identify, assess, and collectively analyze all RCTs that would add to the body of evidence and strengthen inferences about which form of peginterferon may work best. ***Suchzeitraum:*** *systematische Literaturrecherche bis Juli 2009* ***Population:*** *alle Hepatitis C Genotypen (Eine Studie mit vorbehandelten Patienten, eine Studie mit HIV-Koinfektionen)* ***Anzahl der Patienten:*** *5008 Patienten* ***Anzahl der Studien:*** *12 Studien* **Endpunkte*:*** SVR, liver-related morbidity plus all-cause mortality, and adverse events leading to treatment discontinuation. **Ergebnisse** (12 Studien, 5008 Patienten) • Overall, peginterferon alpha-2a significantly increased the number of patients who achieved an SVR (47%) versus peginterferon alfa-2b (41%) (RR 1.11, 95% CI 1.04-1.19; P = 0.004). • The number needed to treat was 25 patients (95% CI 14-100). • Using RR as the measure of effect, the Cochran homogeneity test statistic yielded a P value of 0.58, and the heterogeneity was I^2 = 0% (Fig. 2). • Data from six trials for genotype 1 and 4 yielded an RR in favor of peginterferon alpha-2a (RR 1.21, 95% CI 1.03-1.42). Using relative risk as the measure of effect, the Cochran homogeneity test statistic yielded a P value of 0.21, and the heterogeneity was I^2 = 30%. • Data from five trials for genotype 2 and 3 yielded an RR in favor of peginterferon alpha-2a (RR 1.11, 95% CI 1.02-1.22). Using RR as the measure of effect, the Cochran homogeneity test statistic yielded a P value of 0.89, and the heterogeneity was I^2 = 0%. *Fazit der Autoren* Current evidence suggests that peginterferon alpha-2a is significantly superior to peginterferon alfa-2b regarding benefits (SVR, which is clearance of the virus from the blood). However, there is insufficient evidence to detect any differences regarding harms (mortality and adverse events). Future trials must further the correlation between achieving SVR and clinically relevant outcomes such as risk of cirrhosis, hepatocellular carcinoma, and mortality.
Alavian, 2010 The comparative efficacy and safety of peginterferon alpha-2a vs. 2b for the treatment of	**Fragestellung:** The purpose of this meta-analysis is to compare the advantages and disadvantages of dual therapy with PEG-IFN-α2a, with dual therapy with PEG-IFN-α2b, based on the results of head-to- head randomized controlled trials. ***Suchzeitraum:*** *Syst. Literaturrecherche; Suchzeitraum 2006-2010*

chronic HCV infection: a meta-analysis [1]	***Population:*** *Pat mit HepC Genotyp 1 + 4 treated for at least 48 weeks* *Pat mit HepC Genotyp 2 + 3 treated for at least 24 weeks* *(Pat mit Ko-infekionen HIV wurden ausgeschlossen)* ***Anzahl der Patienten:*** *3518 Patienten* ***Anzahl der Studien:*** *7 Studien* ***Endpunkte:*** SVR (defined as undetectable HCV-RNA for the 6 months after treatment cessation) **Ergebnisse (7 Studien, n=3518 Patienten)** The probability of achieving SVR was higher in patients treated with PEG-IFN-α2a and ribavirin when compared with PEG-IFN-α2a and ribavirin, with an OR of 1.38 (95% CI 1.02-1.88; P=0.03). Heterogeneity was significant among the included studies (P=0.05, I^2=55%). In the subset of naïve patients with genotype 1/4 and 2 infection, OR of achieving SVR was also higher in those patients who received PEG-IFN-α2a plus ribavirin. The likelihood of SVR was also greater in PEG-IFN-α2a *vs*. 2b in the subset of naïve patients with both hard-to-treat HCV types: genotype 1/4 [6% (95% CI 0-12)] and genotype 2 [14% (95% CI 6-22)]. *Anmerkung FB Med* *Der Anteil der Patienten mit Genotyp 1 + 4 lag in 3 Studien bei 100%, in den restlichen Studien bei 52-80 %.*
Chou, 2008 Pegylated interferons for chronic hepatitis C virus infection: an indirect analysis of randomized trials [12]	**Fragestellung:** The purpose of this metaanalysis is to compare benefits and harms of dual therapy with pegylated interferon-alfa 2a vs dual therapy with pegylated interferon-alfa 2b, based on an adjusted indirect analysis of randomized controlled trials. ***Suchzeitraum:*** *Systematische Literaturrecherche 1966 – 2007* ***Population*** *Pat. mit Hep. C (alle Genotypen), auch Ko-infektionen mit HIV,* ***Anzahl der Patienten:*** *k.A.* ***Anzahl der Studien:*** *16 Studien* *Vergleich* 1) Dual therapy with pegylated Interferon alfa-2a plus ribavirin *vs* dual therapy with non-pegylated interferon a1fa-2a plus ribavirin or dual therapy with non-pegylated interferon alfa-2b plus ribavirin 2) dual therapy with pegylated interferon alfa-2b plus ribavirin *vs* dual therapy with non-pegylated interferon alfa- 2b plus ribavirin ***Endpunkte:*** SVR (absence of detectable HCV RNA in the serum 6 months after the end of a course of therapy) **Ergebnisse (insgesamt 16 Studien)** In pooled analysis, dual therapy with pegylated Interferon alfa-2a was superior to dual therapy with non-pegylated interferon alfa-2a or alfa-2b (six trials, RR = 2.03, 95% CI: 1.36--3.03). Heterogenity was high (I^2 = 86%).

	In a stratified analysis, there was no significant difference between estimates based on the subgroup of five trials (n = 1157) comparing dual therapy with pegylated interferon alfa-2a to dual therapy with non-pegylated Interferon alfa-2a (RR = 2.33, 95% CI: 1.68-3.23). A single, large (11 = 897) trial comparing dual therapy with pegylated interferon alfa-2a to dual therapy with non-pegylated interferon alfa-2b (RR = 1.28. 95% Cl: 1.12-1.46; P = 0.098 for difference in RR estimates). Dual therapy with pegylated interferon alfa-2b was also superior to dual therapy with non-pegylated interferon alfa- 2b for achieving an *SVR* (1 0 trials. RR = 1.28. 95% CI: l.ll-1.48). Heterogeneity was moderate (I^2 = 0.39%). *HIV Status* Three trials compared pegylated Interferon alfa- 2a *vs* dual therapy with non-pegylaled Interferon alfa-2a or alfa-2b. And three trials compared pegylated Interferon alfa-2b *vs* dual therapy with non-pegylated interferon alfa-2b in HiV and HCV co-lnfected patients. Pooled relative risks for SVR were 3.22 {95% CI: 2.36-4.39. I^2 = 0%) for dual therapy with pegylaled interferon alfa-2a and 1.70 (95% CI: 1.26-2.30. I^2 = 20%) for dual therapy with pegylated interferon alfa-2b. *HCV genotype* Nine trials of dual therapy with pegylated interferon *vs* dual therapy with on-pegylated Interferon restricted enrolment *to* genotype-l patients or reported subgroup results for patients with genotypc-1 infection. Four trials reported results for patients with either genotype-1 or -4 infection. Six trials reported results for patients infected with HCV genotype-2 or -3 and five trials reported results for patients infected with HCV genotype-4. Stratifying the trials of dual therapy with pegylated interferon alfa-2a *vs* dual therapy with non pegylated Interferon by genotype did not reduce heterogeneity. In general, dual therapy with pegylated Interferon alfa-2a or alfa-2b was superior to dual therapy with non-pegylated interferon for all HCV genotypes, hut some estimates did not reach statistical significance or were imprecise (wide confidence intervals) because of small numbers of trials. ***Fazit der Autoren*** There is insufficient evidence to support conclusions that dual therapy with one pegylated interferon is superior to the other.
Zhao, 2008 Peginterferon vs. interferon in the treatment of different HCV genotype infections in HIV patients [51]	**Fragestellung:** The aim of this study was to perform a meta-analysis of randomized controlled trials (RCTs) comparing peginterferon with interferon in the treatment of patients carrying different genotypes of hepatitis C virus (HCV) and coinfected with HIV. **Suchzeitraum: 1966 bis zum Zeitpunkt der Publikation** **Vergleich:** peginterferon vs interferon **Population :** HCV/HIV-coinfected patients. ***Anzahl der Patienten:*** *1717 Patienten* ***Anzahl der Studien:*** *6 Studien*

	Endpunkte: SVR **Ergebnisse (6 Studien)** Comparison of the efficacy of peginterferon plus ribavirin and interferon plus ribavirin therapies • The SVR was greater for patients treated with peginterferon plus ribavirin than for patients treated with interferon plus ribavirin (RR, 3.23; 95% CI, 2.27–4.6; P<0.01). • The combined SVR in patients treated with peginterferon plus ribavirin was 26% (ranging from 14 to 46% in the five included trials) and was higher than that in patients treated with interferon plus ribavirin (8%, ranging from 6 to 18%). Meta-analysis of the treatment of patients infected with HCV genotypes 2 or 3 and coinfected with HIV • Although a bigger sample size was needed for the statistics test, a trend was evident. A higher SVR was achieved in the HCV genotypes 2 or 3 plus HIV-coinfected patients treated with peginterferon plus ribavirin compared with patients treated with interferon plus ribavirin (55% vs. 33%; RR, 1.56; 95% CI, 0.88–2.77; P=0.13). Comparison of the efficacy of peginterferon plus ribavirin in the treatment of patients infected with different genotypes of HCV and coinfected with HIV • At present, peginterferon plus ribavirin is superior in the treatment of patients infected with different genotypes of HCV and coinfected with HIV, but the efficacies were different, probably because of the potential different pathological characteristics of the different genotypes of HCV. When the SVR were stratified according to genotype, the probability of achieving an SVR with peginterferon plus ribavirin was greater in HCV genotypes 2 or 3 plus HIV-coinfected patients compared with genotypes 1 or 4 plus HIV-coinfected patients (SVR, 55% vs. 26%) (RR, 2.0; 95% CI, 1.59–2.5; P<0.01).

Leitlinien

Allgemeine Empfehlungen

Christensen et al. 2012: Treatment for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection - Danish national guidelines 2011. [14]	**Monitoring during treatment** **Patients with genotype 1** • For patients with genotype 1 treated with pegylated interferon-alpha/ribavirin/telaprevir HCV-RNA should be measured after 4, 8, and 12 weeks of treatment. Telaprevir is administered for 12 weeks. For patients without cirrhosis, who have undetectable HCV-RNA at both 4 and 12 weeks of treatment, pegylated interferon-alpha and ribavirin can be stopped after 24 weeks. • For patients with HCV-RNA >1000 IU/mL at either 4 or 12 weeks of treatment, and/or detectable HCV-RNA after 24 weeks, treatment must be stopped as it is unlikely to lead to SVR. • For patients with genotype 1 treated with pegylated interferon-alpha/ribavirin/boceprevir after a lead-in phase of pegylated interferon-alpha/ribavirin HCV-RNA should be measured after 4, 8, 12, and 24 weeks of treatment. If HCV-RNA is negative at these measurements, treatment can be stopped after 28 weeks (4 weeks of lead in with pegylated interferonalpha/ ribavirin and 24 weeks of pegylated interferon-alpha /ribavirin/boceprevir). Patients who are HCV-RNA positive at week 8 and negative week 24 should continue tipple therapy until week 36 and receive an additional 12 weeks of pegylated interferon-alpha/ribavirin (total treatment duration 48 weeks). • If HCV-RNA is > 100 IU/mL after 12 weeks of treatment or positive after 24 weeks, treatment must be stopped, as it is unlikely to lead to SVR. • If lead-in is used and the patient has a RVR, then treatment with pegylated interferon-alpha/ribavirin, without DAAs, is continued for a total of 24 weeks. HCV-RNA should be measured after 4, 12, and 24 weeks. • If HCV-RNA has not decreased by 2 log after 12 weeks or is detectable after 24 weeks of treatment, treatment must be stopped as the likelihood to obtain SVR is <2%. • All patients negative of HCV-RNA 24 weeks after end of treatment are cured for hepatitis C. **Patients with genotype 2 and 3** • If HCV-RNA has not decreased by 2 logs after 12 weeks,treatment must be stopped as it is unlikely to lead to SVR. • In contrast to patients with genotype 1 where duration may be shortened by “response-guided therapy” several studies have shown that for patients with genotype 2 and 3 who obtain RVR, treatment duration should generally not be shortened to 12-16 weeks as this has been associated with decrease in SVR [60]. For patients with favorable baseline factors (see above) and severe side effects treatment shortening may be considered **Patients with genotypes 4, 5, 6** • Treatment for 48 weeks with pegylated interferon and ribavirin is recommended. HCV-RNA should be measured after 4, 12, 24, and 48 weeks of treatment, and 3 and 6 months after end of treatment.
	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche. k.A. • LoE und GoR: k.A.

Brok et al. 2010: European Guideline for the management of Hepatitis B and C virus infections. [9]	• Chronic HCV infection: Peginterferon alfa with ribavirin will cure chronic infection in approximately 50% of patients **(Ia, A)** • However, the treatment required will vary according to the genotype, initial treatment response and other factors. Treatment should be for 12-24 weeks for patients with genotypes 2 or 3 although HCV genotype 3 patients with advanced liver fibrosis and detectable HCV-RNA at week 4 of therapy may benefit from longer treatment duration (12 months). All other HCV genotypes (including 1 and 4) should be treated for 12-18 months. Treatment should be discontinued if there has not been a reduction in HCV viral load >2 log at week 12 of therapy or undetectable levels at week 24. Patients achieving undetectable viral load at week 4 (rapid virological responders) have the greatest chances of cure and may benefit from shorter courses of therapy. Patients are more likely to respond if they have less advanced liver fibrosis low serum HCV-RNA levels (<500,000 IU/ml), if they are infected with certain HCV genotypes (types 2 and 3) **(Ib, A)** • Patient selection for therapy depends mainly on HCV genotype and viral load. A liver biopsy is not necessary for making treatment decisions **(1b, A)** **ANMERKUNGEN FBMED** • Evidenzbasierte LL
de Bruijne et al. 2008: Treatment of chronic hepatitis C virus infection – Dutch national guidelines. [18]	**Recommendations:** • Antiviral therapy consists of the administration of peginterferon and ribavirin for 24 or 48 weeks. Patients with HCV genotype 1 or 4 are treated for 48 weeks. Patients with HCV genotype 2 or 3 are treated for 24 weeks (Level 1). • In patients with an undetectable HCV RNA after 4 weeks of treatment and baseline HCV RNA <600,000 IU/ml, a shorter treatment is equally effective (12 to 16 weeks for HCV genotype 2 or 3, 24 weeks for HCV genotype 1 or 4 with baseline HCV RNA ≤600,000 IU/ml) (Level 1). **ANMERKUNGEN FBMED** **Grade Definition:** • Level 1, Study of level A1 or at least two independent studies of level A2
Makara et al. 2012: [Hungarian consensus guideline for the diagnosis and treatment of B, C, and D viral hepatitis.] Ajanlas a B-, a C- es a D-virus hepatitisek diagnosztikajara es antiviralis kezelesere. Orv Hetil 2012; 153 (10): 375-94.[34]	Leitlinie in Ungarisch! Angaben lediglich dem Abstract entnommen!!! • „Naive Patienten mit chronischer Hepatitis C sollten zunächst eine Kombinationstherapie aus Interferon (pegylated) und Ribavirin erhalten." • Wenn die Response bei **Genotyp 1 Patienten** nach 4 oder 12 Wochen unzureichend ausfällt, wird die Gabe von Boceprevir oder Telaprevir empfohlen. Die Behandlungsdauer beträgt i.d.R. 48 Wochen, bei früher viraler Response wird eine kürzere Behandlung empfohlen. • Treatment-failure Patienten mit **Genotyp 1 Infektion** sollten für die Dauer von 48 Wochen eine Dreifachtherapie mit einem Protease-Inhibitor bekommen. Allerdings ist bei einem Rückfall (relapse) ohne Zirrhose und mit schneller viraler Response eine kürzere Behandlungen mit Telaprevir ausreichend. • Für Genotyp 2 oder 3 und Genotyp 4 Patienten wird i.d.R. eine Therapie mit pegyliertem Interferon plus Ribavirin-Therapie von 24, 48

	oder 72 Wochen empfohlen.
	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche. nicht im Abstract angegeben • LoE und GoR: k.A.
EASL Clinical Practice Guidelines 2011: Management of hepatitis C virus infection. [19]	• The combination of pegylated IFN-a and ribavirin is the approved SoC for chronic hepatitis C (LoE: A; GoR: 1). • Two pegylated IFN-a molecules, pegylated IFN-a2a (180 lg once per week) and pegylated IFN-a2b (1.5 lg/ kg once per week), can be used in combination with ribavirin. • Ribavirin should be given at a weight-based dose of 15 mg/ kg per day for genotypes 1 and 4–6 (LoE: A, GoR: 2) and at a flat dose of 800 mg/day for genotypes 2 and 3 (LoE: A; GoR: 2). • Patients with genotypes 2 and 3 with baseline factors suggesting low responsiveness should receive weight-based ribavirin at the dose of 15 mg/kg per day (LoE: C; GoR: 2).
	ANMERKUNGEN FBMED
	• LL nach dem GRADE-approach [High (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2)]

NICE 2012: Boceprevir for the treatment of genotype 1 chronic hepatitis C. [36]	• standard treatment for genotype 1 chronic hepatitis C in the UK is peginterferon alfa plus ribavirin for both treatment-naive and previously treated patients.
	• Boceprevir in combination with peginterferon alfa and ribavirin is recommended as an option for the treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease:
	  • who are previously untreated or
	  • in whom previous treatment has failed.
	• Boceprevir plus peginterferon alfa and ribavirin is clinically more effective that peginterferon alfa and ribavirin alone in inducing a sustained virological response in treatment-naive patients and previously treated patients, irrespective of baseline fibrosis level.

	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
NICE 2012: Telaprevir for the treatment of genotype 1 chronic hepatitis C. [38]	Telaprevir in combination with peginterferon alfa and ribavirin is recommended as an option for the treatment of **genotype 1 chronic hepatitis C** in adults with compensated liver disease: • who are previously untreated **or** • in whom previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin has failed, including people whose condition has relapsed, has partially responded or did not respond. • Telaprevir plus peginterferon alfa and ribavirin was clinically more effective than peginterferon alfa and ribavirin alone in inducing a sustained virological response in previously untreated and previously treated patients.
	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
NICE 2010: Peginterferon alfa	Combination therapy with peginterferon alfa (2a or 2b) and ribavirin is recommended as a treatment option for adults with chronic hepatitis C:

and ribavirin for the treatment of chronic hepatitis C.[37]	• who have been treated previously with peginterferon alfa (2a or 2b) and ribavirin in combination, or with peginterferon alfa monotherapy, and whose condition either did not respond to treatment or responded initially to treatment but subsequently relapsed **or** • who are co-infected with HIV. Shortened courses of combination therapy with peginterferon alfa (2a or 2b) and ribavirin are recommended for the treatment of adults with chronic hepatitis C who: • have a rapid virological response to treatment at week 4 that is identified by a highly sensitive test **and** • are considered suitable for a shortened course of treatment. When deciding on the duration of combination therapy, clinicians should take into account the licensed indication of the chosen drug (peginterferon alfa-2a or peginterferon alfa-2b), the genotype of the hepatitis C virus, the viral load at the start of treatment and the response to treatment (as indicated by the viral load). ***Peginterferon alfa-2a:*** • When peginterferon alfa-2a is given in combination with ribavirin, people with HCV genotype 1 or 4 infections who have detectable HCV RNA at week 4 (that is, there is not a rapid virological response) should receive 48 weeks of treatment. • People with genotype 2 or 3 infections and undetectable HCV RNA at week 4 (that is, a rapid virological response) should receive 24 weeks of treatment. • An extension to the licence for peginterferon alfa-2a now means that some people with hepatitis C are eligible for shortened courses of treatment. People with HCV genotype 1 and a low viral load at the start of treatment, a rapid virological response at week 4 and undetectable HCV RNA at week 24 may complete treatment at week 24 rather than receiving the standard 48 weeks of therapy. • The licence extension also allows people with HCV genotype 2 or 3 who have a low viral load (equal to or less than 800,000 IU/ml), undetectable HCV RNA by week 4 (that is, a rapid virological response) and undetectable HCV RNA at week 16 to stop treatment at week 16 rather than receiving the standard 24 weeks of therapy. • People with HCV genotype 4 may be treated in line with the regimen for people with genotype 1, but without requiring a low viral load. • People with genotype 5 or 6 should be treated for 48 weeks. • People with HCV genotype 1 whose condition has not responded to prior treatment with peginterferon alfa and ribavirin combination therapy and who are considered for re-treatment should receive 72 weeks of combination therapy. ***Peginterferon alfa-2b*** • People with HCV genotype 1 who have undetectable HCV RNA at week 12 (that is, who have an early virological response) should receive 48 weeks of treatment with peginterferon alfa-2b. • People with a genotype 1 infection without an early virological response are considered unlikely to have a sustained virological response, and consideration should be given to withdrawing treatment. • People with HCV genotype 4 should be treated with the same regimen as for genotype 1 infections.

	• People with HCV genotype 2 or 3 infections should be treated for 24 weeks. • Re-treatment with peginterferon alfa-2b in combination with ribavirin is recommended in the marketing authorisation for people whose hepatitis C has not shown an adequate response to treatment (non-response) or has responded but subsequently relapsed. • All people re-treated with peginterferon alfa-2b, irrespective of HCV genotype, who have undetectable serum HCV RNA at week 12 should receive 48 weeks of treatment. • People re-treated with peginterferon alfa-2b in whom HCV RNA is still detectable at week 12 are unlikely to have a sustained virological response after 48 weeks of therapy.
	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
Ghany et al. 2009: Diagnosis, Management, and Treatment of Hepatitis C: An Update. [24]	*Genotypes 1 and 4 HCV Infection:* • Treatment with peginterferon plus ribavirin should be planned for 48 weeks; the dose for peginterferon alfa-2a is 180 µg subcutaneously per week together with ribavirin using doses of 1,000 mg for those <75 kg in weight and 1,200 mg for those >75 kg; the dose for peginterferon alfa-2b is 1.5 µg/kg subcutaneously per week together with ribavirin using doses of 800 mg for those weighing <65 kg; 1,000 mg for those weighing >65 kg to 85 kg, 1,200 mg for >85 kg to 105 kg, and 1,400 mg for >105 kg (Class I, Level A). • Treatment may be discontinued in patients who do not achieve an early virological response (EVR; >2 log reduction in HCV RNA at week 12 of treatment) (Class I, Level A). • Patients who do not achieve a complete EVR (undetectable HCV RNA at week 12 of treatment) should be re-tested at week 24, and if HCV RNA remains positive, treatment should be discontinued (Class I, Level A). • For patients with genotype 1 infection who have delayed virus clearance (HCV RNA test becomes negative between weeks 12 and 24), consideration should be given to extending therapy to 72 weeks (Class IIa, Level B). • Patients with genotype 1 infection whose treatment continues through 48 to 72 weeks and whose measurement of HCV RNA with a highly sensitive assay is negative at the end of treatment should be retested for HCV RNA 24 weeks later to evaluate for a sustained virological response (SVR; HCV RNA negative 24 weeks after cessation of treatment) (Class I, Level A). *Genotype 2 or Genotype 3 HCV Infection:* • Treatment with peginterferon plus ribavirin should be administered for 24 weeks, using a ribavirin dose of 800 mg (Class I, Level A). • Patients whose treatment continues through 24 weeks and whose measurement of HCV RNA with a highly sensitive assay is negative should be retested for HCV RNA 24 weeks later to evaluate for an SVR (Class I, Level A). • Patients with HCV-related cirrhosis who achieve an SVR, regardless of the genotype, should continue to be monitored at 6 to 12 month intervals for the development of HCC (Class IIa, Level C).
Ghany et al. 2011: An Update on Treatment of	• The optimal therapy for genotype 1, chronic HCV infection is the use of **boceprevir or telaprevir** incombination with peginterferon alfa and ribavirin (**Class 1, Level A**).

Genotype 1 Chronic Heaptitis C Infection: 2011 Practice Guideline by the American Association for the study of Liver diseases. Hepatology **2011**; 54(4):1433-44. [23]	• **Boceprevir and telaprevir** should not be used without peginterferon alfa and weight-based ribavirin (**Class 1, Level A**). **ANMERKUNGEN FBMED** • Evidenzbasierte LL
Haute Autorité de Santé (HAS). Hepatite chronique C. Guide ALD no 6, Actes et prestations sur l'hepatite chronique C. Stand: Juni 2012. [29]	• Behandlungsstandard: Génotype 1, in Abhängigkeit vom Polymorphismus IL28-B: - IFN PEGα-2a oder IFN PEGα-2b + ribavirine: • Dreifachthérapie (mit boceprevir bzw. telaprevir), möglich für folgende Patienten : génotype 1 - therapienaiv oder Versager unter vorheriger Therapie bei nicht-dekompensierter Lebererkrankung: - IFN PEGα-2a ou IFN PEGα-2b + ribavirine + boceprevir oder telaprevir **ANMERKUNGEN FBMED** Methodik der Leitlinienerstellung ungenügend beschrieben, so dass Beurteilung der methodischen Qualität nicht möglich; aufgrund Aktualität dennoch aufgenommen
Ramachandran et al. 2012: UK consensus guidelines for the use of the protease inhibitors boceprevir and telaprevir in genotype 1 chronic hepatitis C infected patients. Aliment Pharmacol Ther 2012; 35 (6): 647-62[41]	CONSENSUS STATEMENTS 1. Which patients to treat? • Due to the improvements in cure rates and potential for shortened therapy, protease inhibitor-based regimens should be considered for all genotype 1 chronic HCV-infected patients. This is applicable for treatmentnaïve patients and patients who have had virological failure following prior exposure to SoC [Standard of care] therapy 2. Which treatment regimens to use? **(a) Which peginterferon-ribavirin to use?** The treatment regimens used differ between the two PIs and the different trials. One critical difference between the studies is the use of different peginterferonribavirin preparations and doses. In general, in the boceprevir studies, pegylated IFN-a2b (PegIntron; Merck, Whitehouse Station, NJ, USA) at a dose of 1.5 lg/kg once weekly and ribavirin (Rebetol; Merck) at weightbased dose of 600–1400 mg daily in two divided doses were used. In the telaprevir studies, pegylated IFN-a2a (Pegasys; Roche, Welwyn Garden City, UK) at a dose of 180 lg/week and ribavirin (Copegus; Roche) at a weight dependent dose of 1000 mg (<75 kg) or 1200 mg (_75 kg) per day were used. Direct comparison studies between Peg IFN-a2a and Peg IFN-a2b in SoC treatment have not shown any significant difference in overall response rates.10 Furthermore, in small studies, telaprevir has been used with Peg IFN-a2b45 and boceprevir with IFN-a2a46 with no detrimental effect. **(i) Peg IFN-a2a or Peg IFN-a2b can be used interchangeably with either telaprevir or boceprevir according to local preferences.** **(ii) Ribavirin brands can be used interchangeably in treatment regimens.**

(b) Which protease inhibitor to use?

The documented evidence clearly shows a benefit for the use of either boceprevir or telaprevir as part of a triple therapy regimen in both treatment-naïve patients and patients with previous virological failure. Largely, the magnitude of beneficial effect is similar for either drug. No direct comparison studies between boceprevir and telaprevir have been conducted, and thus, neither drug can be recommended over the other. However, specific characteristics of each drug may lead to their use in certain circumstances. Boceprevir-based regimens use a 4-week lead-in with peginterferon-ribavirin, which may offer extra information on treatment tolerability and the likelihood of achieving an SVR. In addition, differences in side-effect profiles and the duration of treatment may lead to the choice of either PI for specific patients. Furthermore, the pill burden for patients differs, with boceprevir currently four tablets t.d.s., whereas telaprevir is two tablets t.d.s. It is therefore important that both drugs are available to treating units to enable selection of the most appropriate regimen for individual patients.

(i) Both boceprevir and telaprevir are effective and should be available for use by treating units.

<u>ADVERSE EFFECTS</u>

- Whilst the appropriate use of PIs with peginterferon+ribavirin provides significant increases in cure rates of genotype 1 chronic HCV infection, there is also an increased rate of adverse effects with the use of triple therapy.
- … the principal side-effects associated with **boceprevir** treatment are dysgeusia (altered sense of taste), anaemia and neutropenia. The dysgeusia does not usually need any alteration in treatment. Dose reduction of boceprevir should not be used in the management of adverse effects, as suboptimal dose will promote the emergence of resistant species in failing regimens.
- With **telaprevir** treatment regimens, the adverse effect profile is slightly different from boceprevir. Studies have shown an increase in skin rash and anorectal symptoms (discomfort and pruritus) with telaprevir treatment. The anorectal symptoms are usually tolerable for the duration of telaprevir treatment, and rarely (0.5%) led to discontinuation.
  One of the principal adverse events in telaprevir treatment is rash. This leads to discontinuation of telaprevir in 5–7% of cases,19, 21, 41 at which point the rash invariably resolves (although this may take several weeks). The rash is predominantly eczematous and pruritic. Fifty percent of patients developing rash do so within the first 4 weeks of treatment, although it can occur at any time.

<u>The provision of care</u>

(a) Due to the importance of RGT and stopping rules in PI-based regimens and the increased risk of adverse effects, the use of PI treatment should be limited to centres providing the following standards of care:
(i) Adherence to national standards for HCV.
(ii) Continuous audit of SVR rates to therapy.
(iii) Continuous audit of treatment discontinuation rates.
(iv) A high level of expertise in the use of antiviral drugs.
(v) Access to viral load estimation results within five working days of

	sampling. (vi) Access to HCV PCR with a lower limit of detection of at most 15 IU/mL.43 (vii) Access to non-invasive investigations and/or liver biopsy to assess the degree of hepatic fibrosis. (viii) Sufficient specialised medical and nursing staff to provide year round support to patients on therapy. (ix) A series of protocols to minimise the risk of developing and to manage adverse reactions to therapy. (x) A comprehensive and skilled consultation service for patients emphasising the risks and benefits of therapy along with the requirement for adherence. (b) Where possible, all patients should be invited to participate in ongoing research initiatives (e.g. enrolment to the HCV research UK3 database). (c) Ongoing recruitment to clinical trials should continue where feasible.
	ANMERKUNGEN FBMED
	Methodik der Leitlinienerstellung ungenügend beschrieben, so dass Beurteilung der methodischen Qualität nicht möglich; aufgrund Aktualität dennoch aufgenommen
Yee et al. 2012: Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. The American Journal of Gastroenterology 2012; 107 (5): 669-89. [50]	**Recommendations for PegIFN alfa with or without RBV treatment in genotype 1 patients:** • PegIFN alfa monotherapy may be used to treat patients with contraindications to RBV (Class I, Level A). • For patients who achieve RVR and have a low baseline viral load (HCV RNA < 400,000 IU / ml), 24-weeks of treatment with PegIFN – RBV may be sufficient (Class I, Level B). **Recommendations in patients with genotype 4 infection:** • Appropriate candidates with HCV genotype 4 infection should be treated with PegIFN alfa-2a 180 mcg per week or PegIFN alfa-2b 1.5 mcg / kg per week, plus RBV up to 1,400 mg per day for 48 weeks (Class I, Level A). **Recommendations in patients with cirrhosis:** • HCV genotype 1-infected patients with compensated cirrhosis (Child-Pugh Class < 7), adequate neutrophils (> 1.5 k/ mm 3), and adequate platelet counts (> 75 k/ mm 3) should be considered for treatment with BOC (for 44 weeks) or TVR (for 12 weeks) combined with PegIFN – RBV at standard doses for 48 weeks (Class I, Level B). • Patients with cirrhosis remain at risk for HCC and should undergo routine screening regardless of viral clearance status, in accordance with current guidelines (Class I, Level B). **Recommendations in patients with decompensated cirrhosis:** • Liver transplantation is the treatment of choice in patients with decompensated cirrhosis (Class I, Level B). • Antiviral therapy is contraindicated in most patients with decompensated cirrhosis (Class II, Level B). • IFN-based therapy in combination with RBV may be considered in patients awaiting liver transplantation with a Child-Pugh score < 7 and a MELD score ≤ 18 (Class I, Level A). • If antiviral therapy is undertaken, reduced IFN doses should be used and growth factors can be given to counteract treatmentassociated cytopenias (Class II, Level B).
	ANMERKUNGEN FBMED
	Evidenzbasierte LL

Ghany et al. 2011: An Update on Treatment of Genotype 1 Chronic Heaptitis C Infection: 2011 Practice Guideline by the American Association for the study of Liver diseases. Hepatology **2011**; 54(4):1433-44. [23]	**Recommendations for Treatment-Naive Patients:** • The recommended dose of **boceprevir** is 800 mg administered with food three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 24-44 weeks preceded by 4 weeks of lead-in treatment with peginterferon alfa and ribavirin alone (**Class 1, Level A**). • Patients without cirrhosis treated with **boceprevir**, peginterferon, and ribavirin, preceded by 4 weeks of lead-in peginterferon and ribavirin, whose HCV RNA level at weeks 8 and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (4 weeks lead-in with peginterferon and ribavirin followed by 24 weeks of triple therapy) (**Class 2a, Level B**). • Treatment with all three drugs (**boceprevir**, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24 (**Class 2a, Level B**). • The recommended dose of **telaprevir** is 750 mg administered with food (not low-fat) three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 12 weeks followed by an additional 12-36 weeks of peginterferon alfa and ribavirin (**Class 1, Level A**). • Patients without cirrhosis treated with **telaprevir**, peginterferon, and ribavirin, whose HCV RNA level at weeks 4 and 12 is undetectable should be considered for a shortened duration of therapy of 24 weeks (**Class 2a, Level A**). • Patients with cirrhosis treated with either **boceprevir** or **telaprevir** in combination with peginterferon and ribavirin should receive therapy for a duration of 48 weeks (**Class 2b, Level B**). • Treatment with all three drugs (**telaprevir**, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >1,000 IU/mL at treatment weeks 4 or 12 and/or detectable at treatment week 24 (**Class 2a, Level B**).
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL
EASL Clinical Practice Guidelines 2011: Management of hepatitis C virus infection. [19]	• SVR is achieved in 40–54% of patients infected with HCV genotype 1 treated with pegylated IFN-a plus ribavirin at approved doses for 48 weeks (LoE: A; GoR: 1). • SVR is achieved in 65–82% of patients infected with HCV genotypes 2 or 3 treated with pegylated IFN-a plus ribavirin at approved doses for 24 weeks (LoE: A; GoR: 1). • SVR rates are slightly higher in patients infected with HCV genotype 2 than in those with genotype 3 (LoE: B; GoR: 2). • Strongest baseline predictors of SVR are: o HCV genotype (LoE: A; GoR: 1) o Genetic polymorphisms located in chromosome 19 (IL28B), particularly in genotype 1 patients (LoE: A; GoR: 1). o Stage of liver fibrosis (LoE: A; GoR: 1).
	ANMERKUNGEN FBMED
	• LL nach dem GRADE-approach [High (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2)]
Leroy et al. 2012: Protease inhibitor-based triple therapy	*Recommendations:* • Treatment-naive genotype 1 patients with predictive factors of poor response (non-CC genotypes of IL28B or fibrosis F3-F4) should

in chronic hepatitis C: guidelines by the French Association for the Study of the Liver. [33]	receive triple therapy (PI plus PegIFN-RBV) as the first-line treatment (LoE: A; GoR: 1, level of agreement 84%). **ANMERKUNGEN FBMED** • Evidenzbasierte LL
Yee et al. 2012: Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. The American Journal of Gastroenterology 2012; 107 (5): 669-89. [50]	*Recommendations for therapy among treatment-naïve patients with genotype 1 infection:* • PegIFN alfa and RBV, in combination with BOC (800 mg orally every 7 – 9 h with food) or TVR (750 mg orally every 7 – 9 h with 20 g of fat) is the standard of care for most treatment-naïve genotype 1-infected patients (**Class I, Level A**). • If a TVR-containing regimen is used in treatment-naïve noncirrhotic patients who achieve eRVR, TVR should be discontinued at week 12 and PegIFN – RBV should be continued for an additional 12 weeks. If HCV RNA is detectable, but < 1,000 IU/ ml at treatment week 4, and remains < 1,000 IU/ml or becomes undetectable by week 12, TVR should be discontinued at week 12, and PegIFN and RBV can be continued for another 36 weeks (**Class I, Level A**). • If a TVR-containing regimen is used in treatment-naïve cirrhotics • who achieve an HCV RNA that is undetectable or < 1,000 IU / ml at treatment weeks 4 and 12, TVR should be discontinued at week 12, and PegIFN – RBV can be continued for another 36 weeks (**Class I, Level A**). • If a BOC-containing regimen is used in treatment-naïve noncirrhotics, if HCV RNA declines by ≥ 1 log 10 during the 4-week lead-in, and HCV RNA is undetectable at weeks 8 – 24, treatment with BOC – PegIFN – RBV for 24 weeks is suffi cient. If HCV RNA is detectable at week 8, but < 100 IU / ml at week 12, and negative at week 24, BOC – PegIFN – RBV should be continued until week 36, followed by PegIFN – RBV alone for 12 more weeks. If HCV RNA declines by < 1 log 10 during the lead-in, BOC– PegIFN– RBV can be continued for 44 weeks (**Class I, Level A**). • If a BOC-containing regimen is used in treatment-naïve cirrhotics, 44 weeks of BOC – PegIFN – RBV is required after the 4-week lead-in (**Class I, Level A**). *Recommendations for treatment-na ï ve and -experienced patients with genotype 2 or 3 infection:* • Treatment-naïve patients should be treated with PegIFN – RBV for 24 weeks (Class I, Level A). • For patients with low viral load (HCV RNA < 600,000 IU / ml) and mild fibrosis who achieve a RVR, 12 – 18 weeks of treatment may be sufficient (Class I, Level A). • For patients with genotype 3 infection and a high HCV RNA (> 600,000 IU / ml), steatosis or advanced fibrosis, treatment beyond 24 weeks may improve response (Class I, Level B). • Retreatment duration is 48 weeks (Class I, Level A). **ANMERKUNGEN FBMED** • Evidenzbasierte LL
Sarazzin et al.: Leitlinie der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten: Leitlinie Prophylaxe,	**Nicht vorbehandelte Patienten** Empfehlung: • Die Standardtherapie erfolgt mit einem pegylierten Interferon alfa in Kombination mit Ribavirin [A]. • Bei Kontraindikationen für Ribavirin wird eine Monotherapie mit einem pegylierten Interferon alfa durchgeführt [A]. • Ribavirin sollte körpergewichtsadaptiert dosiert werden [A]. • Die Therapiedauer richtet sich im Wesentlichen nach dem

Diagnostik und Therapie der **Hepatitis-C-Virus (HCV)-Infektion. [42]**	HCV-Genotyp, der HCV-RNA-Konzentration vor Therapie und dem virologischen Verlauf unter der Behandlung [A]. • Die Therapie sollte bei fehlendem virologischem Ansprechen (Non-Response) vorzeitig beendet werden [A]. **ANMERKUNGEN FBMED** • Evidenzbasierte S3-LL • Die Leitlinien-Erstellung wurde am 12.11.2007 begonnen und am 07.09.2009 formal abgeschlossen. • **Gültigkeit abgelaufen-LL wird z.Zt. überprüft**

Leitlinien – Vorbehandelte Patienten und Nonresponder

Ghany et al. 2009: Diagnosis, Management, and Treatment of Hepatitis C: An Update. [24]	**Retreatment of Persons Who Failed to Respond to Previous Treatment:** • Retreatment with peginterferon plus ribavirin in patients who did not achieve an SVR after a prior full course of peginterferon plus ribavirin is not recommended, even if a different type of peginterferon is administered (for relapsers, Class III, Level C; for non-responders, Class III, Level B). • Retreatment with peginterferon plus ribavirin can be considered for non-responders or relapsers who have previously been treated with non-pegylated interferon with or without ribavirin, or with peginterferon monotherapy, particularly if they have bridging fibrosis or cirrhosis (Class IIa, Level B). • Maintenance therapy is not recommended for patients with bridging fibrosis or cirrhosis who have failed a prior course of peginterferon and ribavirin (Class III, Level B). **ANMERKUNGEN FBMED** • Evidenzbasierte LL
Ghany et al. 2011: An Update on Treatment of Genotype 1 Chronic Heaptitis C Infection: 2011 Practice Guideline by the American Association for the study of Liver diseases. Hepatology **2011**; 54(4):1433-44.[23]	**Recommendations for treatment-experienced patients:** • Re-treatment with boceprevir or telaprevir, together with peginterferon alfa and weight-based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or peginterferon alfa and/or ribavirin (**Class 1,Level A**). • Re-treatment with telaprevir, together with peginterferon alfa and weight-based ribavirin, may be considered for prior null responders to a course of standard interferon alfa or peginterferon alfa and/or weight-based ribavirin (**Class 2b, Level B**.) • Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir- based regimen can be considered for relapsers (**Class 2a, Level B for boceprevir; Class 2b, Level C for telaprevir**), may be considered for partial responders (**Class 2b, Level B for boceprevir; Class 3, Level C for telaprevir)**, but cannot be recommended for null responders (**Class 3, Level C**). • Patients re-treated with boceprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA > 100 IU at week 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance (**Class 1, Level B**). **ANMERKUNGEN FBMED** • Evidenzbasierte LL
Leroy et al. 2012: Protease inhibitor-based triple therapy	Recommendations: • Patients with PegIFN-RBV treatment failure should receive triple therapy with TVR or BOC and this should be the standard of care

in chronic hepatitis C: guidelines by the French Association for the Study of the Liver. [33]	(LoE: C; GoR: 2, level of agreement 89%). • In patients who relapsed after PegIFN-RBV therapy, triple therapy should be quickly started in patients with severe fibrosis (F3–F4), is indicated for those with moderate fibrosis (F2) and should be discussed on a case-by-case basis in patients with minimal lesions (F0–F1) (LoE: B; GoR: 2, level of agreement 91%). • Patients who showed a partial response to PegIFN-RBV therapy but have severe fibrosis (F3–F4) should start triple therapy as soon as possible. For those with minimal to moderate fibrosis (_F2), treatment should be discussed on a case-by-case basis (LoE: B; GoR: 2, level of agreement 89%). • In null responders to PegIFN-RBV therapy with severe fibrosis, an SVR with triple therapy can be expected only in about 15% of F4 patients and 40% of F3 patients. • This treatment is indicated in the absence of any alternative (clinical trials). For F0–F2 patients, the chance of success is about 30% and the benefit–risk ratio should be evaluated on a case-by-case basis (LoE: B; GoR: 2, level of agreement 86%).
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL
Yee et al. 2012: Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. The American Journal of Gastroenterology 2012; 107 (5): 669-89. 53[50]	**Recommendations for retreatment of nonresponders and relapsers with genotype 1 infection:** • For patients who previously failed PegIFN – RBV, retreatment with BOC or TVR, and PegIFN – RBV may be considered, particularly in patients who were relapsers (**Class I, Level A**). • If a BOC-containing regimen is used for re-treatment of noncirrhotic prior partial responders or relapsers, the recommended treatment duration is 36 weeks if HCV RNA is undetectable from weeks 8 to 24. If HCV RNA is detectable at week 12, but < 100 IU / ml, and is undetectable from weeks 24 to 36, BOC can be discontinued at week 36 and PegIFN – RBV can be continued for an additional 12 weeks (**Class I, Level B**). • If a BOC-containing regimen is used for re-treatment in cirrhotics, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but < 100 IU/ ml, and becomes undetectable from weeks 24 to 36 (**Class I, Level B**). • If a BOC-containing regimen is used for re-treatment of prior null responders, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but < 100 IU / ml, and become undetectable from weeks 24 to 36 (**Class II, Level C**). • If a TVR-containing regimen is used for re-treatment of prior relapsers and HCV RNA is undetectable from weeks 4 and 12, TVR should be discontinued at week 12 and PegIFN – RBV should be continued for an additional 12 weeks. If HCV RNA is detectable, but < 1,000 IU / ml at week 4 and / or 12, TVR can be discontinued at week 12 and PegIFN – RBV can be continued for an additional 36 weeks (**Class I, Level B**). • If a TVR-containing regimen is used for re-treatment of prior partial responders or null responders, and HCV RNA is < 1,000 IU / ml at weeks 4 and 12, TVR should be discontinued at week 12 and PegIFN alfa plus RBV should be continued for an additional 36 weeks (**Class I, Level B**).
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL
Sarazin et al.: Leitlinie der	**Patienten mit einem Rückfall auf eine Vortherapie (Relapse)** Empfehlung:

Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten: Leitlinie Prophylaxe, Diagnostik und Therapie der **Hepatitis-C-Virus (HCV)-Infektion. [42]**	• Patienten mit einem Rückfall auf eine PEG-Interferon alfa-Monotherapie sollten mit PEG-Interferon alfa und Ribavirin behandelt werden [A]. • Bei Patienten mit einem Rückfall auf eine PEG-Interferon alfa/ Ribavirin-Kombinationstherapie sollte die Vortherapie überprüft werden (Dosierung PEG-Interferon alfa und Ribavirin, Dosisreduktionen, Therapiepausen, Therapiedauer, HCV RNA Kinetik, Management von Nebenwirkungen, Compliance, u.a.) [C]. • Diese Faktoren sollten bei einer Re-Therapie optimiert werden [C]. • Patienten mit einem Rückfall auf eine PEG-Interferon alfa / Ribavirin-Kombinationstherapie sollten unabhängig vom Genotyp 48 [A] bzw. bei langsamem virologischen Ansprechen 72 Wochen [C] behandelt werden. • Fehlender HCV-RNA-Negativierung (HCV RNA nachweisbar mit einem hochsensitiven Assay) zu Woche 12 [A] bzw. 24 [C] bei langsamem Ansprechen in der Ersttherapie sollte die Therapie abgebrochen werden. **Konsens: 95%** **Patienten mit einem fehlenden Ansprechen auf eine Vortherapie (Non-Response)** Empfehlung: • Therapieversager unter einer PEG-Interferon alfa-Monotherapie sollten wie unvorbehandelte Patienten mit PEG-Interferon alfa und Ribavirin behandelt werden [B]. • Bei Therapieversagern auf eine PEG-Interferon alfa/ Ribavirin-Kombinationstherapie sollte die Vortherapie überprüft werden (Dosierung PEG-Interferon alfa und Ribavirin, Dosisreduktionen, Therapiepausen, Therapiedauer, HCV RNA Kinetik, Management von Nebenwirkungen, Compliance, u.a.) [C]. • Eine erneute Therapie mit PEG-Interferon alfa und Ribavirin kann bei einer suboptimalen Vortherapie und Verbesserungsmöglichkeiten in der Re-Therapie versucht werden [B] • Eine erneute Therapie mit PEG-Interferon alfa und Ribavirin kann bei einer suboptimalen Vortherapie und Verbesserungsmöglichkeiten in der Re-Therapie versucht werden [B] • Bei fehlender HCV-RNA-Negativierung (HCV RNA nachweisbar mit einem hochsensitiven Assay) zu Woche 12 [A] bzw. 24 [C] bei langsamem Virusabfall in der Ersttherapie sollte die Therapie abgebrochen werden. • Bei einem virologischen Ansprechen sollte die Therapie möglichst über insgesamt 72 Wochen fortgeführt werden [A]. • Eine niedrig-dosierte Langzeitmonotherapie mit PEG-Interferon alfa zur Verhinderung der Fibroseprogression bzw. klinischen Komplikationen der Lebererkrankung kann gegenwärtig nicht generell empfohlen werden [A]. **Konsens: 98%**
	ANMERKUNGEN FBMED
	• Evidenzbasierte S3-LL • Die Leitlinien-Erstellung wurde am 12.11.2007 begonnen und am 07.09.2009 formal abgeschlossen. • **Gültigkeit abgelaufen-LL wird z.Zt. überprüft**

Übersicht aus Leitlinie von Yee et al. 2012

Table 6. **HCV PI (BOC or TVR): RGT criteria and futility rules (34,35)**

	BOC–PegIFN/RBV	TVR–PegIFN/RBV
Candidates for RGT	Noncirrhotics: Treatment-naïve: 28 weeks Prior relapser/partial responder: 36 weeks	Noncirrhotics: Treatment-naïve: 24 weeks Prior relapser: 24 weeks
Criteria for RGT	HCV RNA undetectable (<10–15 IU/ml) weeks 8–24	HCV RNA undetectable (<10–15 IU/ml) weeks 4 and 12
Futility rules (stop all treatment if any of the following occur)	Week 12: HCV RNA ≥100 IU/ml Or Week 24: HCV RNA detectable Or HCV RNA rebounds at any timepoint (≥1 $\log_{10}$ increase from the nadir HCV RNA)	Week 4 or 12: HCV RNA >1,000 IU/ml Or Week 24: HCV RNA detectable Or HCV RNA rebounds at any timepoint (≥1 $\log_{10}$ increase from the nadir HCV RNA)

HCV, hepatitis C virus; PegIFN, peginterferon; PI, protease inhibitor; RBV, ribavirin; RGT, response-guided therapy; TVR, telaprevir.

Leitlinien – HIV Koinfektion

Brook et al. 2010: European Guideline for the management of Hepatitis B and C virus infections. [9]	• HIV-positive patients respond to treatment, although not as well as HIVnegative patients **(Ib, A)**. • Sustained virological response in those completing therapy is 11-29% for genotypes 1 or 4 and 43-73% for genotypes 2 or 3 **(1b, A)** **ANMERKUNGEN FBMED** • Evidenzbasierte LL
Brook et al. 2010: British HIV Association guidelines for the management of coinfection with HIV-1 and hepatitis B or C virus 2010. [8]	Patients with HCV infection who are co-infected with HIV: • Anti-HCV treatment should be started before the CD4 count falls below 350 cells/mL and before ART is started, if possible (LoE: I). • The aim of treatment is an SVR (undetectable viral load 24 weeks post treatment) (LoE: I). • An RVR (viral load undetectable) at 4 weeks of treatment predicts response. Lack of EVR (nondetectable viral load or 42 log10 fall at 12 weeks) or detectable viral load at 24 weeks of treatment predicts nonresponse and therapy should be stopped (LoE: I). • Any ART should be stabilized before anti-HCV therapy is commenced (LoE: I). • Careful assessment of liver fibrosis is recommended, especially for patients with HCV genotypes 1 and 4 or those with suspected cirrhosis (LoE: I). • In patients with genotype 2 or 3 infection, liver biopsy is not necessary if there is no clinical evidence of advanced liver disease. For genotypes 1 and 4, a pretreatment liver biopsy is recommended, or a hepatic elastography if the biopsy is refused (LoE: I). • Consider treatment for all patients with genotypes 2/3. Consider treatment for all patients with genotypes 1/4, especially if there is significant liver fibrosis (Ishak grade F3 or more) (LoE: I). • Treatment in all genotypes should be with pegylated interferon weekly plus ribavirin at 1000–1200mg daily, supported by erythropoietin/growth factors if necessary (LoE: I). • Treat patients with genotype 2 or 3 infection for 24 weeks if there is an RVR (II), otherwise for 48 weeks (I). • Treat patients with genotypes 1 and 4 for 48 weeks if there is an RVR, or 72 weeks if there was a 2 log10 drop but detectable HCV RNA at week 12 and they become PCR negative at 24 weeks (LoE: I). **ANMERKUNGEN FBMED** • Evidenzbasierte LL

Ghany et al. 2009: Diagnosis, Management, and Treatment of Hepatitis C: An Update. [24]	<u>Patients with HCV infection who are co-infected with HIV:</u> • Anti-HCV testing should be performed in all HIV-infected persons (Class I, Level B). • HCV RNA testing should be performed to confirm HCV infection in HIV-infected persons who are positive for anti-HCV, as well as in those who are negative and have evidence of unexplained liver disease (Class I, Level B). • Hepatitis C should be treated in the HIV/HCV co-infected patient in whom the likelihood of serious liver disease and a treatment response are judged to outweigh the risk of morbidity from the adverse effects of therapy (Class I, Level A). • Initial treatment of hepatitis C in most HIVinfected patients should be peginterferon alfa plus ribavirin for 48 weeks at doses recommended for HCV mono-infected patients (see recommendation 13) (Class I, Level A). • When possible, patients receiving zidovudine (AZT) and especially didanosine (ddI) should be switched to an equivalent antiretroviral agent before beginning therapy with ribavirin (Class I, Level C). • HIV-infected patients with decompensated liver disease (CTP Class B or C) should not be treated with peginterferon alfa and ribavirin and may be candidates for liver transplantation (Class IIa, Level C).
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL
EASL Clinical Practice Guidelines 2011: Management of hepatitis C virus infection. [19]	<u>Patients with HCV infection who are co-infected with HIV:</u> • Indications for HCV treatment are identical to those in patients with HCV monoinfection (LoE: B; GoR: 2). • The same pegylated IFN-a regimen should be used in HIVco-infected patients as in patients without HIV infection, but ribavirin should always be weight-based dosed (LoE: B; GoR: 2). • Longer treatment duration (72 weeks for genotype 1) may be needed (LoE: B; GoR: 2) and 48 weeks for genotypes 2 and 3) may be needed (LoE: B; GoR: 2).
	ANMERKUNGEN FBMED
	• LL nach dem GRADE-approach [High (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2)]
NICE 2012: Boceprevir for the treatment of genotype 1 chronic hepatitis C. [36]	<u>Patients with HCV infection who are co-infected with HIV:</u> • The Committee considered the use of boceprevir plus peginterferon alfa and ribavirin in patients with HCV infection who are co-infected with HIV*. * Although these patients were not represented in the pivotal clinical trials, based on the current evidence available, the Committee concluded that there was no reason to make any different provision for these patients.
	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
NICE 2012: Telaprevir for the treatment of genotype 1 chronic hepatitis C. [38]	<u>Patients with HCV infection who are co-infected with HIV:</u> The Committee considered what impact excluding from trials patients co-infected with HIV and intravenous drug users had on the generalisability of the results to the UK population. It concluded that although these patients were not represented in the pivotal clinical trials, based on the current evidence available, there was no reason to make any different provision for these patients.

	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
NICE 2010: Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. [37]	***Peginterferon alfa-2a*** • People co-infected with HIV should also be treated for 48 weeks, regardless of genotype. ***Peginterferon alfa-2b*** • People co-infected with HIV should be treated for 48 weeks regardless of HCV genotype.
	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
New York State Department of Health (NYSDH) 2010: Hepatitis C virus.[39]	RECOMMENDATIONS: • Pegylated interferon with ribavirin for 48 weeks is the standard recommended therapy for HIV/HCV co-infected patients with chronic HCV. (LoE: A; GoR:I) • Weight-based ribavirin dosing is recommended in HIV/HCV co-infected patients with genotypes 1, 4, 5, and 6. (LoE:A; GoR:I)
	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
Yee et al. 2012: Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. The American Journal of Gastroenterology 2012; 107 (5): 669-89.[50]	*Patienten mit HIV / HCV-Ko-Infektionen:* • Patients with controlled HIV infection and evidence of liver disease on biopsy should be considered for HCV antiviral therapy (Class I, Level B). • Patients should be treated with PegIFN – RBV at doses similar to those with HCV monoinfection (Class I, Level B). • Patients should be treated with PegIFN – RBV for 48 weeks, regardless of genotype (Class I, Level A).
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL
Sarazin et al: - Leitlinie der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten: Leitlinie Prophylaxe, Diagnostik und Therapie der **Hepatitis-C-Virus (HCV)-Infektion. [42]**	*Patienten mit HIV / HCV-Ko-Infektionen:* • Bei HIV-positiven Patienten mit gleichzeitiger Hepatitis C kommt es zu einer beschleunigten Progression der Lebererkrankung. Diese Progression ist bei fortgeschrittenem Immundefekt besonders rasch. Daher sollte eine Behandlungsindikation großzügig gestellt werden. (B) • HIV-positive Patienten mit gleichzeitiger Hepatitis C tragen ein erhöhtes Risiko, unter einer antiretroviralen Therapie (HAART) Lebertoxizität zu entwickeln. Bei der Auswahl der antiretroviralen Medikamente sind daher Substanzen mit geringem lebertoxischem Potential zu bevorzugen. (B) • Eine gleichzeitige Hepatitis C ist keine Kontraindikation für eine antiretrovirale Therapie. (A) **Konsens: 100%**

	ANMERKUNGEN FBMED
	• Evidenzbasierte S3-LL • Die Leitlinien-Erstellung wurde am 12.11.2007 begonnen und am 07.09.2009 formal abgeschlossen. • **Gültigkeit abgelaufen-LL wird z.Zt. überprüft**

Leitlinien – Virusresitenz, Dosismodifikationen und Monitoring

Ghany et al. 2011: An Update on Treatment of Genotype 1 Chronic Heaptitis C Infection: 2011 Practice Guideline by the American Association for the study of Liver diseases. Hepatology **2011**; 54(4):1433-44. [23]	**Recommendations:** • Patients who develop anemia on protease inhibitor-based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose (**Class 2a, Level A**). • Patients on protease inhibitor-based therapy should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if virological breakthrough (>1 log increase in serum HCV RNA above nadir) is observed (**Class 1, Level A**). • Patients who fail to have a virological response, who experience virological breakthrough, or who relapse on one protease inhibitor should not be re-treated with the other protease inhibitor (**Class 2a, Level C**).
Yee et al. Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. The American Journal of Gastroenterology 2012; 107 (5): 669-89. [50]	**Recommendations for dose modification:** • PegIFN alfa and RBV doses should be reduced in response to decreases in white blood cells, neutrophils, hemoglobin, or platelets, as outlined in Table 5 (**Class I, Level A**). • If RBV is stopped for 7 days or more in patients who are concomitantly receiving BOC or TVR, then the PI also should be permanently discontinued (**Class I, Level A**). • HCV PIs should be either continued at full dose or discontinued (**Class I, Level A**). • Initial management of HCV treatment-related anemia should consist of RBV dose reduction in a symptomatic patient with a hemoglobin < 10g/ dl, or as clinically indicated. Erythropoietin may be administered in patients with symptomatic anemia related to PegIFN – RBV therapy with or without BOC / TVR to limit anemia-related RBV dose reductions or dose discontinuations (**Class II, Level C**). • Initial management of HCV treatment-related neutropenia should consist of PegIFN dose reduction for an ANC < 750, or as clinically indicated. Granulocyte colony-stimulating factor should not be given as primary therapy to prevent PegIFN alfa dose reductions (**Class I, Level C**). **Recommendations for treatment monitoring:** • Patients should be monitored for treatment-related adverse effects at intervals of at least 2 weeks early in the course of therapy, and at intervals of 1 – 2 months during treatment as clinically indicated (**Class I, Level C**). • Patient adherence to therapy should be assessed at every visit (**Class I, Level C**). • Patients should be evaluated for depression, suicidal ideation, alcohol, and illicit drug use at each visit (**Class I, Level C**). • Patients should be counseled about avoiding pregnancy by using two forms of contraception during treatment and for 6 months post-treatment, and pregnancy tests should be performed as indicated

	in. • If a patient is receiving a BOC- or TVR-containing regimen, two alternative effective methods of contraception, such as intrauterine devices and barrier methods, should be used in at-risk patients and partners during and for at least 6 months after treatment (**Class I, Level B**). • Serum markers of biochemical and virologic response should be measured, and treatment-related adverse eff ects monitored at intervals as outlined (**Class I, Level C**). • In patients receiving TVR – PegIFN – RBV, all treatment should be stopped if any of the following occur: (i) HCV RNA level > 1,000 IU / ml at week 4 or 12; or (ii) detectable HCV RNA levels at week 24 or at any timepoint thereaft er; or (iii) HCV RNA rebounds at any timepoint (≥ 1 log10 increase from the nadir HCV RNA) (Class I, Level C). • In patients receiving BOC– PegIFN– RBV, all treatment should be stopped if any of the following occur: (i) HCV RNA level ≥ 100 IU / ml at week 12 with a BOC-containing regimen; or (ii) detectable HCV RNA levels at week 24 or at any timepoint thereafter; or (iii) HCV RNA rebounds at any timepoint (≥ 1 log 10 increase from the nadir HCV RNA; **Class I, Level C**). • If virologic failure occurs with a BOC- or TVR-containing regimen, the other PI must not be substituted (**Class I, Level C**).

Zusätzliche Referenzen

Sarazin et al. 2012: Expertenempfehlungen zur Triple-Therapie der HCVInfektion mit Boceprevir und Telaprevir. [42]	**Genotyp 1:** *Ersttherapie:* • Unvorbehandelte Patienten mit HCV-Genotyp-1-Infektion profitieren signifikant von der Triple-Therapie und sollten primär mit einer proteaseinhibitorbasierten Therapie behandelt werden. • Bei unvorbehandelten Patienten mit günstigen Voraussetzungen für ein rasches virologisches Ansprechen (RVR) auf eine PEG-Interferon/Ribavirin Therapie (d. h. keine fortgeschrittene Fibrose, HCVRNA < 600 000 – 800 000 IU/ml, günstiger IL28B-Genotyp) kann auch primär eine alleinige Therapie mit PEG-Interferon plus Ribavirin erwogen werden. • Dies sollte individuell mit dem Patienten besprochen werden. *Re-Therapie:* • Bei Patienten mit fehlendem dauerhaften Ansprechen auf eine antivirale Vortherapie leitet sich die prinzipielle Indikation zur Re-Therapie aus der bereits erfolgten Vorbehandlung ab. • Therapieerfahrene Patienten mit HCV-Genotyp-1-Infektion ohne dauerhaftes virologisches Ansprechen (SVR) sollten eine Re-Therapie mit einem Proteaseinhibitor basierten Regime erhalten. • Das individuelle Ausmaß des Ansprechens (virale Suppression) auf die Vorbehandlung mit PEG-Interferon alpha und Ribavirin stellt den entscheidenden Faktor für die Effektivität und den Erfolg der Triple-Re-Therapie dar **Genotyp 4:** • Die antivirale Wirkung von Telaprevir in der Monotherapie beim HCV-Genotyp 4 ist gering.

	• In Kombination mit PEG-Interferon alpha und Ribavirin konnte jedoch eine erhebliche Reduktion der Viruslast um mehr als 4 log10 Stufen innerhalb von 15 Tagen induziert Werden **Koinfektionen HIV/HCV-Koinfektion:** • Für Patienten mit einer HCV-Genotyp 1 Infektion bestand die Standardtherapie bisher aus einer Behandlung mit PEG-Interferon alpha und Ribavirin (1000 – 1200 mg/d) über 48 Wochen bei RVR und Fibrosegrad < F2 und ansonsten über 72 Wochen. • Mit der Zulassung der beiden HCV-Proteaseinhibitoren Boceprevir und Telaprevir haben sich nun die therapeutischen Optionen für Patienten mit einer HCV-Genotyp 1 Infektion erweitert.
Vogel et al. 2010: HIV- und Hepatitis-C-Koinfektion. [48]	**Therapie der akuten Hepatitis-C-Infektion** • Therapie der Wahl ist eine Kombinationstherapie mit pegyliertem Interferon und Ribavirin. • HIV-positive Patienten sollten unabhängig vom HCV-Genotyp eine gewichtsadaptierte Dosierung des Ribavirins erhalten. • Bisherige Studien zeigen, dass eine frühe Behandlung der akuten HCV-Infektion hohe Ausheilungsraten erreicht. **Non-Responder** • Bei Nicht-Ansprechen auf eine Therapie ist das weitere Vorgehen abhängig von der Ursache. • War das verwendete Interferon nicht pegyliert oder aber das Ribavirin niedrig dosiert kann eine „Re-Therapie“ sinnvoll sein. • Wurde hingegen aktuelle Empfehlungen für eine moderne Therapie berücksichtigt, sind eine erneute Therapie oder Interferon-Erhaltungstherapie nicht sinnvoll. • Neue Substanzen zur Behandlung der Hepatitis C stellen hier auch für HIV-positive Patienten eine Hoffnung auf bessere Behandlungsmöglichkeiten dar.

Hinweise zu den Leitlinien

Evidenzgraduierung bei Ghany 2011 und Yee 2012:

Class 1 Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective

Class 2 Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure, or treatment

Class 2a Weight of evidence/opinion is in favor of usefulness/efficacy

Class 2b Usefulness/efficacy is less well established by evidence/opinion

Class 3 Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure/treatment is not useful/effective and in some cases may be harmful

Level of Evidence Description

Level A Data derived from multiple randomized clinical trials or meta-analyses

Level B Data derived from a single randomized trial, or nonrandomized studies

Level C Only consensus opinion of experts, case studies, or standard-of-care

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library am 04.06.2013

Suchschritt	Suchfrage	Treffer
#1	MeSH descriptor Hepatitis C, Chronic explode all trees	1163
#2	MeSH descriptor: [Hepatitis C, Chronic] explode all trees and with qualifiers: [Drug therapy - DT]	913
#3	MeSH descriptor Drug Therapy explode all trees	108957
#4	#1 and #3	644
#5	#2 or #4	968
#6	(HCV):ti,ab,kw	2251
#7	(chronic):ti,ab,kw and (hepatitis):ti,ab,kw and (c):ti,ab,kw	2966
#8	#1 or #6 or #7	3882
#9	#8 and #3	877
#10	#9 or #2	1211
#11	#10 from 2008 to 2013	367

Cochrane Reviews [11] | Other Reviews [44] | Clinical Trials [293] | Methods Studies [0] | Technology Assessments [3] | Economic Evaluations [16] | Cochrane Groups [xx]
→ importiert: 3 Cochrane Reviews, 32 Other Reviews, 2 Technology Assessments

SR, HTAs Pubmed am 04.06.2013

#	Suchfrage	Treffer
1	("Hepatitis C, Chronic/drug therapy"[Mesh])	7089
2	((chronic[Title/Abstract]) AND hepatitis[Title/Abstract]) AND c[Title/Abstract]	24350
3	HCV[Title/Abstract]	36292
4	(#2) OR #3	47107
5	(drug[Title/Abstract]) AND therap*[Title/Abstract]	195162
6	(#4) AND #5	1992
7	(#1) OR #6	8564
8	"Hepatitis C, Chronic"[Mesh]	14787
9	"drug therapy"[MeSH Terms]	991227
10	(#8) AND #9	3564
11	(#7) OR #10	8933
12	(#11) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])	407
13	((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract])))	148897
14	(#13) AND #11	198
15	(#12) OR #14	438
16	(#15) AND ("2008/06/01"[PDAT] : "2013/06/04"[PDAT])	244

→ nach Dublettenkontrolle importiert: 112 von 244 Treffer

Leitlinien in Pubmed am 04.06.2013

#	Suchfrage	Treffer
#1	("Hepatitis C, Chronic/drug therapy"[Mesh])	7089
#2	((chronic[Title/Abstract]) AND hepatitis[Title/Abstract]) AND c[Title/Abstract]	24350
#3	HCV[Title/Abstract]	36292
#4	(#2) OR #3	47107
#5	(drug[Title/Abstract]) AND therap*[Title/Abstract]	195162
#6	(#4) AND #5	1992
#7	(#1) OR #6	8564
#8	"Hepatitis C, Chronic"[Mesh]	14787
#9	"drug therapy"[MeSH Terms]	991227
#10	(#8) AND #9	3564
#11	(#7) OR #10	8933
#12	(#11) AND (Guideline[ptyp] OR Practice Guideline[ptyp])	43
#13	(#11) AND guideline*[Title]	33
#14	(#12) OR #13	59
#15	(#14) AND ("2008/06/01"[PDAT] : "2013/06/04"[PDAT])	39

→ nach Dublettenkontrolle importiert: 26 von 39 Treffer

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