Educazione & Prevenzione sull'Epatite

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Alla C.A. del Direttore Generale AIFA Prof. **Luca Pani**

Alla C.A. del Presidente dell'AIFA Prof. **Sergio Pecorelli**

e p.c.

Al Direttore Area Strategia e Politiche del Farmaco dott. **Paolo Siviero**

Al direttore Ufficio Ricerca e Sperimentazione Clinica Dott. **Carlo Tomino**

Al Ministro della Salute Prof. **Renato Balduzzi**

Al Segretario Associazione Italiana Studio Fegato Prof. **Paolo Caraceni**

Oggetto: **Proposta di inserimento degli inibitori della proteasi Telaprevir (INCIVO®)e Boceprevir (VICTRELIS®) nell'elenco delle specialità medicinali ai sensi della legge 648/96, per le seguenti indicazioni:**

- **Terapia antivirale di associazione con PEG-Interferone/ribavirina nei pazienti adulti affetti da Epatite C genotipo 1, con recidiva dell'infezione dopo il trapianto di fegato**

Gent.mo

La sottoscritta Associazione EpaC onlus (Educazione, Prevenzione e Ricerca sull'Epatite C), con sede Legale ed Amministrativa in Via Luigi Cadorna 17/A, 20871 Vimercate (MB), Italia si premura da molti anni di tutelare i malati di epatite virale.

Uno degli obiettivi statutari è quello di agevolare le sperimentazioni di nuovi farmaci per pazienti con HCV, con particolare riguardo ai *"difficult to treat".*

In questa ottica, l'associazione opera a livello europeo ed internazionale, facendo parte di Community Board creati ad hoc per interagire con gli enti regolatori (EMA ed FDA), con le aziende farmaceutiche, con le associazioni Scientifiche e tutti gli stakeholders interessati.

La stessa EMA, nel *draft Guideline on clinical evaluation of medicinal products for the treatment of chronic hepatitis C* (EMEA/CHMP/51240/2011) sottolinea l'importanza di sperimentare le nuove molecole in sottogruppi di pazienti ad alto rischio appena gli studi di sicurezza e tollerabilità lo consentono[1].

Il riferimento al gruppo dei pazienti sottoposti a trapianto epatico con recidiva da HCV non è casuale ed è l'oggetto della presente richiesta. Questo sottogruppo di pazienti particolarmente vulnerabile è quantificabile in circa 500 ogni anno (circa il 50% di tutti i trapiantati di fegato ogni anno in Italia) i quali, nella maggior parte dei casi (70%), non risponde al trattamento antivirale con pegIFN e ribavirina.

La progressione della fibrosi spesso induce alla necessità di un secondo trapianto nell'arco di 5-10 anni, talvolta anche prima. Diversamente, il paziente muore.

Considerata la scarsità di organi, gli aspetti etici legati al re-trapianto, i costi sociali ed economici derivanti da questa situazione oggettivamente drammatica, è necessario a tale fine **promuovere interventi urgenti per diminuire la percentuale di mortalità dei paziente trapiantato con recidiva da HCV.**

La nostra Associazione – a fronte delle **numerose richieste già pervenute da pazienti e familiari** (allegato A) e colpita favorevolmente dai risultati incoraggianti (e per certi versi sorprendenti) ottenuti dall'uso dei nuovi inibitori della proteasi boceprevir e telaprevir anche nei pazienti trapiantati di fegato con recidiva da HCV recentemente presentati ai congressi EASL e AASLD 2012 - chiede all'Agenzia Italiana del Farmaco una particolare attenzione nel valutare gli studi clinici sin qui prodotti e dei quali alleghiamo bibliografia e abstracts (Allegato B).

Efficacia – Eventi avversi

Una prima, nostra, e informale disamina degli studi proposti, fa emergere quanto segue:

- La maggior parte degli studi sono ancora in corso.
- Sono stati reclutati 167 pazienti trapiantati di fegato ai quali è stato somministrato Telaprevir (n. 133) o Boceprevir (n.34).
- I tassi di SVR, misurati alla settimana 12 o 24, vanno dal 55 al 100%.
- I decessi sono stati 4, in due studi su 8, facendo registrare un tasso di mortalità leggermente superiore a quella riscontrata nello studio Francese di early access *"ANRS CO20-CUPIC".*
- Gli effetti collaterali segnalati sono quelli già noti e riportati in letteratura sui pazienti non trapiantati con una frequenza maggiore di anemia ed eventi avversi (principalmente infezioni).

Benchè la maggior parte degli studi clinici non siano ancora stati completati tutti gli autori concludono affermando che:

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(1) LINE 70: …"The guidelines emphasize the importance of new DAA/HTA for usage in special populations including patients with decompensated liver disease, patients pre/post transplantation, HCV/HIV co-infected patients, patients intolerant to pegIFN and/or ribavirin and patients with prior DAA experience."…

LINE 83: …."Regarding special populations, the need to start trials as early as can safely be done for groups with an important unmet medical need.."

post transplant treatment

Line 724 – 729: As stated above, reinfection of the liver graft is almost inevitable in patients with detectable HCV-RNA prior to transplantation. Progress to cirrhosis is rapid, and the prognosis of patients transplanted due to HCV is worse than for many other indications. The tolerability of pegIFN and ribavirin is compromised in this group, and the overall efficacy of pegIFN and ribavirin is low, particularly in patients with GT1 infection. ***Thus there is an urgent need for new therapies, both as add-on to pegIFN + ribavirin, as well as regimens without these components****.*

- ***Il trattamento in triplice terapia può essere somministrato nei trapiantati di fegato;***

- ***I tassi di SVR sono molto robusti e più che raddoppiati rispetto al solo PEG INF/RIBA;***

- ***E' necessario eseguire il trattamento sotto stretta sorveglianza e da personale altamente specializzato****.*

Costo efficacia
Un trapianto di fegato costa mediamente tra i 120 e 180.000 Euro e un paziente trapiantato ha un costo medio annuo di 26.809 Euro[2], (Allegato B). In questo gruppo di pazienti il rapporto Costo-efficacia è dunque indiscutibile (Allegato C).

Guadagno in qualità e quantità di vita
Numerosi studi evidenziano un netto miglioramento delle funzionalità epatiche dopo l'eradicazione virale nel trapiantato di fegato con HCV, una migliora qualità di vita e diversi anni di vita guadagnati stimati in almeno 3-5 anni[3] (Allegato D).

Costi farmaceutici
Gli esperti da noi consultati, ritengono inopportuno intervenire su tutti i pazienti trapiantati.
In particolare appare proficuo intervenire nei pazienti con evidenza di patologia evolutiva in OLT e con le seguenti caratteristiche: **HAI > 9 a 6 mesi | Fibrosi > F1 a 6 mesi.**
Per questo motivo, riteniamo che il pool di pazienti candidabili al trattamento siano meno di 300/anno e quindi un costo farmaceutico del tutto sostenibile.

Considerata la particolare tipologia dei pazienti che rientra nella categoria dei *"difficult to treat",* che la gestione clinica migliora notevolmente con l'esperienza acquisita, e che i pazienti trapiantati con recidiva da HCV non hanno alternative terapeutiche valide ma un bisogno urgente di eradicare l'infezione, riteniamo esistano tutti i presupposti per prendere in seria considerazione l'utilizzo dei nuovi inibitori telaprevir e boceprevir con la legge 648/96.

D'altra parte, la stessa agenzia intende promuovere studi su popolazioni speciali non incluse o insufficientemente incluse negli studi registrativi come descritto nella tematica A.9 del Bando AIFA 2012 per la ricerca indipendente sui farmaci.

Infine, ci pare doveroso sottolineare che l'utilizzo di tali farmaci deve essere affidato a personale altamente specializzato all'interno di strutture idonee alla gestione del paziente trapiantato di fegato. Fortunatamente, in Italia queste strutture esistono.

Alla luce di quanto sopra esposto, e in virtù del fatto che **possiamo salvare vite umane con farmaci già disponibili,**

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(2) *(The COME Study, Fagiuoli et al, 2012)*
(3) *Clinical Benefits of Antiviral Therapy in Patients with Recurrent Hepatitis C Following Liver Transplantation" Berenguer et al. AJT 2008.*

LA NOSTRA ASSOCIAZIONE PROPONE

l'inserimento nell'Elenco Specialità Medicinali, ai sensi della Legge 648/96, dei medicinali Telaprevir (INCIVO®) e Boceprevir (VICTRELIS®) per le indicazioni riportate in oggetto.

Confidando nel favorevole accoglimento della presente richiesta la Scrivente porge distinti saluti.

Presidente Associazione EpaC onlus

Vimercate, 03 Gennaio 2013

Allegati alla presente:

ALLEGATO A – Alcune comunicazioni di trapiantati giunte ad EpaC negli ultimi 2 mesi

ALLEGATO B - Lista abstracts trials su pazienti trapiantati con recidiva HCV

ALLEGATO C - The COME study

ALLEGATO D - Benefici clinici della guarigione post trapianto

Richieste di aiuto giunte recentemente all'associazione EpaC onlus per terapia con inibitori della proteasi su pazienti trapiantati con recidiva da HCV

[OMISSIS Dati personali]

Oggetto: Recidiva HCV trapiantato fegato - URGENTE

Testo: Buongiorno Sig. Ivan Gardini, sono Simila Laiatici, moglie di un trapiantato di fegato, brevemente segue una mia "relazione".
Mio marito M. Rolando, è stato trapiantato 27/12/2010. Come sapevamo (perchè succede nella totalità dei casi) il virus dell' HCV ha ripreso ad attaccare, aiutato dall'uso degli immunosoppressori (e di alcuni interventi sulle via biliari che si sono intasate 2 volte e per le quali è stato necessario ERCP) e nonostante sia stato sottoposto a cura con Interferone e ribavirina, la recidiva si è stata precoce.
Per quanto riguarda il centro trapianti di Pisa non sono previsti retrapianti in caso di recidiva HCV. Per questo mi sono rivolta altrove. Ho contattato Padova Prof. Cillo che dovrò incontrare a breve, Policlinico di Milano Prof. Rossi che mi ha chiamato 3 volte di persona e che attende un pò di documentazione per valutare e Niguarda di Milano Prof. De Carlis con il quale non sono ancora riuscita a mettermi in contatto.
Poi ho un contatto a Nizza con il Prof.Gugenain che valuta retrapianti per recidive……
Insomma, andremmo anche in USA, basterebbe trovare un posto serio e d'eccellenza che fosse disposto a darci la possibilità.
La situazione è veramente peggiorata…..Un sincero ringraziamento anche solo per l'interesse e per il tempo che ci dedicate.

Simila L.

[OMISSIS Dati personali]

ho 66 anni recidiva di epatite c 1b con sviluppo di fibrosi del fegato trapiantato(ott. 2012 kpa_9.5 al fibroscan) negli anni scorsi relapse dopo 2cicli di terapia. ipertensione arteriosa in terapia, da tempo creatinina 1.6. diabete mellitopost trapianto da 22 anni. ecografia addome nella norma e cosi anche gli altri esami. Chiedo: è urgente la triterapia con telaprevir(visto gli effetti collaterali) o posso aspettare altri farmaci grazie mille?

Salvatore G.

[OMISSIS Dati personali]

Oggetto: epatite C al figlio Giacomo - già fatto trapianto

Testo: mio figlio a 21anni ha già subito un trapianto di fegato preso 8mesi presa da una trasfusione. dato ke un immunodeficenza comune variabile sta aspettando con grande ansia i nuovi farmaci. è una vergogna bloccare la sanità e illudere e giocare con vite umane e giovani come mio figlio!sono già una vostra socia. Cosa dobbiamo fare affinkè il ministro metta in circolo le nuove cure?

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buonasera ,penso che la mia voce di disperazione, l'abbiano sentita in molti…..
tra cui una lettera personale al Presidente della repubblica Giorgio Napolitano e al Ministro della Sanità. Ora aspetto risposte chiare se il nuovo farmaco verrà distribuito a tutti gli ospedali o si ferma ani a Bergamo e Napoli se lo potranno usare i trapiantati e i trapiantati affetti come mio figlio di 23 anni affetto da un immunodeficienza comune o variabile!Premetto che mio figlio trapiantato a dicembre da due anni se ha speranze di farcela con l'introduzione del nuovo farmaco INCIVO bene altrimenti starà alla sorte perchè mai riaffronterebbe un altro trapianto a 21 anni ha sofferto troppo e preferirebbe morire a casa. Se sapete qualcosa di ciò che ho detto VI PREGO informatemi ditemi la verità devo sapere anche per il bene della mia salute!Grazie e buon lavoro!Paola mamma di Giacomo.

Paola

[OMISSIS Dati personali]

Oggetto: trapianto HCV

Testo: Salve sono stato trapiantato di fegato il 23 /1/2010 dopo tre mesi è tornato l' HCV vorrei sapere se e quando i nuovi farmaci per trattare HCV saranno utilizzabili per persone Come me o se ci sono centri in Italia o europa dove stanno facendo studi con i nuovi farmaci . Sono stato trattato con interferone e ribovarina per 8 volte senza risultato , l'ultimo trattamento e' stato terminato questo maggio. Grazie e buona giornata

Pio C.

[OMISSIS Dati personali]

Oggetto: Quando la possibilità di ripetere la terapia antivirale con gli inibitori della proteasi?

Testo: Ho 28 anni, trapiantato di fegato e affetto da epatice C cronica contratta con trasfusioni. Ho già fatto un tentativo con Interferone e Ribavirina senza successo. Quando potrò ripetere la terapia con i 3 farmaci? E' questione di qualche mese o di tempi più lunghi? Grazie e saluti.

Daniele C.

[OMISSIS Dati personali]

Sono Paziente affetto da epatite c non rispondente a vari cicli di interferone, trapiantato di fegato con successo in ottobre 2009 e senza nessuna complicazione post operatoria, presenta nell'ultimo mese già una carica virologica alta e vari malesseri generali oltre che valori altalenanti (kf intorno a 15) che non consentono un facile dosaggio del farmaco antirigetto (prograf). quale terapia è possibile somministrare per cercare di rallentare il virus ? ho letto sulle news, di nuovi farmaci sperimentali non legati all'interferone è già possibile il loro utilizzo?
Grazie cordiali saluti

Salvatore U.

[OMISSIS Dati personali]

Buongiorno mio padre ha subito un trapianto di fegato 3 anni fa in seguito ad una epatite C genotipo 1. come previsto il fegato si è reinfettato e da due anni sta seguendo la terapia con interferone e ribavirina col risultato di abbassare leggermente transaminasi e carica virale, ma ad ogni biopsia si osserva comunque un lieve peggioramento. quando chiediamo di nuovi farmaci ci rispondono che sicuramente non verranno sperimentati su un trapiantato. Cosi, nonostante la meravigliosa possibilità che ci è stata concessa viviamo nella preoccupazione di quanto tempo rimarrà "funzionale" il nuovo fegato.. grazie

Barbara F.

[OMISSIS Dati personali]

Sono trapiantato di fegato da 2 anni , è tornata HCV molto aggressiva, assumo interferone e ribavirina ma senza risultato. A quado un nuovo farmaco per curare hep C per pazienti come me? grazie

Nicola C.

CONTROL ID: 1425983

PRESENTATION TYPE: Oral or Poster

CURRENT CATEGORY: Clinical Liver Transplantation and Liver Surgery

CURRENT DESCRIPTORS: E01. Viral Hepatitis

TITLE: Multicenter Preliminary Experience Utilizing Boceprevir with Pegylated Interferon and Ribavirin for Treatment of Recurrent Hepatitis C Genotype 1 after Liver Transplantation

AUTHORS (FIRST NAME, LAST NAME): Bashar Aqel[1], Ludi Koning[2], Michael Charlton[2], Elizabeth J. Carey[1], Thomas J. Byrne[1], Jorge Rakela[1], Hugo E. Vargas[1]

Institutional Author(s):

INSTITUTIONS (ALL): 1. Divisions of Gastroenterology & Hepatology, Mayo Clinic, Phoenix, AZ, United States.
2. Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, United States.

ABSTRACT BODY: Background: Hepatitis C virus (HCV) recurrence after liver transplant is universal and causes significant reduction in both graft and patient(pt) survival. The use of protease inhibitors combined with pegylated interferon (PEG) and RBV significantly improve sustained virological response in non-LT patients. There is limited experience regarding their use post LT
Aim: To describe our experience with boceprevir-based triple therapy for recurrent HCV post LT
Methods: Multicenter study describing the outcome of HCV treatment post LT, utilizing a strict and standardized clinical protocol. All pts were converted to cyclosporine based immunosuppression (IS) regimen prior to treatment. cyclosporine dose was halved and levels were closely monitored once boceprevir was initiated. All pts had a lead-in phase with PEG and RBV for 4 weeks followed by addition of boceprevir. Demographic, clinical, biochemical and virological data was collected at baseline and during therapy. Ribavirin levels were monitored every 4 weeks

Results: Total of 23 patients with genotype 1 recurrent HCV were treated with boceprevir bases regimen between 06/11-04/12. Treatment characteristics are shown in table-1. Ten patients (43%) achieved complete early virological response; four of them continue to be negative at week 24. Six (26%) met the futility rules with inadequate virological response. Treatment was stopped in four patients (17%)due to adverse events. All patients required growth factors support on treatment

Conclusions: Boceprevir based triple therapy can be used post LT but requires close clinical monitoring. Antiviral efficacy of this regimen is better than standard therapy in difficult to treat population. Patients should be closely monitored for adverse events. Ongoing follow up will provide additional data regarding safety and efficacy of this regimen.

Patients' Characteristics

	Boceprevir based treatment (n=23)
Mean Age (years)	59
Gender: Male	17(74%)
HCV genotype	
-1a	12 (52%)
-1b	11 (48%)
IL-28 B polymorphism	
-CC	1 (4%)
-CT	12 (52%)
-TT	5 (21%)
Unknown	5
Mean Duration of treatment (weeksZ)	16 (4-34)
-Completed 4 weeks	22 (95%)
-Completed 12 weeks	20 (87%)
-Completed 24 weeks	4(17%)

CONTROL ID: 1405420

PRESENTATION TYPE: Oral or Poster

CURRENT CATEGORY: Clinical Liver Transplantation and Liver Surgery

CURRENT DESCRIPTORS: E01. Viral Hepatitis

TITLE: 100% cEVR Post-Liver Transplant with Telaprevir Triple Drug Therapy

AUTHORS (FIRST NAME, LAST NAME): Jacqueline G. O'Leary[1], Greg J. McKenna[2], Goran Klintmalm[2], Gary L. Davis[1]

Institutional Author(s):

INSTITUTIONS (ALL): 1. Hepatology, Baylor University Medical Center, Dallas, TX, United States. 2. Transplant SUrgery, Baylor University Medical Center, Dallas, TX, United States.

ABSTRACT BODY: Graft loss from hepatitis C remains a major problem after liver transplantation (LT), and the response to pegylated interferon (PEG) and ribavirin (RBV) is poor. Aim: Examine the safety and tolerability of telaprevir (TVR) in combination with PEG & RBV after LT.

Methods: We treated 12 post-LT patients with telaprevir triple therapy. 83% of patients were male, median age of 59, and MDRD>55 mL/min (mean, 75.6). 8 patients had genotype 1a, 2 genotype 1b, and 2 genotype 1. 4 patients had stage 2 fibrosis and 8 patients had advanced fibrosis or fibrosing cholestatic hepatitis. 5 patients were naïve to treatment post-LT, and 7 experienced prior treatment failure. 10/12 patients were treated with lead-in to determine the maximum tolerated doses of PEG & RBV. Lead-in was not needed in 2 recent treatment failure patients. Immunosupression on therapy was rapamune in 4 patients, tacrolimus in 5 patients, and cyclosporine in 3 patients. 7 patients were on dual therapy with mycophenolate mofitil.

Results: After lead-in established doses of PEG (Pegasys 180 mcg weekly, except one - 135 mcg) and RBV (mean 600mg/day), TVR was initiated at 1125 mg orally q12 hours. 7/12 (58%) patients had undetectable viral loads at wk 4 of triple therapy, 5/12 patients had +<43 IU/mL. All 9/9 patients treated for 12 weeks had no detectable virus (cEVR). 5/5 patients treated for 24 weeks are virus negative, and 2/3 patients who completed therapy had an end of treatment response. Immunosuppression was dramatically reduced during TVR (Table 1). All patients tolerated the medications, no one stopped early, and drug-drug interactions were manageable.

Conclusion: Triple therapy with TVR after a Peg-RBV lead-in was safe and achieved 100% cEVR in LT recipients on rapamune, tacrolimus, or cyclosporine. However, drug interactions necessitate close monitoring and use only in highly compliant patients with good renal function.

CONTROL ID: 1424291

PRESENTATION TYPE: Oral or Poster

CURRENT CATEGORY: Clinical Liver Transplantation and Liver Surgery

CURRENT DESCRIPTORS: E01. Viral Hepatitis

TITLE: Early and End of Treatment Virologic Responses in Patients with Hepatitis C (HCV)genotype I Recurrence After Liver Transplant Treated with Triple Therapy using Telaprevir: A Single Center Experience.

AUTHORS (FIRST NAME, LAST NAME): Parvez S. Mantry[1], Chunxia Wu[1], Jeffrey S. Weinstein[1], Abdullah Mubarak[1], Hector E. Nazario[1], Bahar Madani[1], Alejandro Mejia[1], Tiffany Anthony[1], Stephen Cheng[1]

Institutional Author(s):

INSTITUTIONS (ALL): 1. The Liver Institute at Methodist Dallas Medical Center, Dallas, TX, United States.

ABSTRACT BODY: Background: We report the first experience of treating a cohort of patients with HCV genotype I recurrence after liver transplant using off label telaprevir(TVR) based triple therapy in patients on Tacrolimus (TAC) based immunosuppression.

Methods: Since June 2011, we have treated 17 patients with genotype 1 HCV infection recurrence post liver transplant using combination therapy with pegylated interferon alpha 2a or 2b, Ribavirin (RBV), and TVR folowed by PEG/RBV combination therapy for additional 12 or 36 weeks. All patients were on TAC at a stable dose prior to start of the antiviral regimen. At the start of therapy, the TAC dose was reduced to approximately half the pre-treatment dose and the frequency was reduced to once a week with frequent level checks . After completing TVR, TAC was re-introduced slowly to pre-TVR dosing. CBC, Chemistry, HCV RNA, TAC levels and clinic evaluation of patients was performed once a week during the first 4 weeks of Rx and every 2 weeks there after.

Results: There were 9 male and 8 female patients in the cohort who were from 6 months to 8 years out post transplant. 11/17 patients were genotype 1a. Of the 17 patients, 6 had rapid virologic response and extended (e)RVR; additionally 6 patients became aviremic at 32,33,40,55,62 84 and 90 days and had complete early virologic response. 4 patients were non responders and 1 patient had a breakthrough during treatment. 4 patients received response guided therapy and stopped at 24 weeks; the other 6 patients are still on therapy. Anemia was the most prominent side effect of treatment with all patients requiring growth factor support and 8 of them needing blood transfusions despite lower doses of RBV.

Conclusions : We report the first experience of treating HCV recurrence in post liver transplant recipients with TVR based triple therapy in setting of TAC based immunosuppression. We observed robust virologic responses in a majority of patients and TAC/TVR interactions and side effects were manageable. Our preliminary data show that this treatment shows promising

virologic responses in patients and merits prospective evaluation.

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Sex	M	M	F	F	M	F	F	M	M	M	M	F	F	M	F	M	F
Race	W	W	W	W	H	W	W	H	W	W	W	B	B	W	W	W	W
Age	62	57	60	57	56	57	73	53	59	60	50	63	62	57	62	61	61
Biopsy Grade, Stage	2,2	2,0	2,1	2,1	2,4	1,2	3,0	2,2	3,0	3,0	3,1	2,1	2,3	2,1	1,2	2,2	2,2
Prior Treatment status, NR=Non responder	NR	NR	NR	Naive	NR	NR	NR	NR	Intolerant	Naive	Intolerant	NR	Intolerant	Naive	NR	NR	Naive
Baseline HCV RNA	6,110,000	2,070,000	33,800,000	941,230	2,260,000	1,160,670	371,000	12,771,000	2,725,500	576,000	16,992,000	27,536,000	5,570,000	8,510,000	9,920,000	2,880,000	4,500,000
Mean RBV dose in mg/day	800	738	473	725	600	600	500	1111	666	800	800	600	666	1200	650	422	800
Days to aviremia/RVR/eRVR	4 RVR, eRVR	28 RVR eRVR	33	19 RVR eRVR	40	NR	12 RVR eRVR	90	27 RVR eRVR	NR	32	NR	55	NR	84	62	27 RVR eRVR
Genotype	1a	1a	1a	1a	1	1a	1a	1b	1a	1a	1a	1a	1	1	1	1a	1
IL28B	Unknown	CT	CT	TT	CC	CT	CT	TT	CT	CT	TT	Unknown	Unknown	CC	Unknown	Unknown	TT

CONTROL ID: 1423196

PRESENTATION TYPE: Oral or Poster

CURRENT CATEGORY: Clinical Liver Transplantation and Liver Surgery

CURRENT DESCRIPTORS: E01. Viral Hepatitis

TITLE: Telaprevir can be used Effectively and Safely to treat recurrent HCV in Liver Transplant Recipients Receiving Tacrolimus based Immunosuppression.

AUTHORS (FIRST NAME, LAST NAME): Satheesh Nair[1], Bradford Waters[2]

Institutional Author(s):

INSTITUTIONS (ALL): 1. Univeristy Of Tennessee Health Science Center, Memphis, TN, United States.
2. Veteran Administration Hospital , Memphis, TN, United States.

ABSTRACT BODY: Telaprevir can be used effectively and safely in Liver Transplant Recipients with Recurrent Hepatitis C while receiving tacrolimus based immunosuppression. Background: Recurrent hepatitis C infection is a is a major cause of graft loss in liver transplant recipients. Pegylated interferon based treatment is not very effective in many patients. Background: Recurrent hepatitis C infection is a is a major cause of graft loss in liver transplantation recipients.

Aim: to study the safety and efficacy of Telaprevir based therapy in post-transplantation Hepatitis C patients.

Patients:. 12 patients (9 Caucasians and 3 African-Americans; Age range 51-61 years) with prior null response to interferon treatment and stage 2 or more fibrosis on liver biopsy were given treatment. 7 patents had biopsy confirmed cirrhosis . Post-transplantation duration was 2-5years;

Methods: All patients received of PEG interferon alpha 2a 180 µg q week, Ribavirin 400mg BID, Telaprevir 750 mg q 8 hours for 12 weeks followed by PEG interferon and ribavirin for an additional 36 weeks. Tacrolimus doses were reduced to one dose of 0.5 mg /week at the start of treatment and the levels were monitored on day 3 and day 7 and then weekly . One patient was on sirolimus and another patient was on cyclosporine

2 patients (16%) was HCV RNA undetectable at week 4, All patients who received 12 weeks of therapy with Telaprevir were RNA undetectable at week 12. Three patients had to discontinue therapy due to severe pancytopenia. Two of these patients (both non cirrhotics) had severe thrombocytopenia (platelet count < 10000/mm3) 6 patients required dose adjustments of ribavirin. 6 patients required Filgrastim or Erythropoietin. Three patients required red blood cell transfusions.
No episodes of rejection was observed. The lowest tacrolimus level was 1.8 ng/l and the highest level was 12 ng/l . No adverse event related to tacrolimus was noted

Conclusion: Telaprevir based regimens can be used in post-transplantation patients with reduced dosing of tacrolimus. Once a week dosing of tacrolimus is sufficient to keep the level in therapeutic range and avoid toxicity. Early virological response indicates effectiveness in these difficult to treat patients. As anticipated, pancytopenia is a major concern in these patients and requires intense monitoring.

CONTROL ID: 1415901

PRESENTATION TYPE: Oral or Poster

CURRENT CATEGORY: Clinical Liver Transplantation and Liver Surgery

CURRENT DESCRIPTORS: E01. Viral Hepatitis

TITLE: Preliminary Experience using Telaprevir with Peginterferon and Ribavirin for Treatment of HCV Genotype 1 after Liver Transplantation

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Institutional Author(s):

INSTITUTIONS (ALL): 1. Transplantation, Mayo Clinic, Jacksonville, FL, United States.

ABSTRACT BODY: Background: Successful antiviral therapy of recurrent HCV after liver transplantation (LT) can improve graft and patient outcomes. To date, experience using a regimen consisting of telaprevir (TVR) with peginterferon and ribavirin (PR) in LT recipients with HCV genotype (GT) 1 has been limited. We report a large single-center experience using TVR+PR in this population.

Methods: LT recipients with significant HCV recurrence on liver biopsy (METAVIR grade≥3 and/or stage≥2) participated in a clinical protocol using TVR+PR 12 weeks, followed by PR 36 weeks. Maintenance immunosuppression (IS) was changed to cyclosporine (CyA), where possible. Close monitoring of trough IS levels was performed. PR dose adjustments were based on patient tolerability.

Results: To date 28 patients (18 GT1a; 8 TT, 17 CT IL-28B rs12979860; 21 prior PR failure) have started therapy and been followed for up to 42 weeks (mean 20 weeks); 26, 19 and 11 patients have completed 4, 12 and 24 weeks of therapy. CyA was used in 26 patients. At the steady state of TVR+PR administration, CyA dose was 50-100% of the original q12hr dose given once daily. The median rise in serum creatinine from baseline was 0.4 mg/dL. **Table** shows on-treatment virological response rates. Overall, 21 patients (75%) achieved undetected HCV RNA by week 1-16 of thepary (mean week 6); however 3 patients relapsed after stopping TVR. Adverse events included biopsy-proven moderate acute rejection in 2 patients and 1 death due to sepsis after rejection treatment. Unstable angina requiring coronary angioplasty, sinusitis, cellulitis, pneumonia, rash, ascites and trigeminal zoster occurred in individual patients. Cytopenias were common requiring EPO and G-CSF in 19 and 4 patients, 11 patients received red cell transfusions, and eltrombopag was used in 1 patient. Dose reductions in peginterferon and ribavirin were required in 18 and 23 patients. Overall, 4 patients discontinued therapy prematurely (3 PR intolerance, 1 financial issue).

Conclusions: We report our experience treating 28 LT recipients with recurrent HCV GT1 using TVR+PR. Viral suppression was robust with 68% (13/19) and 55% (6/11) of patients who completed 12 and 24 weeks of therapy achieved undetected HCV RNA. Three patients relapsed after stopping TVR. Drug-drug interactions were managed by close monitoring. Adverse events, particularly cytopenias, were common. Additional follow-up is required to determine the safety and efficacy of TVR+PR therapy after LT.

Based on ITT Analysis	HCV RNA <1,000 IU/mL	Undetected HCV RNA
Patients Completed Week 4 of Therapy	20/26 (77%)	4/26 (15%)
Patients Completed Week 12 of Therapy	16/19 (84%)	13/19 (68%)
Patients Completed Week 24 of Therapy	6/11 (55%)	6/11 (55%)

CONTROL ID: 1423883

PRESENTATION TYPE: Oral or Poster

CURRENT CATEGORY: Viral Hepatitis C

CURRENT DESCRIPTORS: S07. HCV: Treatment

TITLE: A Multicenter Study of Protease Inhibitor-Triple Therapy in HCV-Infected Liver Transplant Recipients: Report From The CRUSH-C Group

AUTHORS (FIRST NAME, LAST NAME): James R. Burton[1], Jacqueline G. O'Leary[2], Elizabeth C. Verna[3], Jennifer C. Lai[4], Gregory T. Everson[1], James F. Trotter[2], Robert S. Brown[3], Richard Stravitz [5], Norah Terrault[4]

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5. Virginia Commonwealth University, Richmond, VA, United States.

ABSTRACT BODY: Background: Triple therapy [TT; peginterferon (P), ribavirin (R) and protease inhibitor (PI)] offers improved sustained virologic response (SVR) rates in non-liver transplant (LT) patients with HCV genotype 1 (G1). Therapy with P+R in LT recipients has a low (30%) SVR. The efficacy and safety of TT post-LT is unknown.

Methods: Cohort study of consecutive HCV-infected G1 LT recipients receiving TT from 5 U.S. centers (CRUSH-C). HCV RNA was measured every 2-4 wks during the first 16 wks. Early virologic response (VR) rates (wks 4 and 12) and adverse events (AEs) (rejection, hospitalizations, transfusions and death) were determined. HCV RNA less than limit of detection (<LOD) on-treatment (Tx) was the primary endpoint. Telaprevir was used in 92% with P+R lead-in (LI) in 95%. Nine had extended LI (≥60 days) and were excluded from efficacy but not safety analyses

Results: 61 patients were enrolled (median age 57 yrs, 84% male, 38% Hispanic, 8% AA). 51% had prior Tx (31% null, 50% partial, 19% relapsers), 43% bridging fibrosis/cirrhosis and 10% fibrosing cholestatic hepatitis. Median time from LT to Tx was 33.6 months. (IQR 16.7-64.3). Primary immunosuppression was cyclosporine (CsA) in 62% and tacrolimus (Tac) in 27%; 30% were on steroids and 77% on MMF. Mean daily CsA and Tac doses prior/after PI addition were 200/50 mg and 1.0/0.06 mg, respectively. Median Tx duration (including LI) was 136 days with median LI of 28 days. Median HCV RNA pre-LI and pre-PI addition was 6.59 (IQR: 5.78-7.04) and 5.17 log IU/mL (3.59-6.16), respectively. HCV RNA was <LOD at 4 and 12 wks in 63% (28/44) and 72% (21/29), respectively. The median time to HCV RNA <LOD from start of Tx and from start of PI was 55 (IQR: 46-98) and 28 days (IQR: 54-134). Ten (16%) patients stopped Tx early for AEs (N=4) or virologic failure (N=6). During TT, 37% required transfusion and 33% had a creatinine increase ≥0.5 mg/dL from pre-Tx. Growth factors were used in 77% and P/R dose reductions were required in 60%/46%. Hospitalizations due to SAEs were required in 18%, rejection occurred in 2 patients and 2 patients died during Tx (sepsis and

hepatorenal syndrome).

Conclusions: A high rate of early on-Tx VR is achievable with TT exceeding previously rates with P+R alone despite a "difficult to treat" patient population (prior non-response, advanced fibrosis, high baseline HCV RNA) but with a high rate of AEs, including renal dysfunction likely reflecting PI/CNI interactions. Whether this rapid VR will correlate with improved SVR is unknown. Future studies should focus on identifying predictors for non-response to avoid unnecessary treatment and associated toxicities.

CONTROL ID: 1421772

PRESENTATION TYPE: Oral or Poster

CURRENT CATEGORY: Clinical Liver Transplantation and Liver Surgery

CURRENT DESCRIPTORS: E01. Viral Hepatitis

TITLE: Efficacy and safety of protease inhibitors for hepatitis C recurrence after liver transplantation: a first multicentric experience.

AUTHORS (FIRST NAME, LAST NAME): Audrey Coilly[1, 4], Bruno Roche[1, 2], Jérôme Dumortier[8], Danielle Botta-Fridlund[3], Vincent Leroy[5], Georges-Philippe Pageaux[6], Si-Nafaa Si-Ahmed[7], Teresa Maria Antonini[1, 2], Didier Samuel[1, 2], Jean-Charles Duclos-Vallée[1, 2]

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ABSTRACT BODY: Background: Protease inhibitors (PI), telaprevir and boceprevir, in combination with peg-interferon/ribavirine improved sustained virological response rate in HCV genotype 1 patients (pts), naive or previously treated with dual therapy. We describe for the first time their use after liver transplantation (LT) for HCV recurrence on the graft.

Patients and Methods: This cohort study enrolled 25 liver transplant pts (male: 92%, mean age 54±11 years [31-75]), with an active genotype 1 hepatitis C, in 5 centers between March 2011 and February 2012 and treated with boceprevir (n=14) or telaprevir (n=11) immediately or after a 4-weeks lead-in phase (n=21). The meantime between LT and PI initiation was 49.5±52.3 months [1.6 to 180]. Indication for therapy was HCV recurrence defined by ≥ F2 in the METAVIR scoring system (n=21) or a cholestatic hepatitis (n=4). Eleven (44%) pts were naive and 11 (44%) non-responders to a previous course of dual therapy after LT. Fifteen pts received cyclosporine (60%), 10 tacrolimus (40%).

Results: The mean follow-up was 20.3±8.8 weeks [2-40]. At baseline, HCV viral load, total bilirubin and hemoglobin levels were 6.86±1.17 log10 IU/mL [3.11 to 8.49], 50.9±95.7 µmol/L [5-372], 13.2±1.8 g/dL [8.7-16.3] respectively. After 4 weeks of PI, a rapid virological response was obtained for 6 (43%) boceprevir pts and 5 (45%) telaprevir pts. After 12 weeks of PI, a complete early virological response was obtained for 11 (79%) boceprevir pts and 8 (73%) telaprevir pts. 6 pts experienced an early discontinuation of therapy, 5 for a virological breakthrough (boceprevir n=2, telaprevir n=3) and a null non-responder in the boceprevir group. Three severe infections occurred, leading to death in two pts (boceprevir: 1 at week 20; telaprevir: 1 at week 2). The most common side effect was anemia in 64% of pts: 92% and

91% in boceprevir and telaprevir groups received erythropoietin (EPO) alone or combined with ribavirin reduction and 4 pts received red blood cell transfusions. The cyclosporine dose was reduced by 1.5±0.4 fold [1.0 to 2.0] and 2.8±1.1 fold [1.3-4] with boceprevir and telaprevir, respectively. The tacrolimus dose was reduced by 5.8±2.8 fold [3.1-9.5] and 40.0±14.8 fold [21.4-57.1with boceprevir] and telaprevir, respectively.

Conclusion: A complete early virological response after 12 weeks of triple therapy was observed in 76% of liver transplant pts in our cohort. More than 90% pts used EPO for anemia which was the most common adverse event. Interactions between PI and calcineurin inhibitors were constant but easily managed thanks to a close monitoring. Final results will be presented.

Liver Transpl. 2012 Sep 1. doi: 10.1002/lt.23542. [Epub ahead of print]

Short report: Telaprevir-based triple therapy in liver transplanted HCV patients: A 12 week pilot study providing safety and efficacy.

Werner CR, Egetemeyr DP, Lauer UM, Nadalin S, Königsrainer A, Malek NP, Berg CP.

Source

University Hospital Tuebingen, Medical Clinic, Department of Gastroenterology, Hepatology, and Infectiology, Tuebingen, Germany.

Abstract

Following liver transplantation, management of recurrent Hepatitis C virus (HCV) infection still remains a major challenge. In non-transplanted HCV genotype 1 patients the introduction of protease inhibitor based regimens has increased the rate of sustained virological response, significantly. This pilot study investigated both safety and efficacy data of a telaprevir-based triple therapy in liver transplant HCV patients with special emphasis on drug-drug interactions between immunosuppressants and protease inhibitors.

Gathering week 12 safety and efficacy data in 9 liver transplant HCV patients who have been treated with a combination of telaprevir, pegylated interferon, and ribavirin, in parallel with immunosuppressive drugs such as tacrolimus (n=4), cyclosporine (n=4), or sirolimus (n=1). 7 of the transplanted patients accomplished the 12 week triple therapy. At week 4, 4 of the patients were found to be HCV RNA negative and importantly 8 at week 12. During the course of the 12 week triple therapy, short-termed measurements of immunosuppressant trough levels required individual dose reductions in all patients (cyclosporine 2.5 fold, sirolimus 7 fold, tacrolimus 22 fold, respectively). Furthermore, two thirds of patients exhibited hematological side effects requiring ribavirin dose reductions, administration of erythropoietin, or even blood transfusions.

This pilot study provides evidence that telaprevir-based triple therapy is effective within the first 4 to 12 weeks in liver transplant patients suffering from HCV genotype 1 recurrence and also provides evidence that drug-drug interactions between telaprevir and the immunosuppressants can be handled appropriately by close monitoring of trough levels and adequate dosage adjustment. Liver Transpl, 2012. © 2012 AASLD.

Lo studio C.O.M.E

Costi e qualità di vita nei pazienti con malattia epatica cronica

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Background and aims:

The burden of Chronic liver diseases' (CHDs) is little known. We aimed to assess direct cost (medical and non medical), loss of productivity (days of work/study/doing everyday activities lost) and Health Related Quality of Life (HRQoL) in CHDs patients.

Methods:

We conducted a naturalistic, multicenter, retrospective Cost of Illness study, named COME. Costs occurring during the 6 months before enrollment were assessed from the societal perspective (i.e., healthcare third party payer, patients, their family caregivers). Direct costs included non medical costs (traveling/accommodation, formal caregiver payments) and medical costs: conventional drug and unconventional treatment (e.g., homeopathy, herbal medicines, vitamins, etc), hospitalization for reasons attributable to hepatic condition, outpatient medical visits and diagnostic examinations.. Loss of productivity was measured for patients and caregivers. Results are expressed as €/patient-month (direct costs) and days/patient-month (loss of productivity). Patients' HRQoL was assessed with the EQ-5D questionnaire and is reported as percentage of patients with problems and as mean±SD visual analogue scale (VAS) score.

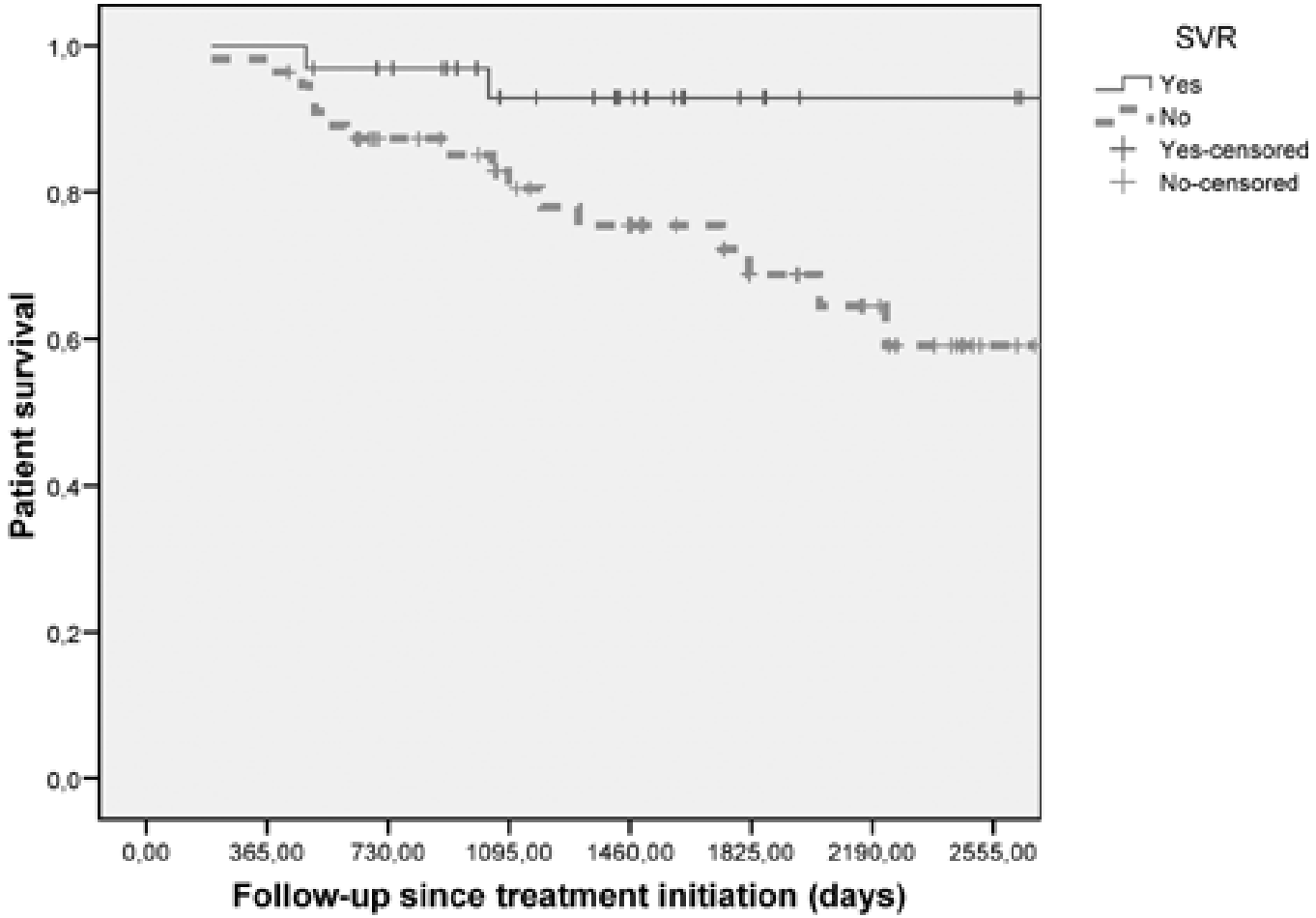
Results:

We enrolled 1,088 valid patients, 62.0% male, aged 19-90 (median=60) years: 31.8% had hepatitis C, 20.4% cirrhosis, 20.3% hepatitis B, 11.9% had liver transplantation (LT), 7.8% hepatic carcinoma (HCC), 7.8% had other hepatic diseases (cholestasis, NASH, etc.). Overall, mean direct cost was 664.77€/patient-month. Hospitalizations contributed to the 50.6% of direct costs; treatment contributed 41.2% of costs; outpatient accesses contributed 2.7% and non medical costs contributed to 5.5% of direct costs. Patients and their family caregivers lost 1.15 days/patient-month of productivity. Both direct and indirect costs were on average lower in patients with hepatitis (258 €/patient-month and 0.5days/patient-month), increased in patients with cirrhosis (494€/patient-month and 1.73days/patient-month) and HCC (1224€/patient-month and 1.75days/patient-month) and among patients undergoing LT (2629€/patient-month and 2.99days/patient-month). As regards HRQoL, 23.8% of patients reported problems in walking about, 13.7% had problems with self-care,28.7% had problems in doing usual activities, 37.5% had pain/discomfort, 46.3% complained with anxiety/depression. The mean±SD VAS was 69.1±20.8, with no relevant differences between the patients subgroups

Conclusions: CHDs' generates high costs to the healthcare system. The use of efficient treatments is necessary to reduce worsening of patients' health, direct and indirect costs.

Congresso	Sede	Data	Pubblicazioni	Poster/Presentazione Orale
Epatiti Summit 2010 (Senato)	Roma	18 Maggio 2010	-	Presentazione orale
ISPOR	Praga	6-9 Novembre 2010	Testing the performance of the newly developed version of the eq-5d with 5 levels of severity: application on a cohort of patients with chronic hepatic diseases; L Scalone Value in Health (November 2010), 13 (7), pg. A240-A240	Presentazione Orale
AISF	Roma	24-25 febbraio 2011	Treatment and productivity costs of chronic hepatic diseases; ; S Fagiuoli. Digestive and Liver disease-AISF 43S (2011);pgS106	Poster
Impatto Clinico, Economico e Sociale delle Malattie Epatiche (Palazzo Pirelli)	Milano	22 Novembre 2012	Costs and quality of life in patients with chronic hepatic diseases: the COME study results	Presentazione Orale
ISPOR	Madrid	5-8 Novembre 2011	Comparison of treatment and indirect costs between hepatitis, cirrhosis, liver transplantation and hepatic carcinoma: results of the come study; Fusco F. Value in Health (November 2011) 14, (7), Page A394.	Poster
ISPOR	Madrid	5-8 Novembre 2011	Comparison of health related quality of life between hepatitis, cirrhosis, liver transplantation and hepatic carcinoma: results of the come study; Ciampichini R. Value in Health Vol. 14, Issue 7, Page A397	Poster
AISF	Roma	23-24 febbraio 2012	Costs and quality of life in patients with chronic hepatic diseases: the COME study results; S Fagiuoli. Digestive and Liver disease- AISF 44S (2012);pgS11.	Presentazione Orale
EASL	Barcellona	18-22 Aprile 2012	Societal burden in patients with Chronic Hepatic Diseases: the COME study results	Presentazione Orale
EASL	Praga	14-16 Settembre 2012	Societal burden in hepatits c patients: the come study results	Poster
ILTS	San Francisco	16-19 Maggio 2012	Cost and quality of life in patients with liver transplantation	Poster
ISPOR	Washington	2-6 Giugno 2012	Abstract accettato	Poster 1 Poster 2 Poster 3

Clinical Benefits of Antiviral Therapy in Patients with Recurrent Hepatitis C Following Liver Transplantation



Patients at risk								
SVR	33	33	29	21	14	7	4	4
NR	56	55	42	34	29	19	13	2

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http://onlinelibrary.wiley.com/doi/10.1111/j.1600-6143.2007.02126.x/full#f3