Pegylated-interferon alpha 2b and ribavirin for recurrent hepatitis C after liver transplantation: From a Canadian experience to recommendations for therapy

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M Babatin, L Schindel, KW Burak. Pegylated-interferon alpha 2b and ribavirin for recurrent hepatitis C after liver transplantation: From a Canadian experience to recommendations for therapy. Can J Gastroenterol 2005;19(6):359-365.

BACKGROUND: Recurrent hepatitis C (HCV) after liver transplantation (LT) is often more aggressive and treatments tend to be less successful. Pegylated-interferon and ribavirin are the standard of care for the treatment of HCV; however, there is limited published experience of its use after LT.

OBJECTIVE: To report the results of pegylated-interferon alpha 2b (PEG-IFN) plus ribavirin for the treatment of recurrent HCV after LT and compare the results with published data.

METHODS: Thirteen patients with recurrent HCV were treated with PEG-IFN plus ribavirin. Liver biopsies demonstrated early-stage disease in eight patients and advanced fibrosis in five patients. The average starting dose of PEG-IFN was 0.91 µg/kg (range 0.5 µg/kg to 1.1 µg/kg) per week and ribavirin was started at 662 mg (range 0 mg to 1200 mg) per day. PEG-IFN treatment began an average of 24 months after LT (range six to 73 months). The dose of PEG-IFN was increased in four patients but only two reached 1.5 µg/kg. The ribavirin dose was increased in four, reduced in six and only seven patients reached a ribavirin dose greater than 10.6 mg/kg.

RESULTS: A sustained virological response was seen in four of 13 (30.7%) patients and in four of eight (50%) patients with early-stage disease compared with zero of five patients with advanced fibrosis (P=0.1). Cytopenias were common and therapy was poorly tolerated in four of five patients with advanced fibrosis, including acute cellular rejection in three, renal failure in two, liver decompensation in four and death in three.

CONCLUSIONS: Although a reasonable sustained virological response can be achieved with the use of PEG-IFN and ribavirin, the treatment is very poorly tolerated by patients with advanced-stage recurrent HCV. Treatment should be instituted before the development of significant fibrosis after LT.

Key Words: *Acute cellular rejection; Antiviral therapy; Fibrosis; Hepatitis C; Liver transplantation*

Interféron pégylé alpha 2b et ribavirine en cas d'hépatite C récurrente après une greffe hépatique : De l'expérience canadienne aux recommandations de traitement

HISTORIQUE : Le virus de l'hépatite C (VHC) récurrent est souvent plus agressif après une greffe hépatique (GH), et les traitements tendent à être moins efficaces. L'interféron pégylé et la ribavirine sont les normes de traitement du VHC. Toutefois, peu de données publiées portent sur leur usage après une GH.

OBJECTIF : Rendre compte de résultats de l'interféron pégylé alpha 2b (interféron PEG) associé à la ribavirine pour traiter un VHC récurrent après une GH et comparer les résultats avec ceux des données publiées.

MÉTHODE : Treize patients souffrant de VHC récurrent ont été traités à l'interféron PEG associé à la ribavirine. Les biopsies hépatiques ont démontré une maladie de stade précoce chez huit patients et une fibrose avancée chez cinq patients. La dose de départ moyenne d'interféron PEG était de 0,91 µg/kg (fourchette de 0,5 µg/kg à 1,1 µg/kg) par semaine, et la dose de ribavirine commençait à 662 mg (fourchette de 0 mg à 1 200 mg) par jour. En moyenne, le traitement à l'interféron PEG était entrepris 24 mois après la GH (fourchette de six à 73 mois). La dose d'interféron PEG a été accrue chez quatre patients, mais seulement deux ont fini par recevoir 1,5 µg/kg. La dose de ribavirine a été accrue chez quatre patients, réduite chez six patients, et seulement sept patients ont atteint une dose de ribavirine supérieure à 10,6 mg/kg.

RÉSULTATS : Une réponse virologique soutenue a été observée chez quatre des 13 (30,7 %) patients et chez quatre des huit (50 %) patients souffrant d'une maladie de stade précoce par rapport à zéro des cinq patients atteints de fibrose avancée (P=0,1). Les cytopénies étaient courantes, et le traitement était peu toléré par quatre des cinq patients atteints de fibrose avancée, y compris un rejet cellulaire aigu chez trois patients, une insuffisance rénale chez deux patients, une décompensation hépatique chez quatre patients et un décès chez trois patients.

CONCLUSIONS : Bien qu'il soit possible d'obtenir une réponse virologique soutenue raisonnable grâce à l'interféron PEG et à la ribavirine, le traitement est très mal toléré par les patients atteints d'un VHC récurrent de stade avancé. Après la GH, le traitement devrait être entrepris avant l'apparition d'une fibrose considérable.

Hepatitis C virus (HCV)-related cirrhosis is the most common indication for liver transplantation (LT), with approximately one-third of all patients worldwide being transplanted for HCV-related complications (1). Virological recurrence of HCV after LT is universal and histological recurrence may appear in as many as 90% of patients (2). The natural history of HCV after LT is often accelerated and cirrhosis may develop in up to 20% of patients within five years of transplantation (3). Thus far, the treatment of recurrent HCV after LT using interferon alpha and ribavirin, alone or in combination, has yielded

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Received for publication January 3, 2005. Accepted February 14, 2005

TABLE 1
Patient, histological and treatment characteristics in 13 patients with recurrent hepatitis C (HCV) following liver transplantation (LT)

	Patient characteristics					Histological recurrence			Treatment		
Patient	Mean age at LT (years)	Sex	HCV genotype	Drugs	Rebetron after LT (months)	Months after LT	Grade	Stage	Started months after LT	Type	Duration (weeks)
1	46.1	F	2	S	–	11.5	1	0	13.9	P + R	43.3
2	44.3	M	6	T + S	–	4.3	2	1	5.9	P + R	48.0
3	51.7	M	1	T	–	2.5	2	1	5.5	P + R	11.7
4	39.4	F	1	C	–	71.3	2	2	73.2	P + R	48.0
5	45.6	M	1	C	–	39.0	2	2	45.5	P + R	38.4*
6	61.4	F	2	S	–	6.4	2	2	8.9	P + R	38.6
7†	44.3	M	3	C	10	20.3	2	2	24.1	P + R	33.4
8	52.6	M	1	T	–	7.3	3	2	8.5	P + R	48.0
9	50.0	M	1	S	6	12.9	3	3	16.2	P + R	2.4
10	53.3	M	1	C	–	32.9	3	3	33.2	P + R	6.7
11†	52.9	M	1	C	5	13.0	3	3	17.5	P	5.0
12†	55.5	M	1	C	9	45.0	2	4	51.3	P + R	93.0
13†	44.9	M	4	C	12	16.4	3	4	38.9	P + R	31.7
Average	**49.4**	–	–	–	–	**21.8**	–	–	**26.4**	–	**34.5**

**Patient discontinued therapy because of depression and lack of a virological response; however, two months later he developed a flare in his alanine aminotransferase level and pegylated-interferon alpha 2a monotherapy was introduced as a suppressive therapy; †Patients received Rebetron (Schering, Canada; standard interferon alpha 2b three times a week and ribavirin) after LT and were switched directly from Rebetron to pegylated-interferon alpha 2b with or without ribavirin. C Cyclosporine; F Female; M Male; P Pegylated-interferon alpha 2b; R Ribavirin; S Sirolimus; T Tacrolimus*

disappointing results (4,5). The combination therapy of standard interferon alpha 2b and ribavirin offers an end of treatment response (ETR) in 10% to 50% of patients but a sustained virological response (SVR) is more rarely observed (6). The pegylation of interferon leads to a longer half-life and increased efficacy (7); however, there has been limited experience with the combination of pegylated-interferon alpha 2b (PEG-IFN) and ribavirin in the treatment of recurrent HCV after LT (8-11). We report our experience using PEG-IFN and ribavirin in 13 LT recipients with recurrent HCV.

METHODS

Beginning in January 2002, treatment with PEG-IFN began in a total of 13 patients (10 men and three women) with recurrent HCV following LT (Table 1). These 13 patients represent one-third of the 39 HCV-positive LT recipients among the 144 LT recipients followed by the Southern Alberta Transplant Clinic in Calgary, Alberta. The mean age of these patients was 49.4 years (range 39.4 to 61.3 years) at the time of LT. Recurrent HCV was established histologically by liver biopsy in all patients. The average time between LT and biopsy-proven recurrence was 21.8 months (range 2.5 to 71.3 months). The grade and stage of histological recurrence is shown in Table 1. Upon biopsy, all patients had at least grade 1 inflammation, and all had elevated alanine aminotransferase (ALT) levels when antiviral therapy was introduced. Five patients had bridging fibrosis (stage 3) or established cirrhosis (stage 4) when therapy began. None of the patients in this series had fibrosing cholestatic recurrent HCV. Eight patients had genotype 1 HCV, with six patients having genotype 1b (46%) and two patients having genotype 1a (15%). Two patients had genotype 2 (15%), one had genotype 3 (7%), one had genotype 4 and one had genotype 6. Immunosuppression was minimized before beginning PEG-IFN therapy and no patients at the time of treatment were on prednisone, mycophenolate mofetil or azathioprine. Seven patients were on cyclosporine monotherapy, three patients were on sirolimus monotherapy, two patients were on tacrolimus monotherapy and one patient was on a combination of tacrolimus and sirolimus (Table 1).

Therapy was initiated an average of 24 months after transplantation (range six to 73 months). One patient had previously failed six months of standard interferon three times a week and ribavirin (Rebetron, Schering, Canada) after LT, and four patients were converted to PEG-IFN after five, nine, 10 and 12 months of Rebetron after LT (Table 1). The average starting dose of PEG-IFN was 0.91 µg/kg once weekly by subcutaneous injection (Table 2). The average starting dose of ribavirin was 660 mg per day in two daily divided doses (Table 3). The goal was to dose escalate PEG-IFN to 1.5 µg/kg weekly and to increase ribavirin to a minimum of 10.6 mg/kg daily. It was intended that all patients would be treated with 48 weeks of therapy regardless of HCV genotype. One patient, who was experiencing significant hemolysis on Rebetron, was converted to PEG-IFN monotherapy. The other 12 patients received a combination of PEG-IFN and ribavirin.

RESULTS

The average duration of PEG-IFN treatment was 34.5 weeks (range two to 93 weeks). Six patients (46%) completed at least 48 weeks of antiviral treatment with PEG-IFN (and/or standard interferon) and ribavirin. Patient 12 was still HCV-RNA-positive by polymerase chain reaction after nine months of Rebetron and 48 weeks of PEG-IFN and ribavirin therapy. He remained on low doses of PEG-IFN and ribavirin as suppressive therapy for a total of 93 weeks.

The biochemical and virological responses to therapy are shown in Table 4. The pretreatment ALT levels ranged from 70 U/L to 553 U/L (average 248 U/L). The average ALT level at the end of PEG-IFN therapy was 88 U/L. Nine patients (69%) had a biochemical response with a normal ALT level at the end of treatment. Despite the normal ALT level, four of these patients did not have a virological response after 48 weeks of treatment. Patient 12, who had cirrhosis, had a biochemical but not a virological response after 48 weeks of PEG-IFN and

TABLE 2
The starting and maximum doses of pegylated-interferon alpha 2b (PEG-IFN) achieved and the impact of therapy on neutrophil and platelet counts

Patient	PEG-IFN start (μg/kg)	PEG-IFN maximum (μg/kg)	PMN start ($\times 10^9$/L)	PMN low ($\times 10^9$/L)	Platelets start ($\times 10^9$/L)	Platelets low ($\times 10^9$/L)
11	0.47	0.47	3.7	3.3	108	71
12	0.88	0.88	2.2	0.6*	138	83
5	0.93	0.93	1.5	0.5*	252	155
13	0.97	0.97	3.0	0.7*	61	26†
6‡	0.49	0.98	3.2	1.6	115	46†
10	1.04	1.04	1.8	1.6	139	139
3	1.05	1.05	0.9	0.4*	78	58
1‡	1.07	1.07	3.0	0.9*	176	72
7	1.07	1.07	1.3	0.6*	60	41†
9	1.07	1.07	4.2	1.6	207	153
2‡	0.86	1.38	1.5	1.1	123	70
4‡	1.00	1.48§	2.5	1.4	318	162
8	0.99	1.48§	1.9	0.7*	151	97
Average	**0.91**	**1.07**	**2.36**	**1.15**	**148**	**90.2**

*Note that patients are ranked by the maximum PEG-IFN dose achieved. *Seven patients developed an absolute neutrophil (polymorphonuclear [PMN] cells) count less than 1.0×10^9/L; †Three patients developed a platelet count less than 50×10^9/L on therapy; ‡Patients 1, 2, 4 and 6 ultimately had a sustained virological response; §Only two patients achieved a dose of 1.5 μg/kg*

TABLE 3
The starting and maximum doses of ribavirin achieved and the impact of therapy on hemoglobin (Hb) levels

Patient	Ribavirin start (mg)	Ribavirin max (mg)	Ribavirin max (mg/kg)	Hb start (g/L)	Hb low (g/L)	Drop in Hb (g/L)
11	0	0	0	131	131	0
7	200	400	5.3	118	113	5
10	400	400	5.2	111	81*	30
1†	400	600	8	147	116	31
2†	600	800	13.8‡	132	80*	52§
6†	800	800	12.3‡	124	108	16
4†	800	800	14.8‡	145	112	33
13	800	800	8.6	137	93*	44
12	800	800	11‡	152	99*	53
9	800	800	10.7‡	153	144	9
8	800	1000	12.3‡	138	75*	63
5	1000	1000	9.3	166	131	35
3	1200	1200	12.6‡	130	88*	42
Average	**662**	**723**	**9.53**	**137**	**105.5**	**34.4**

*Note that patients are ranked by the maximum dose of ribavirin achieved. *Six patients developed a Hb level less than 100 g/L on therapy; †Patients 1, 2, 4 and 6 ultimately had a sustained virological response; ‡Seven patients reached a ribavirin dose of 10.6 mg/kg or greater; §Patient 2 had an episode of hematochezia associated with a need for blood transfusion. Max Maximum*

TABLE 4
Biochemical and virological responses to antiviral therapy

Patient	ALT level at start (U/L)	ALT level at finish (U/L)	End of treatment response	Sustained virological response	HCV genotype
1	305	20*	Yes	Yes	2
6	533	19*	Yes	Yes	2
4	102	19*	Yes	Yes	1
2	450	21*	Yes	Yes	6
7	347	67	No	No	3
12	243	35*	Yes†	No	1
8	293	40*	No	No	1
5	70	25*	No	No	1
13	71	43*	No	No	4
3	157	46*	No	No	1
10	204	140	NP	No	1
9	327	233	NP	No	1
11	217	439	NP	No	1
Average	**247.6**	**88.2**	**5/13 (38.5%)**	**4/13 (30.8%)**	**–**

*Virological end of treatment response was seen in five patients (38.5%) and a sustained virological response was seen in four patients (30.8%). *A normal alanine aminotransferase (ALT) level (less than 60 U/L) was seen in nine patients (69%) at the end of treatment. †Patient 12 was hepatitis C virus (HCV)-RNA-positive after nine months of Rebetron (Schering, Canada) and 48 weeks of pegylated-interferon alpha 2b and ribavirin but became hepatitis C RNA-negative by the polymerase chain reaction after 93 weeks of pegylated-interferon alpha 2b and ribavirin therapy. NP Not performed*

ribavirin therapy, but subsequently became HCV-RNA-negative after completing 93 weeks of PEG-IFN and ribavirin therapy. Because of a lack of funding, his treatment was then discontinued and within six weeks of terminating therapy, his ALT level flared to 598 U/L and HCV-RNA was again detectable.

Two patients, who were switched to PEG-IFN monotherapy because of significant hemolysis on Rebetron, experienced a flare in their ALT levels after a change in their interferon. Patient 11 had his ALT level increase from 217 U/L to 439 U/L and he subsequently discontinued PEG-IFN after five weeks because of severe myalgias. The ALT level of patient 7 flared from 28 U/L to 567 U/L after switching to PEG-IFN. At this time, a liver biopsy demonstrated no acute cellular rejection (ACR) and reintroduction of small doses of ribavirin (200 mg to 400 mg) resulted in ALT level normalization.

Five patients had undetectable HCV-RNA while on PEG-IFN therapy. Patient 7, who had genotype 3 HCV and was HCV-RNA negative while on Rebetron for 10 months, subsequently became HCV-RNA positive again while on PEG-IFN and ribavirin combination therapy. A total of five patients were negative for HCV-RNA at the end of therapy, giving an ETR of 38.5%. SVR (HCV-RNA-negative by polymerase chain reaction six months after terminating therapy) was achieved in four of 13 (31%) patients. Two of these patients had genotype 2, one had genotype 1 and the other had genotype 6 (Table 4). SVR was seen in four of eight patients (50%) with early-stage disease compared with none of the five patients with advanced fibrosis or cirrhosis (P=0.1).

The starting and maximum doses of PEG-IFN and the impact of therapy on neutrophil and platelet counts are shown in Table 2. The average starting dose of PEG-IFN was 0.91 μg/kg once weekly. Dose escalation of PEG-IFN was possible in only four patients, and only two patients (15%) received the full 1.5 μg/kg PEG-IFN dose. The average maximum dose of PEG-IFN was 1.07 μg/kg once weekly. Seven patients (54%) developed significant neutropenia on treatment, with an absolute neutrophil count below 1.0×10^9/L; however, dose reductions were only performed in two patients for neutropenia and there were no infectious complications during therapy. None of the patients received granulocyte colony-stimulating factor (G-CSF). Three patients developed significant thrombocytopenia with a platelet count less than 50×10^9/L. Patient 2 had an episode of unexplained hematochezia at a platelet count of 70×10^9/L. Endoscopy and colonoscopy in this patient did not identify the source of blood loss and he was able to continue PEG-IFN at full doses, although his ribavirin was temporarily held because of anemia.

The starting and maximum doses of ribavirin and the impact of therapy on hemoglobin levels are shown in Table 3. The dose of ribavirin was able to be increased in four patients; however, only three patients (23%) received doses of ribavirin greater than 1000 mg/day. Seven patients (54%) received greater than 10.6 mg/kg of ribavirin, although the dose was further reduced in four of these patients. Eleven of the 12 patients receiving ribavirin in combination with PEG-IFN had a drop in their hemoglobin, with a mean decrease of 34.4 g/L (range 5 g/L to 63 g/L). Erythropoietin was used only in patient 8 and although this increased his hemoglobin level and improved his symptoms, he ultimately did not achieve a SVR.

Most patients experienced subjective side effects while on treatment. Neuropsychiatric complaints including depression (patient 5), hallucinations (patient 6) and irritability (patient 7) led to discontinuation of medication in three patients. In patient 5, PEG-IFN and ribavirin treatment was terminated after 38 weeks because of symptoms of depression and lack of virological response. However, his ALT level flared to 636 U/L two months after therapy was discontinued and low doses of pegylated-interferon alpha 2a (90 μg of Pegasys [Hoffman-La Roche, Canada] weekly) were introduced as suppressive therapy. This normalized his liver biochemistry and was reasonably well-tolerated.

The most serious morbidity in the series was seen in patients 9 to 13, all of whom had advanced fibrosis. Patients 9 and 11, who had previously tolerated Rebetron after LT, developed debilitating myalgias requiring the discontinuation of PEG-IFN after only two and five doses, respectively. Subsequently, both of these patients developed episodes of ACR associated with jaundice shortly after terminating the PEG-IFN therapy. Patient 9 recovered with intravenous steroids but later developed decompensated cirrhosis with ascites and peripheral edema. Patient 11 did not respond to steroids and died of decompensated cirrhosis shortly thereafter. Patient 10 developed jaundice and ACR after six weeks of PEG-IFN and ribavirin therapy. Despite discontinuation of HCV therapy and intravenous steroids, he developed hepatic decompensation with encephalopathy and subsequently died of hepatorenal syndrome. Immunosuppression levels, which were stable before initiating therapy in all patients, became subtherapeutic while on PEG-IFN and ribavirin in all three patients who developed ACR.

Patient 13 developed progressive renal failure and had a generalized seizure 32 weeks into PEG-IFN and ribavirin therapy. He had active urine sediment and had antiglomerular basement membrane antibodies in the serum. Goodpasture's syndrome was suspected but a kidney biopsy could not be performed because of a coagulopathy. Increasing his immunosuppression did not slow the progression of his renal dysfunction and he subsequently died of hepatic and renal failure. No autopsy was performed.

The only patient having cirrhosis to tolerate the therapy was patient 12. He completed nine months of Rebetron followed by PEG-IFN and ribavirin. Because he had a biochemical and not a virological response to therapy he remained on PEG-IFN (0.9 μg/kg) weekly and ribavirin (600 mg) daily past 48 weeks. Unfortunately, after 93 weeks of PEG-IFN and ribavirin, coverage for the cost of his medications expired and therapy was withdrawn. At the end of the therapy he was negative for HCV-RNA, but within six weeks of terminating therapy his ALT level flared to 598 U/L and HCV-RNA was again detectable. His cirrhosis remains well-compensated and he has been started on Pegasys as suppressive therapy.

DISCUSSION

Virological recurrence of HCV after LT is universal and histological recurrence of HCV can occur as early as one month after LT. Allograft injury is apparent in 50% of transplanted patients within the first two years and in 80% within five years (4). Multiple factors can influence early HCV recurrence and rapid progression of HCV after LT. Viral factors (genotype and viral load), donor factors (age and steatosis), host factors (age, sex, alcohol use and cytomegalovirus infection) and iatrogenic factors (immunosuppression) have been implicated in HCV recurrence (1-5). The clinical course of the recurrent disease is variable, ranging from mild hepatitis with a mildly elevated liver profile to the severe form of hepatitis leading to cirrhosis in 10% to 33% of patients within five years (1-5). A minority of patients (less than 5%) can develop a severe form of progressive fibrosing cholestatic hepatitis that carries high mortality (12).

Several treatment strategies have been used to deal with recurrent HCV following LT. Most of the published studies are either open-label or small pilot studies and data from large randomized controlled trials are lacking in the post-LT setting. However, it appears that the response to antiviral therapy is less in patients following LT (3-5). The use of standard interferon monotherapy can be associated with a biochemical response and reduction in HCV-RNA levels; however, SVR or histological responses are rare (13-15). Other studies of ribavirin monotherapy have observed improvement in liver enzymes and inflammation, but virological response and improvement in fibrosis are not evident (13,16).

A SVR can be achieved when interferon and ribavirin are used in combination; however, this combination is associated with multiple side effects in LT patients. Firpi et al (6) treated 54 patients with recurrent HCV with standard interferon three times a week and ribavirin for 48 weeks. An ETR was achieved in 21 patients (38%) and a SVR was achieved in 16 patients (30%). Tolerability was poor and the doses of medication were modified in 72% of these patients. Other studies using the standard dose of interferon with ribavirin have reported an ETR ranging from 25% to 53% and a SVR in the range of 17% to 27% (3).

TABLE 5
A comparison of compliance, side effects and success of pegylated interferon alpha 2b and ribavirin (doses from 0 mg to 1200 mg) for the treatment of recurrent hepatitis C after liver transplantation

Author (Reference)	Patients (n)	Finished treatment (%)	Anemia (%)	EPO use (%)	Leukopenia (%)	G-CSF use (%)	TCP (%)	ACR (%)	ETR (%)	SVR (%)
Ross et al (8)	16	100	69	39	38	88	45	0	38	0
Mukherjee et al (9)	39	46	–	0	–	0	–	0	38	31
Rodriguez-Luna et al (10)	19	51	74	74	47	47	47	5	37	26
Dumortier et al (11)	20	80	65	0	25	0	20	25	55	45
Present study	13	46	46	8	54	0	23	23	39	31

ACR Acute cellular rejection; EPO Erythropoietin; ETR End of treatment response; G-CSF Granulocyte colony-stimulating factor; SVR Sustained virological response; TCP Thrombocytopenia

Although PEG-IFN and ribavirin have emerged as the new standard of care in nontransplant HCV patients (17), only a few studies have been conducted to address the efficacy of this therapy after LT (8-11). Ross et al compared (8) 15 patients treated with the standard dose of interferon three times a week and ribavirin with 16 patients treated with PEG-IFN and ribavirin (including 11 patients with persistent viremia on standard interferon who were switched to PEG-IFN) (8). Virological response to therapy was superior in PEG-IFN and ribavirin-treated patients (37% versus 20%). Three of these responders receiving the PEG-IFN treatment previously failed the standard interferon therapy. In this series, a SVR was achieved in only two patients (both received standard interferon) and no patients on the PEG-IFN treatement had a SVR (8). The low SVR rate was thought to be secondary to the poor tolerability of the medications and failure to achieve optimal doses of these medications because of frequent drug toxicity.

Mukherjee et al (9) conducted another pilot study in 39 patients after LT with recurrent HCV (9). Many patients were intolerant to therapy and only 18 of 39 (46%) patients were able to complete the treatment. Of the 18 patients who completed therapy, 15 (83%) had an ETR and a SVR was achieved in 12 (66%); however, with an intent-to-treat analysis, the SVR was actually 31%. Of the 17 patients who were intolerant to therapy, 15 withdrew within the first three months of therapy. Therapy was most frequently discontinued for fatigue (five patients), severe anemia (two patients), thrombocytopenia (two patients) and psychiatric complaints (two patients). Therapy was discontinued because of hepatic decompensation in three patients (9).

Similarly, Rodriguez-Luna et al (10) treated 19 patients with recurrent HCV after LT. Twelve patients (63%) completed the therapy and seven patients (37%) withdrew early. An ETR was achieved in six patients (32%) and five patients had a SVR (26%) (10). Upon repeat liver biopsies, the necroinflammatory scores improved in both virological responders and nonresponders but fibrosis did not improve in either situation.

Dumortier et al (11) treated 20 patients with PEG-IFN and ribavirin after LT. Although 20% withdrew from therapy because of adverse events, they did achieve a virological ETR in 55% and a SVR in 45% (11). The METAVIR score improved in all patients, with the mean activity score improving from A1.8 to A0.3 and fibrosis score from F2.2 to F1.6 ($P<0.05$). Anemia was very frequently observed (65%) and resulted in ribavirin dose reductions in 13 patients.

We also found that therapy was poorly tolerated by our patients, with only six of 13 patients (46%) completing at least 48 weeks of PEG-IFN (or standard interferon) and ribavirin. Leukopenia (absolute neutrophil count below 1.0×10^9/L) was observed in 54% of patients, but no patient developed a serious infection during therapy and no G-CSF was used in our series. Thrombocytopenia was seen in 23% and one bleeding episode (lower gastrointestinal bleed) occurred in a patient with a platelet count of 70×10^9/L. Anemia was very common despite starting at lower doses of ribavirin in most patients. Dose reductions for hemoglobin levels less than 100 g/L were required in 46% of patients but only one patient received erythropoietin. Only seven patients were able to reach a ribavirin dose greater than 10.6 mg/kg, which is a dose reported to be associated with an increased chance of a SVR in non-LT patients (17). Despite these limitations, a biochemical and virological ETR was observed in 69% and 38.5% of patients, respectively. Ultimately, a SVR was achieved in 31% of our patients. A comparison of our results with previously published studies of PEG-IFN and ribavirin for recurrent HCV is shown in Table 5.

ACR is another concern when using interferon after LT. Feray et al (18) reported the development of chronic rejection in five patients (35%) treated with interferon therapy. Despite some earlier series demonstrating an increased risk of ACR with standard interferon, it is still not clear if interferon therapy after LT increases the risk of ACR (19-22). Kugelmas et al (22) proposed the hypothesis of successful viral eradication improving liver microsomal function, thereby lowering immune suppression levels and predisposing the LT recipient to acute rejection. However, other series have not shown an increased risk of ACR (23). In a recent study by Cardarelli et al (24), there was no association between interferon therapy and ACR or the development of antihuman leukocyte antigen antibodies while undergoing therapy for HCV after LT.

It is possible that rejection may be more of a problem with the longer acting and more effective PEG-IFN. Two of the series of PEG-IFN and ribavirin did not report any problems with ACR (8,9); however, in our study, we had three patients (20%) with ACR while on or shortly after terminating PEG-IFN treatment. All three patients had advanced fibrosis and all developed jaundice associated with the rejection episode. In all patients, immunosuppression levels were subtherapeutic at the time of ACR. One patient responded to intravenous steroids with the resolution of his jaundice. The other two patients did not respond to intravenous steroids and eventually died. In the series by Rodriguez-Luna et al (10), there was one patient who had therapy terminated because of ACR, and Dumortier et al (11) reported mild biopsy-proven ACR in five of 20 (25%) patients treated with PEG-IFN and ribavirin. It is therefore apparent that immunosuppression levels must be monitored more frequently during HCV therapy with PEG-IFN.

Most of our patients experienced adverse effects from therapy. Three patients terminated therapy because of psychiatric complaints. However, in our series, the most serious side effects were seen in the five patients with advanced-stage fibrosis on liver biopsy. Interestingly, two of these patients had previously tolerated standard interferon after LT but developed severe myalgias that led to the discontinuation of the PEG-IFN after only a few doses. This suggests that standard interferon may be an option for LT patients intolerant to PEG-IFN. Four of five patients with advanced fibrosis developed decompensated liver disease and three of these patients died. Mukherjee et al (9) also reported hepatic decompensation in three patients treated with PEG-IFN and ribavirin, but did not report on the histological stage of these patients or their ultimate fate. Advanced-stage fibrosis or cirrhosis is associated with lower response rates in non-LT patients receiving PEG-IFN and ribavirin (17); however, the poor tolerability and response to PEG-IFN and ribavirin therapy in patients following LT has not previously been reported.

Overall, PEG-IFN in combination with ribavirin tends to have better response rates compared with older regimens of standard interferon and ribavirin alone or in combination. We were able to achieve a SVR in nearly one-third of all patients treated with this therapy; however, the adverse effects of this treatment limited success. Neutropenia, thrombocytopenia and anemia were very common among our patients. ACR can complicate PEG-IFN therapy and immunosuppression levels must be carefully monitored during antiviral therapy following LT. In our series, patients with allograft cirrhosis were very intolerant to PEG-IFN and ribavirin therapy. This suggests that therapy should be instituted before the development of significant fibrosis in LT recipients.

RECOMMENDATIONS FOR THE TREATMENT OF RECURRENT HCV AFTER LT

Based on our experience and that in the published literature, we have the following recommendations for the use of PEG-IFN and ribavirin to treat recurrent HCV after LT.

Treatment should be instituted early

It was evident in our series that patients with advanced fibrosis had difficulty tolerating therapy. We believe that therapy should begin as early as possible after there is documented histological recurrence. Usually, recurrent HCV is evident within the first year after LT and presents with a nonspecific increase in liver tests. A liver biopsy is necessary to confirm the recurrence of HCV and rule out ACR or other reasons for elevated liver enzymes. Once there is documented histological recurrence, therapy should be instituted as soon as possible in an attempt to halt progression of the recurrent disease.

Begin with lower doses and dose escalate as possible

Neutropenia and thrombocytopenia are more common at baseline in patients following LT and, therefore, it is reasonable to begin at lower doses of PEG-IFN (0.5 μg/kg to 1.0 μg/kg) and increase to 1.5 μg/kg after a few doses if the white blood cell and platelet count will allow. Anemia is also more common at baseline in LT recipients and the decreased glomerular filtration rate associated with the use of calcineurin inhibitors leads to increased problems with hemolysis when using ribavirin in the post-transplant population. It is therefore reasonable to begin at low doses of ribavirin (400 mg to 800 mg daily) depending on the baseline hemoglobin and glomerular filtration rate and to increase to full doses (1000 mg to 1200 mg) as long as the hemoglobin level remains stable. Growth factors like G-CSF and erythropoietin may be of some benefit in helping these patients remain on higher doses of therapy, although the published series that frequently used these products did not necessarily report a higher SVR (11,13).

Minimize immunosuppression before therapy but be mindful of rejection

Immunosuppression is known to increase the HCV viral load and therefore higher levels of immunosuppression are likely to contribute to the lower response rates of antiviral therapy observed after LT. Whenever possible, immunosuppression should be minimized before beginning therapy. All of our patients were weaned from steroids and mycophenolate mofetil before instituting PEG-IFN and ribavirin. However, in our series and in the other published experience, there does seem to be a small but real risk of causing rejection with the use of PEG-IFN. Treatment with PEG-IFN may predispose the allograft to rejection through two mechanisms: direct modulation of the immune system by interferon; and suppression of HCV-related inflammation in the allograft potentially leading to alterations in drug metabolism and subtherapeutic levels of immunosuppression. A liver biopsy should be performed to rule out rejection if liver enzyme levels flare while a LT patient is on antiviral therapy. Immunosuppression levels must be monitored closely throughout the course of antiviral therapy.

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