ICON Literature Search

Doc. ID.	I97107032
Title	Ribavirin Interferon (and Other Modalities) Combination for Chronic HCV-Results of 6 to 12 Months Treatment
Journal	J. Hepatol., (32nd Ann. Mtg. Eur. Assoc. Study Liver, EASL, London, UK, Apr. 9-12, 1997), Vol. 26, Suppl. 1, 1997, P. 233
Authors	Lurie, Y.; Beer-Gabel, M.; Malnick, S. D. H.; Bass, D. D.; et al.
Summary	About 50% of chronic hepatitis C (=CHC) pts are IFN NRs. Ribavirin IFN combination (=Ribinf), first reported in 1993, is a promising option for these pts. Several other therapeutic modalities also seem to benefit CHC pts (ursodiol, phlebotomy). In May 1995 we started Ribinf (and other modalities) in CHC NRs. Pts' characteristics, course and results of treatment are shown in the Tables. Pt 2 had a virological relapse when Ribavirin was stopped. Conclusions: Complete biochemical response was achieved in 3/3 and virological response in 2/3 pts, by combining Ribinf with other modalities. This was despite unfavorable genotype (3/3) and histology (2/3). These results suggest that some IFN non responders do respond to combination therapy. (This summary represents the entire text of the document.)

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Table 1

No	Age Sex	Biopsy/YR	Type	How infected	Previous Rx
1	51 M	CIRR/1992	1a 1b	IVDA	IFN-beta, IFN-alfa2B IFN-alfa2A
2	60 F	CAH+ Fibrosis/ 1995	1b	Lab worker	IFN-alfa2B
3	47 F	CPH/1992	1b	Transfusion	IFN-alfa2A

Table 2

No.	Phleb.	URSO	Ribinf	Course & Results	Side effects
1	+	+	12 MOS (over 14)	Since 8/96 off ribinf Alt 21, HCV RNA neg x 4, (x3 under Rx, X1 off Rx)	Asthenia
2	+	+ stopped	6 MOS	Since 8/96 off ribinf. continues inf. Alt 28, HCV RNA neg x3 On Ribinf, pos x1 off Ribinf	Anorexia, WBC 2.9 diarrhea 12 kg, wt loss, Asthenia
3	-	+	10 MOS	on ribinf. Alt 24, HCV RNA+	Asthenia

Pt 2 had a virological relapse when Ribavirin was stopped.

ICON Literature Search

Doc. ID.	I97210062
Title	Ribavirin Interferon Combination for Chronic HCV-Preliminary Results of an Ongoing Trial
Journal	Gastroenterology, (Dig. Dis. Wk., 97th Ann. Mtg. Am. Gastroenterol. Assoc., Washington, D. C., USA, May 11-14, 1997), Vol. 112, No. 4, 1997, P. 1325
Authors	Lurie, Y.; Beer-Gabel, M.; Malnick, S. D. H.; Bass, D. D.; et al.
Summary	Background: IFN-alpha is currently the only licensed drug for Chronic Hepatitis C (CHC). As monotherapy it is unsatisfactory. Recent data from several countries suggest that Ribavirin IFN combination (Ribinf) is an important improvement. There are also indications that phlebotomy is beneficial in CHC. Aim: To evaluate Ribinf in CHC pts who were either relapsers or non responders to previous IFN therapy. Methods: We undertook a 1 YR open trial of Ribinf (IFN-alfa2b 9 MU/WK plus Ribavirin (1000 mg/day for wt<75 Kg, 1200 mg/day for wt>75 kg) in 21 selected CHC pts. Pts also underwent phlebotomy, mostly prior to Ribinf, aiming at serum ferritin of 10 ng/ml. Pts characteristics: Mean age: 48+/-13 (range 16-68), 13 women, genotypes: 1b-18 3a-2, ND-1. Relapsers/non responders: 8/13 Histology: CIR-3, CPH-2, CAH-5, CAH+Fib-9, ND-2. Results: ALT levels declined into normal range in 20/21 pts. As shown in the figure. (See original text for graph.) Mean levels for the group (expressed as multiples of the upper limit of normal values) and 9/16 pts tested, became serum HCV RNA negative. The combination had few side effects and was well tolerated. Hemoglobin dropped approximately 2 g/dl. The lowest hemoglobin value recorded in the group was 9 g/dl. 1 pt developed thyrotoxicosis and continues treatment. There were 2 dropouts; a pt who developed depression and 1 for unrelated causes. Conclusions: Ribinf (with prior phlebotomy) yielded a 95% biochemical response rate in less than 120 days. Our pts were predominantly non responders to previous IFN therapy with the unfavorable genotype 1b. These results are markedly better than the widely quoted approximately 50% biochemical response rate at the end of IFN treatment. Ribinf and phlebotomy either alone or with other modalities, are an important addition to our therapeutic armamentarium. (This summary represents the entire text of the document.)

ICON Literature Search

Doc. ID. I95116029
Title TREATMENT OF CHRONIC VIRAL HEPATITIS
Journal BAILLIERES CLIN. GASTROENTEROL., VOL. 8, NO. 2, 1994, PP. 233 - 253
Authors MARCELLIN, P.; BENHAMOU, J. P.
Summary

Recent advances have been made in the treatment of chronic viral hepatitis, mainly with recombinant IFN-alfa. However, the present treatment of chronic viral hepatitis is not entirely satisfactory because the efficacy is inconsistent and/or incomplete. In chronic hepatitis B IFN-alfa induces a sustained interruption of hepatitis B virus (HBV) replication, with a HBeAg to anti-HBe seroconversion in about 30% of pts. Pts most likely to respond are those with no immunosuppression, HBV infection acquired during adulthood or active liver disease with low HBV replication. Responders usually show a significant decrease in serum HBV-DNA levels during the 1st 2 MOS of therapy, followed by a significant increase in the level of aminotransferases. New nucleoside analogues might be useful in combination with IFN-alfa in the treatment of those who do not respond to IFN therapy. In chronic hepatitis B-D, the rate of sustained response to IFN-alfa therapy is low. To be effective, IFN-alfa must be used at a high dosage (9-10 MU) with a long duration (1 YR). In chronic hepatitis C, IFN-alfa at a dosage of 3 MU over 6 MOS, induces a sustained response in about 20% of pts. A higher dosage of IFN (5-19 MU) and a longer duration of treatment increases the rate of sustained response but is associated with poor tolerance. Non-responders to the 1st course of IFN do not respond to a 2nd course of treatment. In pts who respond but relapse after treatment, the rate of sustained response after a 2nd course of IFN needs to be assessed. Ribavirin, which has a significant antiviral effect on hepatitis C virus, might be useful in combination with IFN-alfa. At the dosage (3-6 MU) usually used, IFN-alfa is relatively well tolerated. In about 10% of the pts, therapy is interrupted, mainly because of severe fatigue, thyroid dysfunction or depression. (This summary represents the authors abstract.)

ICON Literature Search

Doc. ID. I97283042
Title Utility of Combination Therapy with Ribavirin Plus Interferon in Chronic Hepatitis C Patients Previously Resistant to Interferon
Journal Hepatology, (48th Ann. Mtg. Am. Assoc. Study Liver Dis., AASLD, Chicago, IL, USA, Nov. 7-11, 1997), Vol. 26, No. 4, Pt. 2, 1997, P. 556
Authors Marchi, S.; Ricchiuti, A.; Ciccorossi, P.; Maltinti, G.; et al.
Summary Background: The long term outcome of chronic hepatitis C can be the progression to liver cirrhosis. IFN-alpha is the accepted treatment in chronic hepatitis C, but only ~20% of pts show long-term response. Combination therapy with antiviral drugs and IFN-alfa increases the sustained response rate in pts resistant to previous IFN-alpha treatment. Ribavirin, a nucleoside analogue that has been found to inhibit the replication of a wide range of RNA and DNA viruses, seems to act synergistically with IFN-alpha in suppressing viral replication in pts with chronic hepatitis C.

Aim: The aim of the present study was to verify the efficacy of the combination therapy with ribavirin plus IFN-alpha on ALT and serum HCV RNA serum levels in pts with chronic hepatitis C relapsers or non-responders to a previous IFN-alpha treatment.
Pts and Methods: 32 pts (24 males, 8 females; mean age 47.87+/-12.98 YRS) were treated with oral ribavirin, 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight >75 kg) plus IFN-alfa2b 3 MU TIW for 6 MOS. ALT levels were tested at baseline and every MO during the treatment. Serum HCV RNA was detected at baseline and after 1, 3, and 6 MOS by a second generation branched nucleotide assay. The quantification limit for this assay was 0.2 HCV RNA MEq/ml.
Results: At baseline, ALT mean value was 101+/-52.18 U/l (n.v.<45 U/l) and all the pts showed HCV RNA levels >0.2 MEq/ml (mean value 3.8627+/-4.2995 MEq/ml). At the end of therapy, normal ALT levels were observed in 26/32 pts (81.25%). In the group of the responders, serum HCV RNA levels were <0.2 MEq/ml in 16/26 pts (61.54%) after 1 and 3 MOS and in 20/26 pts (77%) after 6 MOS of therapy. In the group of the non-responders, HCV RNA levels were <0.2 MEq/ml in 2/6 pts (33.33%) after 1,3, and 6 MOS of therapy.
Conclusion: Our data indicate that the association of ribavirin plus IFN is effective in producing a biochemical response during therapy in a high rate of pts resistant to previous treatments with IFN monotherapy. A significant decrease of HCV RNA levels is achieved in a high rate of the responders after 1 MO of treatment. The follow-up of the responders will be useful to evaluate the rate of sustained response. (This summary represents the entire text of the document.)

ICON Literature Search

Doc. ID. I97283051
Title Ribavirin Plus Interferon (Rib+IFN) in IFN Nonresponder or Relapsing Patients with Chronic Hepatitis C (CHC): Kinetics of Response and Adverse Effects
Journal Hepatology, (48th Ann. Mtg., Am. Assoc. Study Liver Dis., AASLD, Chicago, IL, USA, Nov. 7-11, 1997), Vol. 26, No. 4, Pt. 2, 1997, P. 565
Authors Moreno-Monteagudo, J. A.; Fernandez-Bermejo, M.; Garcia-Buey, L.; Moreno-Otero, R.; et al.
Summary Results of Rib+IFN are contradictory regarding rate of CR, as well as sequence of favorable events or adverse effects in order to define the ceasing of treatment and its duration. Aim: To evaluate the biochemical and virological response and tolerance of Rib+IFN in NR or relapsing pts with CHC. Pts and Methods: 54 pts (43 male and 11 female, mean age 40+/-8.9 YRS) with CHC received IFN-alfa-2b (3 MU 3 TIW) + Rib (1-1.2 g/day). Initial and monthly evaluations during treatment: HCV RNA by PCR (Monitor HCV), ALT, AST, gamma-GT, total bilirubin, hemoglobin, leukocytes, platelets, uric acid, creatinine and triglycerides. Basal histological scores (grade/stage) and viral genotype (InnoLIPA) were determined. Adverse effects of treatment were recorded monthly. Statistics: Student's t test with Welch's correction and chi-square test. Results: There was a significant progressive decrease of HCV RNA and ALT levels during treatment. On finalizing the 3rd MO, 16 pts (29.6%) were HCV RNA negative and 35 (64.8%) had normal ALT. Slight side effects appeared in 41 (76%) pts. No severe anemia was detected. Comparing with mean initial values, during the 1st MO of treatment a significant decrease in hemoglobin (16+/-0.9 to 13.8+/-1.4), leukocytes (5,870+/-1,343 to 4,603+/-1,324) and platelets (183,452+/-48,725 to 175,958+/-55,309), and a significant increase in bilirubin (0.63+/-0.3 to 1.08+/-0.4) and uric acid (4.80+/-1.07 to 6.44+/-1.22) appeared. Interestingly, these changes were not aggravated during the successive treatment MOS. 3 pts stopped therapy, 1 for hypothyroidism and thrombocytopenia, and 2 due to lack of response. Conclusions: 1. Rib+IFN progressively decreased HCV RNA and ALT levels, achieving CR (negative HCV RNA and normal ALT) in a higher number of pts according therapy was prolonged beyond the 1st MO. 2. Tolerance was good, with analytical side effects appearing only during the 1st MO and with no aggravation thereafter. (This summary represents the entire text of the document.)

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Time (MOS)	HCV-RNA Levels	HCV-RNA Negative
Baseline	827,580+/-709,153	0
1	223,629+/-264,173	5(9.3%)
2	106,872+/-175,980	9(16.7%)
3	78,708+/-146,372	16(29.6%)
	p<0.001	

Time (MOS)	ALT Levels	ALT Normal
Baseline	144+/-104	0
1	64+/-51	17(31.5%)
2	47+/-40	30(55.6%)
3	40+/-33	35(64.8%)
	p<0.001	

ICON Literature Search

Doc. ID. I97282081
Title Treatment of Severe Chronic Hepatitis C (CHC): Interferon (IFN) Versus IFN + Ribavirin (Riba). Preliminary Results of a Prospective Study
Journal Hepatology, (48th Ann. Mtg., Am. Assoc. Study Liver Dis., AASLD, Chicago, IL, USA, Nov. 7-11, 1997), Vol. 26, No. 4, Pt. 2, 1997, P. 468
Authors Abergel, A.; Kuder, P.; Henquell, C.; Bommelaer, G.; et al.
Summary

Sustained response in cirrhotic pts treated with IFN is obtained in 5-10%. Ribavirin is a nucleoside analogue with an activity against a broad spectrum of RNA viruses including viral hepatitis C. Clinical studies have shown that IFN + Riba may increase the biochemical and virological response.

Aim of the study: to evalaute IFN + Riba in pts with severe CHC (extensive fibrosis or cirrhosis) 61 pts with biopsy proven chronic hepatitis C have been treated with recombinant IFN-alfa2b 3 MU TIW or IFN + Riba 1200 mg/day. The 2 groups were comparable before treatment for age (51.0+/-11.9 vs 48.3+/-13.7 YRS); ALAT (2.9 N+/-2.2 vs 2.3 N+/-1.3) and viremia (bDNA 2.0 Chiron) (4.8+/-8.0 X10E6 vs 9,9+/-17.1 X10E6 Eq/ml). Only 6 pts have a viremia <200,000 Eq/ml.

At 3 MOS: ALAT was lower in the IFN + Riba group: 0.90 N+/-0.96 vs 1.49+/-1.19 ($p<0.03$). 73% of pts have an ALAT<N in the IFN + Riba group vs 48% in the IFN group ($p<0.05$). PCR (Amplicor, Roche) was negative in 35% pts of the IFN + Riba group and 46% pts of the IFN group ($p>0.05$).

Conclusion: These preliminary results suggest that IFN + Riba allows a high biochemical response at 3 MOS. The virological response (PCR- at 3 MOS) is low. The baseline viremia level in pts with severe CHC may explain in part these results. (This summary represents the entire text of the document.)

ICON Literature Search

Doc. ID. I97203006
Title Ribavirin and Interferon-alpha Combination Therapy vs. Interferon-alpha Alone in the Retreatment of Chronic Hepatitis C: A Randomized Clinical Trial
Journal J. Viral Hepat., Vol. 4, No. 3, 1997, P. 185 - 191
Authors Bellobuono, A.; Mondazzi, L.; Tempini, S.; Ideo, G.; et al.
Summary IFN-alpha induces sustained remission of chronic hepatitis C in ~25% of pts. In pts who are non-responders to the 1st course of therapy, retreatment with IFN-alpha is of limited efficacy. Ribavirin has also been used to treat chronic hepatitis C, but it induces only a transient response. In this study, we evaluated the efficacy of ribavirin and IFN-alpha combination therapy for IFN-alpha resistant chronic hepatitis C. From November 1994 to July 1995, 48 pts affected by clinically and histologically proven chronic hepatitis C were enrolled. Pts' ages ranged from 28-67 YRS (median 47 YRS). All the pts had been treated previously with 1 or 2 courses of IFN-alpha therapy. 24 pts had abnormal transaminase values during IFN-alpha treatment and were considered as non-responders to therapy. 24 pts normalized transaminase levels during treatment but showed reactivation of the disease, with an increase in ALT levels above the upper normal limit, after the end of therapy. These pts were considered relapsers to IFN-alpha treatment. All pts had increased serum ALT levels (>2 times the upper limit of normal range) on at least 3 determinations during the 6 MOS before enrollment in the present trial. They were all confirmed to be positive for antibodies to HCV (anti-HCV) in a 2nd generation ELISA test. The 24 pts with previous non-response and the 24 pts with previous relapse to IFN-alpha treatment were randomized to receive either a further course of IFN-alpha treatment or a course of IFN-alpha and ribavirin combination therapy. All pts were given natural leukocyte-derived IFN-alpha (Alfaferone, Alfa Wasserman) TIW for 6 MOS. In order to avoid a bias owing to the possible correlation between body weight and response to treatment, the dosage of IFN-alpha was adjusted to body weight. The single dose of IFN-alpha was 3 MU or 6 MU when the body weight was <60 kg or >=60 kg, respectively. Ribavirin (provided by Alfa Wasserman) was administered at 1000 mg/day, in 2 divided doses, for 6 MOS. Biochemical parameters were monitored monthly during retreatment and for 6 MOS after discontinuation of IFN-alpha. HCV RNA was detected by nested RT-PCR. There were no significant differences in the pts' clinical backgrounds between the 2 groups of pts. IFN-alpha was administered at the dose of 6 MU TIW to 21/24 (87.5%) pts in the group receiving IFN-alpha therapy alone and to 18/24 (75%) pts in the group receiving combination treatment. Overall, short-term, biochemical response was obtained in 24 pts. It was significantly more frequent ($p<0.01$) in the group receiving combination therapy (17/24; 70.8%) than in the group treated with IFN-alpha alone (7/24; 29.2%). The combination of ribavirin and IFN-alpha was significantly more effective than IFN-alpha alone in inducing short-term biological response in earlier non-responders to IFN-alpha (7/12 pts; 58% vs 0/12;;

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p<0.01). Short-term biochemical response was obtained in 17/24 (70.8%) pts who relapsed after the initial course of IFN-alpha treatment. In these pts, no significant difference in the short-term biochemical response rate was observed between the 2 groups of retreatment. Sustained biochemical response was observed in 6 (25%) pts in the group receiving combination therapy and in 1 (4.2%) pt in the group on IFN-alpha alone (p<0.05; 95% CI). The highest sustained response rate was obtained in the pts with relapse to the previous course of IFN-alpha who underwent retreatment with combination therapy (33%). No difference in the short-term or sustained virological response rate was observed between the 2 groups of retreatment. Short-term virological response was more frequent in earlier relapsers than in earlier non-responders to IFN-alpha both in the group treated with IFN-alpha and the group receiving combination treatment (p<0.01 and p<0.05, respectively). Combination treatment induced a greater number of sustained biochemical and virological responses by comparison to retreatment with IFN-alpha alone, but the difference was not statistically relevant (25% vs 4.2%; p=0.09). Combination treatment induced sustained biochemical and virological response in 2/15 pts infected with HCV genotype 1 (13.3%) and in 3/8 pts with HCV genotype 2 (37.5%). Ribavirin and IFN-alpha combination therapy was associated with significant adverse effects in 37.5% of pts. Combination treatment had to be stopped because of side effects in 3 pts (12.5%). Premature withdrawal from this treatment was caused by anemia (hemoglobin 8.9 g/dl), dyspepsia, marked fatigue, and anxiety. In all pts, the dosage of IFN-alpha was 6 MU TIW. In another 2 (8.3%) pts in this group, the administration of ribavirin was discontinued because of urticaria and pruritis, respectively. The dose of ribavirin was reduced from 1000 to 800 mg/day in 4 pts because of mild anemia (hemoglobin 10.1 g/dl) and urticaria and pruritis. In all cases, side effects were reversible after cessation of treatment or reduction in the dosage of ribavirin. In the group receiving IFN-alpha therapy alone, treatment was discontinued prematurely in 2 pts; because of the onset of insulin-dependent diabetes in 1 and because of marked fatigue in the other. In both pts, the dosage of IFN-alpha was 6 MU TIW. The combination of ribavirin and IFN-alpha seems to have a synergistic antiviral effect in chronic hepatitis C. Although the mechanism of this antiviral effect is not understood, the combination of the 2 drugs has been reported to induce sustained remission of hepatitis in some cases of earlier relapse of hepatitis to IFN-alpha alone. Retreatment with ribavirin and IFN-alpha combination therapy was more effective than retreatment with IFN-alpha alone for chronic hepatitis C with earlier relapse on non-response to IFN-alpha. Nevertheless, although only 2/24 pts treated with ribavirin and IFN-alpha were cirrhotic and IFN-alpha was used at high dosage, the sustained response rate was lower than previously reported. Large-scale studies are required to further address the issue of the effects

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of ribavirin and IFN-alpha combination therapy in chronic hepatitis C.

ICON Literature Search

Doc. ID. I97281097
Title Early Changes in HCV RNA Kinetics with Interferon and Ribavirin Compared to Interferon Alone Suggest an Additive Antiviral Effect with Ribavirin
Journal Hepatology, (48th Ann. Mtg. Am. Assoc. Study Liver Dis., AASLD, Chicago, Illinois, USA, Nov. 7-11, 1997), Vol. 26, No. 4, Pt. 2, 1997, P. 367
Authors Nyberg, L.; McHutchison, J.; Albrecht, J.; Conrad, A.; et al.
Summary Ribavirin, a purine nucleoside analog, inhibits replication of RNA and DNA viruses and may also control hepatitis C viral (HCV) infection through modulation of anti-inflammatory and antiviral responses. Although ribavirin monotherapy has no effect on serum HCV RNA levels, combination therapy with IFN and ribavirin has shown promising results. The aim of the present study was to monitor HCV RNA levels early during combination therapy with IFN and ribavirin compared to that previously seen in the same pts during therapy with IFN alone. Methods: 5 male pts, (ages 44-50) whose HCV RNA levels previously showed no response to therapy with IFN-alfa-2b, (INTRON-A) 3 MU TIW for 24 WKS, were treated with INTRON-A 3 MU TIW SC + oral ribavirin 1,000 mg daily. Pretreatment HCV RNA levels were comparable. HCV genotypes were 1a (3 pts), 1b (1 pt), and 2b (1 pt). HCV RNA levels were monitored by PCR (National Genetics Institute). Statistical analysis was performed using the Wilcoxon rank sum test. Results: HCV RNA levels showed a greater decrease when all 5 pts were treated with combination therapy compared to that seen with IFN alone. At WKS 0, 4 and 8 respectively, mean (+/- SEM) HCV RNA levels of the IFN alone group were 3.07 +/- 0.88, 1.19 +/- 0.95 and 1.24 +/- 0.95 x 10E6 copies/ml. This was compared with 6.06 +/- 3.18, 0.33 +/- 0.20 and 0.12 +/- 0.11 x 10E6 for the IFN + ribavirin group ($p<0.04$ at WK 8). 2/5 pts on combination therapy had undetectable HCV RNA (assay lower limit: 100 copies/ml), 1 at WK 4 and 1 at WK 8; and they continue to have undetectable levels. Conclusions: While ribavirin monotherapy has no effect on HCV RNA levels, combination therapy with IFN + ribavirin in prior IFN non-responders significantly reduces serum HCV RNA levels compared to IFN alone. This effect on HCV RNA at least suggests some direct or indirect antiviral effect of ribavirin when given in combination with IFN. (This summary represents the entire text of the document.)

ICON Literature Search

Doc. ID. I96284009
Title Ribavirin-Interferon vs Interferon (Alfa 2b-IFN) Alone In Non Responders To alpha-IFN In Chronic Hepatitis C
Journal Hepatology, (47th Ann. Mtg. Am. Assoc. Study Liver Dis., ASSLD, Chicago, IL, USA, Nov. 8-12, 1996), Vol. 24, No. 4, Pt. 2, 1996, P. 356A
Authors Pol, S.; Berthelot, P.; Brechot, C.
Summary Aim: To compare the combination of IFN-alfa-2b-Ribavirin to IFN-alfa-2b alone in non-responders to a previous standard 6-MO course of 3 MU IFN-alfa-2b. Therapeutic schedule: 127 pts (83 men, 44 women, including 34 cirrhosis) were randomized to receive a long and reinforced IFN-alfa-2b treatment (6 MU 6 MOS then 3 MU 6 MOS TIW SC) in combination (n=62) or not (n=65) with Ribavirin (at a daily dosage of 1.0 or 1.2 gm according to the body weight < or > 70 kg for 4 MOS: 2 MOS alone and 2 MOS in combination with IFN-alfa-2b). Efficacy was defined by the percentage of normal aminotransferase activities and by the disappearance of HCV-RNA by PCR and bDNA test during and at the end of therapy and 6 MOS after the end of the 12-MO course of IFN-alfa-2b therapy. Results: A significant decrease in aminotransferase was observed after 2 MOS in pts receiving Ribavirin (92 vs 149 IU/l initially) as in those treated by IFN-alfa-2b alone (86 vs 141 IU/l). After 3 MOS of therapy, normal aminotransferase was observed in 35% in both groups. Tolerance of the combination was fair: hemolysis (-0.45 of Hb between M4 and M0), toxiderma (n=3), gingivitis (n=3) and cough (n=3) were related to Ribavirin and usually self-limited. Treatment withdrawal was necessary in 8 pts treated by the combination and in 6 pts with IFN-alfa-2b alone. A negative PCR at MO 4 was observed in 33.3% of pts who were given the combination and in 37.7% of those who received IFN-alfa-2b alone. At the end of IFN-alfa-2b, HCV-RNA was not detected in 14.0% of pts who received Ribavirin and in 7.6% (NS) of those who did not. The 36 evaluable pts who had a 6-MO follow-up after the end of treatment all had detectable HCV-RNA. Conclusion: This large controlled study: 1. shows an overall good tolerance to the sequential combination Ribavirin-IFN-alfa-2b and 2. provides however no indication for an improved rate of primary or long-term response with the combination in non-responders to IFN-alfa-2b since most of the pts had no long-term response. (This summary represents the entire text of the document.)

ICON Literature Search

Doc. ID. I97210086
Title One Year Follow Up of Re-Treatment with alpha-Interferon in Combination with Ribavirin versus IFN for Chronic Hepatitis C
Journal Gastroenterology, (Dig. Dis. Wk., 97th Ann. Mtg. Am. Gastroenterol. Assoc., Washington, D. C., USA, May 11-14, 1997), Vol. 112, No. 4, 1997, P. 1361
Authors Porst, H.; Wiese, M.; Meisel, H.; Porst, T.
Summary Background and Aims: In pts with chronic hepatitis C treated with IFN-alpha, sustained normalization of aminotransferases and clearance of HCV-RNA were observed in about 20%, Ribavirin induces only a transient response. The aims of the study were to assess the efficiency of a re-therapy with IFN-alfa2b in combination with Ribavirin versus IFN by IFN-resistance in a previous course in a well defined homogeneous collective of pts in a 1 YR follow-up. Pts and Methods: 20 female pts with chronic hepatitis C, mean age 43.5 YRS, (inclusion criteria: positive HCV-RNA-test by polymerase chain reaction, genotype 1b, aminotransferase more than twice of the standard and previous treatment with IFN alone without sustained response) were treated with -group A- IFN (3x6 MU WKly) in combination with Ribavirin (2x600 mg daily) or with -group B- IFN alone (3x6 MU WKly) in a 24 WK course. Results: At the end of therapy CR (negative HCV-RNA test by PCR and normalization of amino-transferase levels) was observed in group A 7/10 and in group B 4/10. Nearly all pts of group A (9/10) and all pts of group B (10/10) had became HCV-PCR positive in a follow up of 1 YR. A sustained biochemical response of the responders at the end of the retherapy could be considered in A 4/10 and B 1/10. Summary: A combined re-therapy with IFN-alfa2b and Ribavirin after an IFN treatment alone seems to be a successful therapeutic direction for chronic hepatitis C than single IFN treatment. (This summary represents the entire text of the document.)

ICON Literature Search

Doc. ID. I97195077
Title Prophylaxis and Treatment of Hepatitis C
Journal Ann. Gastroenterol. Hepatol., Vol. 33, No. 1, 1997, p. 34 - 38
Authors Poupon, R.; Serfaty, L.
Summary Prophylaxis and treatment of hepatitis C.- IFN is the only treatment shown to be effective on hepatitis C in controlled trials. The response to treatment is generally assessed in terms of a return to normal transaminase activity, but also negative PCR testing for viral RNA and histopathological examination of the liver. At a dose of 3 MU TIW for 6 MOS, 25% of pts have a persistent return to normal transaminase activity, 25% relapse when IFN is withdrawn, and the remaining 50% have persistently high levels at the end of treatment and are considered resistant. The rate of persistent responses increases to 40% when treatment is extended to 1 YR. Viral RNA becomes undetectable in the serum of 80% of these responders. Most also have a histological improvement, but so do a number of pts who relapse or who are resistant. In the longer term, IFN could prevent the onset of liver cancer in pts with viral C cirrhosis. IFN is generally well tolerated at the doses currently used, most side-effects (hematologic, neuropsychiatric and thyroid disorders) resolving when treatment is discontinued. The following factors are clearly predictive of the response to IFN: young age, short time since onset, absence of cirrhosis, lower-level viremia, and infection by HCV genotypes other than 1b. IFN is markedly less effective in immunodeficient pts (transplant, HIV infection, etc.). Several add-on treatments have been tried, but ribavirin appears to be the most promising, both during initial IFN therapy and for pts who relapse or are resistant to a first course. IFN therapy of the acute phase of hepatitis C significantly reduces the risk of chronic liver disease. There is no vaccine against HCV infection. (This summary represents the authors abstract.)

ICON Literature Search

Doc. ID. I97263012
Title * Therapy of Hepatitis C: alpha Interferon and Ribavirin
Journal Hepatology, Vol. 26, No. 3, Suppl. 1, 1997, P. 108 - 111
Authors Reichard, O.; Schvarcz, R.; Weiland, O.
Summary

Ribarvirin is a nucleoside analogue that has been evaluated as a therapy of chronic hepatitis C alone and in combination with IFN-alpha. Ribavirin is well absorbed orally and is typically given in doses of 1,000 to 1,200 mg/d. For this review and analysis, articles on ribarivin therapy of hepatitis C or non-A, non-B hepatitis were identified through a Medline search and supplemented with abstracts and articles known to the authors. Responses to therapy were defined as either end-of-treatment response (ETR) or sustained response (SR) based on biochemical (normal alanine aminotransferase [ALT] levels) or virological criteria (absence of detectable HCV RNA by polymerase chain reaction). Definition of an SR required a follow-up duration of 6 MOS or more after cessation of therapy. Unless otherwise stated, the standard dose of IFN-alpha was 3 MU TIW and that of ribavirin was 1,200 mg daily for pts who weighed more than 75 kg and 1,000 mg daily for pts who weighed less than 75 kg.

Results of 3 randomized, double-blind, placebo-controlled trials of ribavirin therapy have been reported. Ribavirin was administered for 6, 9, and 12 MOS and results were compared with placebo therapy. Biochemical ETRs occurred in 21% to 43% of pts treated with ribavirin but in only rare pts receiving placebo. As in the pilot studies, no pt achieved a virological ETR. In 1 study, there was a slight but statistically significant decrease in serum HCV RNA levels as measured by branched DNA signal amplification assay during ribavirin therapy, but a rebound to pretreatment levels occurred when ribavirin was stopped. Histological responses occurred in some pts, especially in those treated for 1 YR. Comparison of pretreatment and end-of-therapy liver biopsy specimens demonstrated significant reduction of necro-inflammatory activity, and particularly periportal and intralobular inflammation in pts whose serum aminotransferases had improved. The major adverse events were a moderate and reversible hemolysis during treatment that caused a decrease in hemoglobin by 10% to 20% of baseline levels, (necessitating a dose reduction in 10%-15% of pts), and nonspecific symptoms of fatigue, depression, insomnia, vertigo, anorexia, nausea, nasal congestion, and pruritis.

Combinations of antiviral agents are often used in treatment of chronic infectious diseases. The combination of IFN and ribavirin as therapy of chronic hepatitis C was a reasonable approach to increasing response rates. Pilot studies showed that 80% of pts who relapsed after an ETR to a previous course of IFN-alpha had a sustained virological and biochemical response to the combination of ribavirin and IFN-alpha. However, only 0% -25% of pts who did not respond at all to a previous course of IFN-alpha had a long-term beneficial response to the combination. In a meta-analysis from Europe using individual pt results, it was

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shown that pts with low response rates to IFN-alpha, such as pts with genotype 1b and cirrhosis, had a 2-fold to 3-fold increased rate of sustained responses compared with treatment with IFN-alpha alone. Combination therapy also appears to be more effective than IFN alone in IFN-alfa naive pts. In a study of IFN naive pts with chronic hepatitis C from Italy, 45 pts were randomized to receive either lymphoblastoid IFN alone, ribavirin alone, or lymphoblastoid IFN in combination with ribavirin in standard dose. The SR rates were 0% in the ribavirin-treated, 7% in the IFN-treated, and 47% in the combination-treated group. A recent study from Taiwan with long-term follow-up evaluation has provided further support for the efficacy of combination therapy. Virological SRs 2 YRS after 24-WK courses of treatment occurred in 9/21 pts (43%) treated with the combination of IFN-alfa-2a and ribavirin as compared with only 1/19 pts (6%) treated with IFN-alfa-2a alone (P=0.006). Thus, the SRs after combination therapy appear to be as long-lasting as those reported after therapy with IFN alone. The 1st randomized, double-blind, placebo-controlled study of ribavirin and IFN has recently been completed. 100 IFN-naive pts with chronic hepatitis C were treated with IFN-alfa-2b in doses of 3 MU TIW in combination with either ribavirin in doses of 1,000 or 1,200 mg/d (n=50) or placebo (n=50) for 24 WKS. The follow-up period after treatment was 24 WKS. The 2 study groups were comparable with regard to age, sex, mode of transmission, liver histology, pretreatment ALT level, pretreatment HCV RNA level, and HCV genotype. Biochemical and virological ETR rates were the same for the 2 groups. However, virological SRs occurred in 45% of pts who received combination therapy compared with 23% of those who received IFN alone (P<0.05). Side effects were significantly more frequent among pts who received the combination therapy, the most common adverse events being anemia, fatigue, and depression. Ribavirin, either alone or in combination with IFN-alpha, may also be effective in pts with recurrent hepatitis C after liver transplantation. Ribavirin has also been used in the bone marrow transplantation setting.

Ribavirin alone has limited antiviral activity in chronic hepatitis C. For pts who do not respond to IFN-alpha therapy and for pts in whom IFN cannot be used, long-term continuous therapy with ribavirin alone could possibly provide some benefit. Current studies indicate that combination therapy with ribavirin and IFN may be more effective than IFN alone. However, even with the best results of combination therapy, only half of pts with chronic hepatitis C will have sustained beneficial response. Better and more potent antiviral agents are needed in hepatitis C, and future research efforts should be directed at developing in vitro and in vivo systems to evaluate new antiviral substances and at assessing these agents alone and in combination in well-designed controlled clinical trials.

ICON Literature Search

Doc. ID. I97106068
Title Interferon versus Ribavirin Plus Interferon in Chronic Hepatitis C Previously Resistant to Interferon: A Randomized Trial
Journal J. Hepatol., (32nd Ann. Mtg. Eur. Assoc. Study Liver, EASL, London, UK, Apr. 9 - 12, 1997), Vol. 26, Suppl. 1, 1997, P. 198
Authors Salmeron, J.; Perez-Ruiz, M.; Ruiz-Extremera, A.; Palacios, A.; et al.
Summary The aim of this work was to assess the effectiveness of the association ribavirin plus IFN in a group of pts resistant to a first IFN therapy. 62 pts with chronic hepatitis C and serum and hepatic HCV-RNA, relapsers or NRs to IFN, were randomly divided into 2 groups: group A, submitted to 3 megaunits of IFN-alfa-2b, TIW during 6 MOS; group B, given the same dose plus 600 mg/day of ribavirin during 6 MOS. 2 pts from each group abandoned therapy; 1 pt from group A and 2 from group B withdrew from treatment because of adverse effects. Mean alanine aminotransferase levels were the same in both groups throughout the study. No statistical differences were found in the response to therapy: a sustained response was obtained in 2 (7%) of group A versus 2 (7.4%) of group B; relapse, in 11 (39%) versus 16 (59%) pts; and NR in 15 (54%) versus 9 (34%), respectively. At 12 MOS, 4 and 7 pts from groups A and B respectively, cleared serum HCV-RNA; however, only 1 sustained responder from each group cleared PBMC HCV-RNA as well. At 18 MOS only 3 pts remained HCV-RNA negative. Adverse effects were similar. Only hemoglobin values were lower in group b in the first MO of therapy ($p<0.05$); no pt presented hemolytic anemia. Conclusion: The association of 3 MU IFN plus 600 mg of ribavirin is not effective in chronic hepatitis C resistant to IFN therapy. (This summary represents the entire text of the document.)

ICON Literature Search

Doc. ID. I96352005
Title Prospects with Interferon Alfa-2b/Ribavirin Combination Therapy
Journal New Adv. Anti-Viral Ther., Satellite Symp., 31st Ann. Mtg. Eur. Assoc. study Liver, 1996
Authors Schalm, S. W.
Summary A meta-analysis of individual data from 4 European studies, comprising about 90% of the published experience with IFN-ribavirin combination therapy, was carried out to obtain a more precise estimation of the efficacy and tolerability of combination therapy for chronic hepatitis C. Data were collected in 186 individuals who had participated in 3 randomized controlled trials and 1 open study; 51 had received ribavirin monotherapy (1,000-1,200 mg/day), 37 IFN monotherapy (3 MU TIW) and 78 IFN-ribavirin combination therapy (I 3 MU TIW + R 1,000-1,200 mg/day) for 6 MOS; 20 pts were controls. Follow-up after therapy was 6 MOS. The major outcome measures were the sustained response rate of ALT normalization with HCV RNA negativity, and the percentage withdrawals due to adverse events. Pt groups receiving various treatment modalities were assessed by multivariate logistic regression analysis. The sustained response rate was significantly higher for IFN -ribavirin vs. IFN: 6.8); this rate was independent of subgroups such as cirrhosis or genotype 1. The estimated probability of sustained response following IFN-ribavirin combination therapy was 52% for pts without previous IFN therapy, 52% for pts with previous IFN therapy and response-relapse, and 19% for previous IFN non-responders. Tolerability of the IFN ribavirin combination appears to be clinically acceptable, the most common adverse event being hemolysis, with no serious adverse events observed and less than 10% withdrawal. This meta-analysis of individual data strongly suggests a 2-3 fold enhanced efficacy of IFN ribavirin combination therapy over IFN monotherapy in all major subgroups of chronic hepatitis C pts tested. If the large collaborative international trials confirm these findings, IFN-ribavirin combination therapy could become a new standard of therapy for chronic hepatitis C. The implications of the current information on IFN-ribavirin are discussed in relation to the design of randomized controlled trials and in relation to compassionate use in specific groups like non-responders, HCV positive liver transplants, pts undergoing hemodialysis, and HIV coinfected pts. (This summary represents the entire text of the document.)

ICON Literature Search

Doc. ID. I95214003
Title COMBINED TREATMENT WITH INTERFERON ALPHA-2B AND RIBIVIRIN FOR CHRONIC HEPATITIS C IN PATIENTS WITH A PREVIOUS NON-RESPONSE OR NON-SUSTAINED RESPONSE TO INTERFERON ALONE
Journal J. MED. VIROL., VOL. 46, 1995, P. 43 - 47
Authors SCHVARCZ, R.; YUN, Z. B.; SONNERBORG, A.; WEILAND, O.
Summary During IFN-alpha treatment approximately 50% of chronic hepatitis C pts will respond biochemically, of whom more than half will relapse once treatment is withdrawn, but some 50% will not respond at all. Ribavirin, a nucleoside analog, temporarily lowers the transaminase levels in pts during treatment, although clearance of HCV-RNA from serum does not occur. A combination of these 2 drugs thus seemed a logical approach to achieve response. 10 pts aged 26-73 with chronic hepatitis C and a previous non-response or non-sustained response to IFN alone were included. 6 pts had been nonresponders and 4 non-sustained responders to IFN-alpha (3 MU 3x/wk for at least 12 wks). 1 nonresponding pt had also been treated previously with ribavirin alone for 12 wks. All pts had an interval of at least 3 mos since their latest antiviral treatment. Recombinant IFN-alfa2b was given SC at 3 MU 3x/wk with ribavirin 1000 mg/day for pts weighing <= 75 kg and 1200 mg/day for pts weighing > 75 kg, in 2 divided doses orally. Both drugs were given for 24 wks. The 4 non-sustained responders had normal ALT levels at the end of treatment and at follow-up 24 wks post-treatment. The corresponding figures for nonresponders pts were 3/6 and 1/6, respectively. Overall, 7/10 pts had normal ALT levels at the end of treatment, 5 of whom also had normal levels at follow-up. All pts had HCV-RNA before treatment. The 4 pts with a prior non-sustained response to IFN alone all became HCV-RNA negative at the end of treatment, and of these, 3 remained negative at follow-up. 2/6 pts with a prior non-response lost HCV-RNA at the end of treatment, and 1 of these remained negative at follow-up. Adverse effects were generally mild. All pts completed the treatment schedule. It is concluded that combination therapy with IFN-alfa2b and ribavirin offers a chance of sustained biochemical response with eradication of the viremia in pts who have not shown a persistent response to IFN-alpha alone.

ICON Literature Search

Doc. ID. I95116025
Title INTERFERON THERAPY FOR HEPATITIS C
Journal ANTIVIRAL RES?, VOL. 24, NO. 2-3, 1995, PP. 155 - 163
Authors TREPO, C.; HABERSETZER, F.; BAILLY, F.; VITVITSKI, L.; ET AL.
Summary The natural history of chronic hepatitis C leads to progressive inflammation of the liver with development of cirrhosis and its complications, including hepatocellular carcinoma. There is an extreme variability in the proportion of cases with progressive liver disease, and the pace of that evolution. This extreme heterogeneity calls for a careful definition of end points in all the trials devoted to the therapy of chronic hepatitis C. Ideally, the true end-points of therapy should be to abolish the cause of the disease, ie, eradicate HCV infection and suppress its consequences, liver necrosis and inflammation and its sequelae, fibrosis and cirrhosis. Proper definition of response should in fact focus on clearance of HCV RNA and normalization of ALT. Such a response will then invariably be associated with improved histology. A meta-analysis involving 916 pts, enrolled in 17 studies, indicated that around 50% of pts respond to recombinant IFN-alfa by normalizing ALT at the end of therapy. Half of these will relapse within the 6 MOS following cessation of treatment. Histological improvement is present in over 60% of CRs with significant decrease of inflammation and necrosis. Although the many studies published provide very different results, both dose and duration of treatment are critical in the response to therapy. Whether an induction therapy and a maintenance regimen should be distinguished has been the topic of several studies. Higher initial doses may be followed by lower relapse rates. Among the best results reported so far are those obtained by Alberti et al (1993) using an induction dose of 6 MU x 6 MOS + 3 MU x 6 MOS: 76% CR and 51% retaining normal ALT at 12 MOS. In the early randomized studies, 4 groups in Europe and the US used an identical protocol with alfa-2b. They obtained different results emphasizing a surprising heterogeneity of responses between clinical centers using identical protocols and the same alfa-2b recombinant IFN product. This emphasizes that the category of pts treated was certainly as important for the outcome as the therapy regimen itself, and prompted the search for predictive factors of response. Absence of cirrhosis, young age, female sex, and presence of lobular hepatitis were all associated with better response to IFN. The role of duration of disease prior to therapy as a predictive factors of response is most difficult to assess since it can only be known in post-transfusion cases. As far as chronic hepatitis C is concerned, 2 studies may indicate that duration of disease may be important. Far more important is the impact of HCV genotype on the IFN response. The pretreatment level of HCV RNA, when carefully quantified, appears to be also correlated to IFN response, especially if replaced within the frame of a specific genotype. While negativity of HCV RNA in serum and in liver at the end of treatment may not always be predictive of sustained remission, it becomes so after 6 MOS. According to another study,

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absence of both HCV RNA positive and negative strands in liver serum and mononuclear cells at the end of therapy, may be predictive of sustained remission. Finally, pretreatment levels of HCV antigen in liver appear to be lower in pts responsive to IFN therapy. It has been suggested that differences in responses may exist between different types of alfa IFN either recombinant or not. It had also been suggested that the emergence of neutralizing anti-IFN antibodies may account for some breakthroughs. The response to ribavirin appears different to that of IFN. Preliminary results do indicate that association of IFN-alfa or beta with ribavirin may be of benefit.

ICON Literature Search

Doc. ID. I97223011
Title How Should We Treat Hepatitis C in 1997?
Journal Can. J. Gastroenterol., Vol. 11, No. 4, 1997, P. 291 - 292
Authors Williams, C. N.
Summary The dose and the frequency of IFN administration resulting in the greatest number of responses, in association with the least number of relapses after treatment, remain unclear. Return to normal of the transaminases is a clinical measure of response, but measurement of clearance of hepatitis C virus (HCV) in serum by polymerase chain reaction remains the method of choice. To answer the response question, estimating serum HCV-RNA 6 MOS after IFN treatment appears to correlate subsequent long-term benefit better than any other parameter. The effects of dose increment, durtion of treatment and response rates were reported by the first multicentre Australian trial of 230 pts. The dose utilized included 3 x 10E6 U of IFN TIW SC for 6 MOS; 5 x 10E6 U TIW SC for 6 MOS; or 3 x 10E6 U TIW SC for 2 YRS. Short-term response to IFN was independent of the incremental dose, being 64% for 5 x 10E6 U and 58% for 3 x 10E6 U. Long-term response, defined by normal ALT at 6 MOS post-treatment, ranged from 29% for those treated for 6 MOS to 54% for those treated for 2 YRS (P<0.001). Histological change mirrored the clinical response; change was significantly greater among those who had been treated for 2 YRS compared with those treated for 6 MOS. In this study several features were associated with a a better response, such as the absence of cirrhosis. For the source of transmission, a better response was associated with IV drug use; it was less favourable for blood transfusion and worse for sporadic cases.
In another trial reported from the United Kingdom, a sustained response was achieved in 12/88 pts (13.6%) treated with either 10 x 10E6 or 5 x 10E6 U of IFN. Relapsers in those receiving the lower dose were significantly higher (87.5%) than relapses in those receiving the higher dose (59.1%).
The integrated results of a worldwide clinical research program using IFN-alfa in 1831 pts were reviewed in a paper from Denmark. A multivariate analysis of regimens of 1 x 10E6, 3 x 10E6, 4.5 x 10E6 and 6 x 10E6 U for 3, 6 and 12 MOS in 10 clinical trials revealed that the best response rates were obtained with an induction dose of 6 x 10E6 U TIW for 3 MOS, followed in responding pts by a maintenance regimen of 3 x 10E6 U TIW for 3 MOS.
In a 2-YR follow-up report from the United States it was concluded that most sustained responders who have normal ALT levels at short-term follow-up at 6 MOS after IFN treatment, will continue to have durable long-term response response, without relapse of the viremia. Another predictor of response to IFN treatment is iron overload. The percentage of iron saturation was significantly lower in responders (30 +/- 10%) than in nonresponders (53 +/- 12%) (P<0.001). Whether reducing iron overload will improve the response to IFN therapy is unknown.
In another study the response to hepatitis C treatment in elderly persons older than 65 YRS was compared with that in a comparison

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group, mean age 44 YRS. Here the response rates were similar in both age groups, and the safety tolerance likewise did not differ. Thus, age is not a contraindication to treatment and does not differentiate response.
What should we do with pts who do not respond to IFN treatment? Several groups have answered this question: give higher doses or the same dose for a longer time. Higher doses appear to be less well tolerated, but may increase the proportion responding. Another method is to use natural IFN in those who are nonresponders to recombinant IFN. Pts who have antibodies to recombinant IFN appear to respond better to this natural IFN than those who do not mount an antibody response.
Serum HCV-RNA titre at the end of IFN therapy has been used as a predictor of long-term outcome following treatment and appears to be discriminatory. The genotype of the pt being treated appears to influence this response; those with genotype 2a show a better response than those with genotype 1b.
Is combination therapy with another agent, in addition to IFN, worthwhile? The most widely studied agent for use in combination is rabavirin. While ribavirin by itself does not eradicate the HCV, when used in combination with IFN-alfa-2b the response rate is said to double (to 50%). There are multicentre worldwide studies currently addressing this combination therapy question. 1 group who treated a small number of HCV cirrhotic pts with recombinant G-CSF plus recombinant IFN have reported promising results. Ursodeoxycholic acid (UDCA) alone appears to improve the transaminase levels, but does not clear the virus.
Does IFN for hepatitis C exacerbate co-existing conditions? Limited information is available. However, inflammatory bowel disease coexisting with hepatitis C is not apparently influenced by use of IFN, nor is coexistent psoriasis. Sporadic cases of myasthenia gravis and (silent) thyroiditis have been described with IFN therapy.
Finally, is IFN treatment cost effective? Preliminary estimates from the United Kingdom showed a significant cost benefit when values for life were included in the analysis. How should we treat our pts with hepatitis C in 1997? It seems reasonable to give IFN 3 x 10E6 U SC TIW for 2 MOS, continuing for 6 MOS in those with normalization of transaminases and loss of HCV. Treatment for 6 MOS is a minimal time frame; better results are obtained at 12 and 24 MOS. However, cost and side-effects may limit the duration of treatment. How we decide the treatment for 2 YRS is unclear. Should we use an additional agent, such as riavirin or UDCA? We need the results of ongoing studies before we can decide. Can we predict who will respond best? Pts with genotype 2a, who are precirrhotic, have no increased iron stores and show no evidence of autoimmunity (positive antinuclear antibody) have thus far been identified as better responders to IFN therapy.

ICON Literature Search

Doc. ID. I97150006
Title Alpha-Interferon Alone and in Combination with Ribavirin for Hepatitis C Infection in Multiply Transfused Patients with Thalassemia Major - the UK Experience
Journal Bone Marrow Transplant., Vol. 19, Suppl. 2, 1997, P. 163 - 165
Authors Wonke, B.; Telfer, P.; Garson, J. A.; Hoffbrand, A. V.; et al.
Summary 33 thalassemia major (TM) pts anti-HCV, HCV-RNA positive were treated for 6 MOS with IFN-alfa-2b (IFN). Combination therapy IFN and Ribavirin was subsequently given to 13 non-responding TM pts to single therapy. In this communication we report the sustained response rate to hepatitis C with IFN therapy alone in 33 TM pts and report the initial response rate to combination therapy with IFN and ribavirin in 13 TM pts previously unresponsive to single-agent therapy. 33 pts, 7 females and 26 males with a median age of 24.2 (range 10.5-38.4) YRS were studied. All had been transfused to keep their pre-transfusion hemoglobin between 9-10.0 g/dl. The number of donor exposures ranged from 200-650 U of blood. 27 pts were treated with SC desferrioxamine, 6 with the oral iron chelating deferiprone. The serum aspartate (AST) and alanine transaminases (ALT) were persistently or intermittently elevated in pts at least 6 MOS prior to IFN treatment. All pts were anti-HCV and HCV-RNA positive in the serum. Percutaneous liver biopsies were performed in all pts prior to treatment and they all showed either CAH or cirrhosis. IFN 3 MU self-administered by SC injection TIW was given to all pts for 6 MOS. Serum AST and ALT levels were monitored at monthly intervals and anti-HCV and HCV-RNA was tested initially, at the end of the study and then yearly. Post-treatment follow-up period was between 10-67 MOS. All pts remained anti-HCV positive. Of the 33 pts 10 (30.3%) are HCV-RNA negative with a mean of 39.6 (range 10-67) MOS follow-up. There were 3 females and 7 males in the sustained responders, median age 16.9 (range 11.5-23.6) YRS. Non-sustained responders, 4 females and 19 males, had a median age 26.2 (range 10.5-38.4) YRS. There is a significant difference between the ages of sustained responders and non-sustained responders (p=0.02). While HCV serotype showed no apparent association with sustained response, the numbers are too small to make a statistical evaluation. The mean serum ferritin at the start of treatment in the sustained responders to IFN was 1755 (range 747-3242) ug/l, while in the non-sustained responders the mean serum ferritin was 3398 (range 901-7832) ug/l (p=0.02). Cirrhosis was present in 3/10 sustained responders and 16/23 non-sustained responders (p=0.1). The hepatic liver iron content measured by chemical analysis showed a median hepatic iron in the sustained responders of 10.6 (range 3-23.5) mg/g dry weight, in the non-sustained responders the median liver iron content was 24.6 (4.4-73.7) mg/g dry weight (p=0.03). In general, IFN was well tolerated without serious side-effects allowing for the continuation of treatment. 13 TM pts, 4 female and 9 male median pre-treatment age 28 (range 11-42) YRS, were treated with IFN SC 3 MU TIW, self-administered together with ribavirin PO, 1 g/day for 6 MOS. Only pts who did not have sustained responses or

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relapsed after single agent therapy in our previous study, were selected for this treatment. All were anti-HCV and HCV-RNA positive. Pre-treatment liver biopsy showed cirrhosis in 11 and chronic active hepatitis in 2 pts. The median hepatic liver iron concentration was 21.13 (range 4.40-38.50) mg/g dry weight of liver. By the end of 6 MOS combination therapy 9 (69%) of the TM pts were HCV-RNA negative. 6 pts have been followed for longer than 3 MOS after the therapy and 4 remain HCV-RNA negative at 3, 3, 12 and 12 MOS. Neither response during therapy nor sustained response after therapy were associated with HCV serotype (5 pts had HCV serotype 1, 4 serotype 3, 4 were untypable), or with pre-treatment HCV-RNA titer (median pre-treatment HCV-RNA titer 65 x 10E5 (range 7-1700 x 10E5) genomes/ml). Transfusion requirements increased in all pts by up to 30% but returned to normal after completion of therapy. No other significant side-effects were observed. The sustained response rate of HCV infection with IFN treatment alone was higher (30.3%) in our study of TM pts than that reported in non-thalassemic pts where the typical sustained response rate is approximately 20%. The higher response rate may be explained by the lower mean age of our TM pts. TM pts with sustained response have lower serum ferritin, lower liver iron content compared with the non-sustained responders. The exact mechanism of the synergistic anti-viral effect of IFN and ribavirin is not known as yet. Ribavirin accumulates over a period of time in the ageing red cells causing hemolysis. In TM pts, this results in an increased blood requirement which may necessitate intensification of chelation therapy for 6 MOS. In TM pts, combination treatment made viremia undetectable in 69% of pts irrespective of viral serotype, viral titer, cirrhosis or high liver iron content. Long-term follow-up is needed to assess the eventual therapeutic effect of the combination treatment.

ICON Literature Search

Doc. ID. I96283027
Title Quantitative Liver Function (QLF) Testing In Patients Treated With Interferon (IFN) For Chronic Hepatitis C (CHC)
Journal Hepatology, (47th Ann. Mtg. Am. Assoc. Study Liver Dis., AASLD, Chicago, IL, USA, Nov. 8-12, 1996), Vol. 24, No. 4, Pt. 2, 1996, P. 160A
Authors Woolf, G. M.; Wagner, D. A.; Vierling, J. M.
Summary

IFN-alfa-2b treatment for CHC, can result in a CR with ALT normalization and loss of HCV RNA. However, it is unclear whether IFN improves liver function. 1 study of antipyrine clearance in CHC pts with sustained IFN response, documented improved QLF 1 YR after treatment but did not study HCV RNA levels. Thus, the authors tested QLF in 7 pt receiving IFN: 5 with moderate disease, 1 with Child's B cirrhosis and 1 with severe recurrent CHC after liver transplant who was concurrently treated with ribavirin. They assessed QLF before IFN and at MOS 3 and 6 of therapy. They used MEGX, an invasive test of microsomal function, and a non-invasive breath test (BT) measuring cytosolic oxidative function of 13 C-labeled phenylalanine (PBT). After lidocaine (1mg/kg) infusion, a MEGX blood level was measured after 30 MINS using a TDx analyzer (Abbott Labs). After ingesting 100 mg of 13C-phenylalanine, they measured breath 13CO2 every 10 MINS for 1 HR using gas isotope ratio/mass spectroscopy. HCV RNA was detected using PCR and quantitated using the bDNA assay before and after 6 MOS of IFN. 4 pts normalized ALT, 3 of whom became bDNA-. The other 3 pts remained bDNA+, and all pts remained PCR+. Paired analysis showed that QLF did not significantly change during the 6 MOS of therapy. There was also no statistically signfiicant difference in bDNA levels before and after IFN in either pts who became bDNA- or who remained bDNA+. There was no correlation of QLF with ALT, disease severity or bDNA level. The results indicate that normalization of ALT and bDNA is not accompanied by improvement of QLF during 6 MOS of IFN therapy. The authors speculate that failure of QLF improvement in 6 MOS may be due to the slower resolution of hepatic inflammation and cytokine production and/or the effect of viral replication. (This summary represents the entire text of the document.)

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MOS on IFN therapy	ALT (U/L)	bDNA (No.+)	PCR (No.+)	MEGX (ng/ml)	PBT (% oxidation)
Pre	128+/-29	7/7	7/7	49+/-12	4.6+/-0.8
3	36+/-7	---	---	41+/-8	4.3+/-1.0
6	44+/-8	4/7	7/7	42+/-9	4.6+/-0.9
p value	<0.05	---	---	>0.2	>0.7
Normals	<40	<3.5x10E3 Eq/ml	(-)	>70	>4

Data = Mean +/- S.E.

13/5/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09266133 97449199
Therapy of hepatitis C: overview.
Lindsay KL
Department of Medicine, University of Southern California, Los Angeles 90033-4581, USA.
Hepatology (UNITED STATES) Sep 1997, 26 (3 Suppl 1) p71S-77S, ISSN 0270-9139 Journal Code: GBZ
Languages: ENGLISH
Document type: CONSENSUS DEVELOPMENT CONFERENCE; CONSENSUS DEVELOPMENT CONFERENCE, NIH; JOURNAL ARTICLE; REVIEW
JOURNAL ANNOUNCEMENT: 9712
Subfile: INDEX MEDICUS
Based on the first decade of research on alpha interferon in viral hepatitis, one can conclude that up to 40% of patients with compensated chronic hepatitis C and elevated alanine aminotransferase (ALT) levels will respond at least transiently to interferon . Four forms of alpha interferon have been evaluated in large numbers of patients with chronic hepatitis C : alfa -2b , alfa-2a, alfa -n1, and consensus interferon (CIFN). Responses are defined on the basis of biochemical (ALT) or virological (hepatitis C virus [HCV] RNA testing by polymerase chain reaction [PCR]) end points, and as end-of-treatment response (ETR) or sustained response (SR). Biochemical ETR rates to 6 months of therapy range from 35% to 50%, and SR rates 6 months after treatment from 8% to 21%. Although 6-month treatment courses are associated with a significant rate of relapse, 12 months of initial treatment and re-treatment regimens markedly improve the SR rate. Long-term follow-up evaluation in patients with an SR to interferon consistently show long-lasting and significant clinical, virological, and histological improvement. Finally, baseline factors that have been shown to be associated with SR to 6 months of treatment are not accurate enough to predict response. Therefore, the best treatment strategy is a therapeutic trial. Further studies of interferon therapy of hepatitis C are needed to define better virological end points useful in stopping therapy, to understand and better manage significant side effects of interferon, and to evaluate the histological effects of interferon in biochemical nonresponders. Also needed is a better understanding of the causes of resistance to interferon. Finally, newer therapeutic regimens such as the use of induction therapy and combination therapies with ribavirin , other antiviral agents, cytokines, and cytokine modifiers are of primary importance in eventually developing safe and effective means of treatment of hepatitis C . (44 Refs.)

13/5/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09259290 97441764
Severe local cutaneous necrosis during treatment with interferon- alpha and ribavirin for chronic viral hepatitis C (letter)]
Necrose cutanee locale severe au cours d'un traitement par interferon alpha et ribavirine pour hepatite virale chronique C.
de Ledinghen V; Brudieux E; Beylot-Barry M; Belleannee G; Doutre MS; Couzigou P
Gastroenterol Clin Biol (FRANCE) 1997, 21 (6-7) p523-4, ISSN 0399-8320 Journal Code: FGX
Languages: FRENCH
Document type: LETTER
JOURNAL ANNOUNCEMENT: 9712
Subfile: INDEX MEDICUS
Tags: Case Report; Female; Human
Descriptors: Antiviral Agents--Adverse Effects--AE; * Hepatitis C --Drug Therapy--DT; * Interferon Alfa -2b --Adverse Effects--AE; * Ribavirin --Adverse Effects--AE; *Skin--Pathology--PA; Adult; Drug

Therapy, Combination; Necrosis
CAS Registry No.: 0 (Antiviral Agents); 36791-04-5 (Ribavirin) ; 99210-65-8 (Interferon Alfa-2b)

13/5/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09231177 97421215
The effect of interferon in combination with ribavirin on the plus and minus strands of hepatitis C virus RNA in patients with hepatitis]
He Y; Liu W; Zeng L
Department of Infectious Diseases, Xiehe Hospital, Tongji Medical University, Wuhan.
Chung Hua Nei Ko Tsa Chih (CHINA) Jan 1996, 35 (1) p32-5, ISSN 0578-1426 Journal Code: D7V
Languages: CHINESE Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE English Abstract
JOURNAL ANNOUNCEMENT: 9711
Subfile: INDEX MEDICUS
The effect of interferon in combination with ribavirin on the plus and minus strands of hepatitis C virus (HCV) RNA in patients with chronic hepatitis C (CHC) was studied by means of nested RT-PCR. The results showed that in those who respond to the combination of antiviral therapy, their increased serum ALT levels decreased to normal range, but more than half (55.56%) of these patients relapsed 24 weeks after cessation of the antiviral therapy. The positive rate of the plus strand HCV RNA in serum (92.31%) decreased significantly to 38.46% ($P < 0.005$) and that of the minus strands HCV RNA in peripheral blood mononuclear cells (PBMC, 76.92%) to 38.46% ($P < 0.05$) at the end of the treatment, but little effect on the plus strand HCV RNA in PBMC in these patients was found. Relapse occurred in patients whose plus and minus strands of HCV RNA in PBMC remained positive during treatment. These data indicated that absence of HCV RNA in serum do not mean complete clearance of HCV and can not predict a sustained therapeutic response. For evaluating the antiviral effect and prognosis it is essential to measure the plus and minus strands of HCV RNA in serum and PBMC simultaneously. The results of the combined antiviral therapy were similar to that of single interferon treatment; it seems that rib-a-virin do not enhance the antiviral effect of interferon.
Tags: Female; Human; Male; Support, Non-U.S. Gov't
Descriptors: Antiviral Agents--Therapeutic Use--TU; * Hepatitis C --Therapy--TH; *Interferon Alfa -2b --Therapeutic Use--TU; *Ribavirin --Therapeutic Use--TU; *RNA, Viral--Blood--BL; Adult; Chronic Disease; Drug Therapy, Combination; Hepatitis C --Blood--BL; Hepatitis C -Like Viruses--Genetics--GE; Middle Age; RNA, Double-Stranded--Blood--BL
CAS Registry No.: 0 (Antiviral Agents); 0 (RNA, Double-Stranded); 0 (RNA, Viral); 36791-04-5 (Ribavirin) ; 99210-65-8 (Interferon Alfa-2b)

13/5/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08772281 96351139
Combination treatment with interferon alfa- 2b and ribavirin for chronic hepatitis C in patients who have failed to achieve sustained response to interferon alone: Swedish experience.
Schvarcz R; Ando Y; Sonnerborg A; Weiland O
Department of Immunology, Microbiology, Pathology and Infectious Diseases, Karolinska Institute, Huddinge, Sweden.
J Hepatol (DENMARK) 1995, 23 Suppl 2 p17-21, ISSN 0168-8278 Journal Code: IBS
Languages: ENGLISH
Document type: CLINICAL TRIAL; CONTROLLED CLINICAL TRIAL; JOURNAL ARTICLE
JOURNAL ANNOUNCEMENT: 9612
Subfile: INDEX MEDICUS
BACKGROUND: Only 10-20% of patients treated with interferon alfa alone attain long-term benefits. More effective regimens are needed.

METHODS: Twenty Swedish patients with chronic hepatitis C virus infection, ten with a prior non-response and ten with a non-sustained response to interferon alfa treatment alone, were treated with interferon alfa -2b and ribavirin in combination for 24 weeks, then followed up for another 24 weeks. Patients received interferon alfa -2b subcutaneously 3 MU thrice weekly and oral ribavirin 1000-1200 mg/day. RESULTS: All ten patients with a prior non-sustained response to interferon alone had a sustained biochemical response with normal aminotransferase levels at follow-up; nine also had a sustained viral response with a negative HCV -RNA test in serum. Among the ten patients with a prior biochemical non-response to interferon alone, five had normal aminotransferase levels at the end of therapy; four were negative for HCV RNA in serum. At follow-up, three had normal aminotransferase levels and a negative HCV -RNA test in serum. No major adverse effect was seen, apart from fatigue and an expected fall in hemoglobin levels from a mean of 155 g/l to 124 g/l at the end of therapy. All patients completed the treatment schedule, but the ribavirin dose was reduced in one patient because of a fall in hemoglobin to 99 g/l. CONCLUSIONS: These results indicate that combination treatment with interferon alfa -2b and ribavirin offers a chance of sustained biochemical response and virus eradication in a subset of patients who fail to achieve sustained response with interferon alfa alone.

13/5/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08771117 96306676
Treatment of hepatitis C]
Traitement des hepatites C.
Trepo C; Habersetzer F; Bailly F; Berby F; Pichoud C; Berthillon P; Vitvitski L
Service d'Hepato-Gastroenterologie, Hopital Hotel-Dieu, LYON, France.
Pathol Biol (Paris) (FRANCE) Oct 1995, 43 (8) p716-24, ISSN 0369-8114 Journal Code: OSG
Languages: FRENCH Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL English Abstract
JOURNAL ANNOUNCEMENT: 9612
Subfile: INDEX MEDICUS
The treatment of hepatitis C virus (HCV) infections is essentially known for chronic hepatitis C and is mainly restricted to interferon alpha . Initial trials have indicated that around 50% of the patients with chronic hepatitis C respond to alpha interferon (administered at 3 MU, thrice weekly, during 6 months) by normalizing alanine aminotransferase at the end of therapy, although 25% were found to relapse after therapy. Normalization of biochemical tests is associated with an improvement in liver histological features and with decrease or loss of HCV from serum and liver. Response to therapy is influenced by both duration and dose levels of the treatment. Following studies which showed that higher doses and longer duration were more effective than the current recommendations of 3MU thrice weekly for 6 months have recently conducted to the recent recommendation of a 12 month course of therapy using 3 MU. The outcome of therapy was also shown to be negatively influenced by longer duration of disease and presence of cirrhosis. More recently, the critical role of virological markers has been emphasized with a lower rate of response in patients infected with the genotype 1 b and a high viral load. However, these factors do not certainly predict for an individual patient the quality of the response. Therapeutical goals are: to precisely define pre-treatment scores of response able to give each individual patient the optimal treatment regimen, non responders to interferon alpha and patients with a transient benefit of therapy. Thus, development of new treatments appears critical among which those with other interferons and above all the bitherapy using ribavirin and interferon alpha which may have a marked increase in efficacy in comparison with interferon alpha used as monotherapy. (58 Refs.)
Tags: Human
Descriptors: Hepatitis C --Therapy--TH; *Hepatitis C -Like Viruses

--Genetics--GE; *Hepatitis, Chronic Active--Therapy--TH; *Interferon - alpha --Therapeutic Use--TU; *RNA, Viral--Analysis--AN; Antiviral Agents --Therapeutic Use--TU; Interferon Alfa -2a--Therapeutic Use--TU; Interferon Alfa - 2b --Therapeutic Use--TU; Interferon - alpha --Adverse Effects--AE; Prognosis; Ribavirin --Therapeutic Use--TU; Time Factors

13/5/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08754505 95348668
Combined treatment with interferon alpha- 2b and ribavirin for chronic hepatitis C in patients with a previous non-response or non-sustained response to interferon alone.
Schvarcz R; Yun ZB; Sonnerborg A; Weiland O
Division of Infectious Diseases, Karolinska Institutet, Sweden.
J Med Virol (UNITED STATES) May 1995, 46 (1) p43-7, ISSN 0146-6615
Journal Code: I9N
Languages: ENGLISH
Document type: CLINICAL TRIAL; JOURNAL ARTICLE
JOURNAL ANNOUNCEMENT: 9511
Subfile: INDEX MEDICUS
Ten patients with chronic hepatitis C , six of whom had not responded and four of whom had responded in a non-sustained fashion to interferon -alpha treatment alone, were given interferon alpha -2b and ribavirin in combination during 24 weeks. Interferon alpha -2b was given subcutaneously, at a dose of 3 MU thrice weekly, together with ribavirin orally, at a dose of 1,000-1,200 mg/day. All four patients with a prior non-sustained response to interferon alone had normal alanine aminotransferase (ALT) levels at the end of treatment as well as during follow-up (> or = 24 weeks post treatment). Furthermore, all four lost serum HCV -RNA at the end of treatment and three continued to be negative during follow-up. Among patients with a prior non-response to interferon alone three of six had normal ALT levels at the end of treatment and one at follow-up. Two of six became HCV -RNA negative at cessation of treatment, one of whom was negative also at follow-up. All former non-sustained responders and one of six non-responder patients thus showed a sustained biochemical response with eradication of HCV -RNA from serum in all cases but one. It is concluded that combination therapy with interferon alpha - 2b and ribavirin offers a chance of sustained biochemical response with eradication of the viremia in patients who have not shown a persistent response to interferon alpha alone.

13/5/12 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

13635077 BIOSIS Number: 99635077
One year follow up of re-treatment with alpha- interferon in combination with ribavirin versus IFN for chronic hepatitis C
Porst H; Wiese M; Meisel H; Prost T
Dresden, Germany
Gastroenterology 112 (4 SUPPL.). 1997. A1361.
Full Journal Title: Digestive Disease Week and the 97th Annual Meeting of the American Gastroenterological Association, Washington, D.C., USA, May 11-14, 1997. Gastroenterology
ISSN: 0016-5085
Language: ENGLISH
Document Type: CONFERENCE PAPER
Print Number: Biological Abstracts/RRM Vol. 049 Iss. 008 Ref. 141642
Descriptors/Keywords: MEETING ABSTRACT; HUMAN; HEPATITIS C VIRUS; PATIENT; FEMALE; ADULT; PATHOGEN; GASTROENTEROLOGY; INFECTION; CHRONIC HEPATITIS C VIRUS INFECTION; ONE YEAR FOLLOW UP; ALPHA -2B - INTERFERON ; ANTIVIRAL-DRUG; ALPHA -2B -INTERFERON RE-TREATMENT; RIBAVIRIN ; ANTIVIRAL-DRUG; PHARMACOLOGY; HEPATITIS C VIRUS RNA; AMINOTRANSFERASES; VIRAL DISEASE; DIGESTIVE SYSTEM DISEASE; PHARMACOLOGICAL METHOD; THERAPEUTIC METHOD

13/5/13 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

13629555 BIOSIS Number: 99629555
Interferon versus ribavirin plus interferon in chronic hepatitis C previously resistant to interferon: A randomized trial
Salmeron J; Perez-Ruiz M; Ruiz-Extremera A; Torres C; Lavin I; Bellot V; Palacios A
Liver Unit, Univ. Hosp., Granada, Spain
Journal of Hepatology 26 (SUPPL. 1). 1997. 198.
Full Journal Title: 32nd Annual Meeting of the European Association for the Study of Liver, London, England, UK, April 9-12, 1997. Journal of Hepatology
ISSN: 0168-8278
Language: ENGLISH
Document Type: CONFERENCE PAPER
Print Number: Biological Abstracts/RRM Vol. 049 Iss. 008 Ref. 136120
Descriptors/Keywords: MEETING ABSTRACT; HUMAN; HEPATITIS C VIRUS; HCV ; PATIENT; PATHOGEN; INFECTION; GASTROENTEROLOGY; LIVER; VIRAL HEPATITIS; PHARMACOLOGY; INTERFERON -ALPHA -2B ; ANTIVIRAL-DRUG; RIBAVIRIN ; ANTIVIRAL-DRUG; CHRONIC HEPATITIS C VIRUS INFECTION; CHRONIC HCV INFECTION; INTERFERON -ALPHA -2B RESISTANCE; INTERFERON -ALPHA -2B TREATMENT; STATISTICAL ANALYSIS; RANDOMIZED TRIAL; HEPATITIS C VIRUS RNA; HCV RNA; RELAPSERS; NON-RESPONDERS; DIGESTIVE SYSTEM; DIGESTIVE SYSTEM DISEASE; VIRAL DISEASE; PHARMACOLOGICAL METHOD; THERAPEUTIC METHOD

13/5/14 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

13280768 BIOSIS Number: 99280768
Ribavirin- interferon vs interferon (alpha- 2b- IFN) alone in non responders to alpha- IFN in chronic hepatitis C
Pol S; Berthelot P; Brechot C
Hopital Necker, Paris, France
Hepatology 24 (4 PART 2). 1996. 356A.
Full Journal Title: 47th Annual Meeting and Postgraduate Courses of the American Association for the Study of Liver Diseases, Chicago, Illinois, USA, November 8-12, 1996. Hepatology
ISSN: 0270-9139
Language: ENGLISH
Document Type: CONFERENCE PAPER

13/5/15 (Item 4 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11936498 BIOSIS Number: 98536498
Combination treatment of alpha interferon- 2b (alpha IFN) and ribavirin in chronic hepatitis C genotype 4 patients resistant to interferon therapy
El-Zayadi A; Selim O; El Haddad S; Hamdy H
Fac. Med., Ain Shams Univ., Cairo, Egypt
Hepatology 22 (4 PART 2). 1995. 152A.
Full Journal Title: 46th Annual Meeting and Postgraduate Course of the American Association for the Study of Liver Diseases, Chicago, Illinois, USA, November 3-7, 1995. Hepatology
ISSN: 0270-9139
Language: ENGLISH
Document Type: CONFERENCE PAPER

13/5/17 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

10496186 EMBASE No: 97302949
Combination therapy with interferon alpha and ribavirin for chronic hepatitis C virus infection in thalassaemic patients.
Telper P.T.; Carson J.A.; Whitby K.; Grant P.R.; Yardumian A.; Hoffbrand A.V.; Wonke B.
Dr. B. Wonke, Department of Haematology, Whittington Hospital, Highgate Hill, London N19 5NF United Kingdom
British Journal of Haematology (United Kingdom) , 1997, 98/4 (850-855) CODEN: BJHEA ISSN: 0007-1048
DOCUMENT TYPE: Journal
LANGUAGES: English SUMMARY LANGUAGES: English
SUBFILES: 006; 020; 025; 048
NUMBER OF REFERENCES: 23
Hepatitis C virus (HCV) infection is common in multi-transfused thalassaemic patients, and, in combination with transfusional iron overload, can result in progressive liver disease. Therapy with interferon - alpha causes a sustained loss of HCV in only 15-25% of patients, and there is as yet no established effective therapy for those who fail to respond. We have conducted a pilot study of combination anti-viral therapy for patients who failed co respond, or relapsed after an initial response to single-agent interferon -alpha . Patients were treated for 6 months with interferon - alpha 2b , given subcutaneously three mega units thrice weekly, together with ribavirin , orally 1 g daily. 11 patients were enrolled, their median age was 24.9 years. 8/10 evaluable patients had cirrhosis on biopsy, five were infected with HCV type 1 and all but one had initial HCV RNA titres > 106 genomes/ml. Five patients (45.5%) had a sustained virological response with loss of serum HCV RNA for > 6 months after finishing therapy. There was no clear association between response to therapy and age, histology, HCV genotype, or HCV RNA titre. Transfusion requirements were significantly increased during the treatment phase, probably due to ribavirin -induced haemolysis, and this necessitated intensification of iron chelation therapy. Serum ferritin levels decreased significantly in those who responded. These results suggest that combination therapy is potent in clearing HCV infection, and may provide effective second-line therapy for thalassaemic patients who have failed to respond to interferon alpha monotherapy.

BRAND NAME/MANUFACTURER NAME: intron '/USA schering plough; viratek

13/5/18 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

10471573 EMBASE No: 97279443
Factors predictive of a beneficial response to therapy of hepatitis C
Davis G.L.; Lau J.Y.N.
Dr. G.L. Davis, Section of Hepatobiliary Diseases, University of Florida, PO Box 100214, Gainesville, FL 32610-0214 USA
Hepatology (USA) , 1997, 26/3 SUPPL. (122S-127S) CODEN: HPTLD ISSN: 0270-9139
DOCUMENT TYPE: Journal
LANGUAGES: English SUMMARY LANGUAGES: English
SUBFILES: 004; 030; 036; 048
NUMBER OF REFERENCES: 43
Alpha interferon is the only drug that has been shown to be effective in the treatment of chronic hepatitis C , but only half of patients respond, either transiently or permanently. Pretreatment features that are associated with a greater likelihood of response to short courses of interferon include low hepatitis C virus (HCV) RNA levels, viral genotypes 2 or 3, and the absence of fibrosis or cirrhosis on liver biopsy. Each of these features is more predictive of sustained response (SR) than the end-of-treatment response (ETR). However, the accuracy of these

features in predicting response in individual patients is poor. Furthermore, there are several limitations to using these factors in the clinical management of patients. Most importantly, they were identified in 6-month treatment trials. Longer treatment or combination of interferon with ribavirin reduces relapses and will therefore lessen the association of these factors with long-term response. In addition, changes in the definition of treatment end points and the technology used to measure HCV RNA might change the association between these predictive factors and response. The best predictor of a treatment response is the early normalization of the serum alanine aminotransferase (ALT) level during interferon treatment. HCV RNA loss during treatment may also be helpful in predicting response, but it is probably no better than serum ALT levels and is expensive. In summary, several clinical and virological features are associated with higher response rates to interferon treatment. Although pre- treatment factors do not accurately predict treatment outcome in individuals, they may be helpful in counseling patients and making treatment decisions.

EMTAGS:
Infection 0310; Diagnosis 0140; Therapy 0160; Heredity 0137; Virus 0761; Economic aspects 0139; Mammal 0738; Human 0888; Methodology 0130; Conference paper 0061; Priority journal 0007; Enzyme 0990
DRUG DESCRIPTORS:
alanine aminotransferase--endogenous compound--ec; virus rna; alpha interferon --clinical trial--ct; alpha interferon --drug combination--cb ; alpha interferon --drug dose--do; alpha interferon --drug therapy --dt; alpha interferon --pharmacoeconomics--pe; interferon --clinical trial--ct; interferon--drug combination--cb; interferon--drug dose--do; interferon--drug therapy--dt; interferon--pharmacoeconomics--pe; ribavirin --drug combination--cb; ribavirin --drug therapy--dt; dna; corticosteroid; immunosuppressive agent; recombinant alpha2b interferon --clinical trial --ct; recombinant alpha2b interferon --drug combination--cb; recombinant alpha2b interferon --drug dose--do; recombinant alpha2b interferon --drug therapy--dt; recombinant alpha2b interferon --pharmacoeconomics --pe
MEDICAL DESCRIPTORS:
*hepatitis c --diagnosis--di; *hepatitis c --drug therapy--dt prediction; genotype; hepatitis c virus; liver biopsy; liver cirrhosis --complication--co; liver cirrhosis--diagnosis--di; liver fibrosis --complication--co; liver fibrosis--diagnosis--di; cost; treatment outcome; algorithm; patient selection; polymerase chain reaction; human; clinical trial; meta analysis; conference paper; priority journal

13/5/19 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

10471571 EMBASE No: 97279441
* Therapy of hepatitis C: Alpha interferon and ribavirin
Reichard O.; Schvarcz R.; Weiland O.
Dr. O. Reichard, Division of Infectious Diseases, Karolinska Institute, Huddinge Hospital, S-141 86 Huddinge Sweden
Hepatology (USA) , 1997, 26/3 SUPPL. (108S-111S) CODEN: HPTLD ISSN: 0270-9139
DOCUMENT TYPE: Journal
LANGUAGES: English SUMMARY LANGUAGES: English
SUBFILES: 004; 030; 048
NUMBER OF REFERENCES: 29
Ribavirin is a nucleoside analogue that has been evaluated as a therapy of chronic hepatitis C alone and in combination with alpha interferon . Ribavirin is well absorbed orally and is typically given in doses of 1,000 to 1,200 mg/d. Three randomized, placebo-controlled studies comprising more than 150 patients have shown that therapy with ribavirin alone for 24 to 48 weeks resulted in a significant reduction in serum alanine aminotransferase (ALT) levels during therapy. However, ribavirin therapy did not lead to a substantial reduction in hepatitis C virus (HCV) RNA levels; almost all patients remained viremic, and serum aminotransferase levels increased to pretreatment values when therapy was

stopped. The most common adverse event was a moderate and reversible hemolysis during treatment that caused a decrease in hemoglobin by 10% to 20% of baseline levels. Combination therapy of ribavirin with alpha interferon has demonstrated promise both in pilot studies and a recently completed randomized controlled trial. Ribavirin in standard doses combined with alpha interferon in doses of 3 million units (MU) three times weekly for 6 months was found to significantly improve the sustained biochemical and virological response rates compared with interferon alone. Combination therapy offers a promise to become standard therapy for patients with nonsustained response to alpha interferon alone, because the majority of such patients achieve a durable response after treatment with combination therapy. However, nonresponders to alpha interferon alone rarely achieve a sustained beneficial response to combination treatment. For interferon-naive patients, combination therapy is superior to therapy with alpha interferon alone in achieving sustained biochemical and virological responses, but the combination demonstrates clear-cut superiority only in patients with unfavorable profiles for a response to interferon, in particular patients with high levels of HCV RNA. The optimal use and regimen of combination therapy awaits further investigation. New antiviral agents are still needed for the proportion of patients who do not respond to alpha interferon , even in combination with ribavirin .

EMTAGS:
Infection 0310; Diagnosis 0140; Therapy 0160; Virus 0761; Iatrogenic disease 0300; Pharmacokinetics 0194; Mammal 0738; Human 0888; Major clinical study 0150; Methodology 0130; Controlled study 0197; Oral drug administration 0181; Conference paper 0061; Priority journal 0007; Adverse drug reaction 0198; Enzyme 0990; Heredity 0137
DRUG DESCRIPTORS:
*alpha interferon --adverse drug reaction--ae; *alpha interferon --clinical trial--ct; *alpha interferon --drug combination--cb; *alpha interferon --drug dose--do; *alpha interferon --drug therapy--dt; * ribavirin --adverse drug reaction--ae; *ribavirin --clinical trial--ct; * ribavirin --drug administration--ad; *ribavirin --drug combination--cb; * ribavirin --drug dose--do; *ribavirin --drug therapy--dt; *ribavirin --pharmacokinetics--pk; *ribavirin --pharmacology--pd; *alpha2b interferon --adverse drug reaction--ae; *alpha2b interferon --clinical trial--ct; *alpha2b interferon --drug combination--cb; *alpha2b interferon --drug dose--do; *alpha2b interferon --drug therapy--dt alanine aminotransferase--endogenous compound--ec; virus rna; hemoglobin --endogenous compound--ec; iron--endogenous compound--ec
MEDICAL DESCRIPTORS:
*hepatitis c --diagnosis--di; *hepatitis c --drug therapy--dt polymerase chain reaction; hepatitis c virus; hemolysis--side effect --si; drug absorption; liver transplantation; depression--side effect--si; fatigue--side effect--si; anemia--diagnosis--di; anemia--side effect--si; dose response; human; major clinical study; clinical trial; randomized controlled trial; controlled study; oral drug administration; conference paper; priority journal

13/5/21 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

10349178 EMBASE No: 97157076
Consensus panel advocates prolonged interferon treatment for chronic hepatitis C
American Journal of Health-System Pharmacy (USA) , 1997, 54/10 (1140+1145) CODEN: AHSPE ISSN: 1079-2082
DOCUMENT TYPE: Journal
LANGUAGES: English
SUBFILES: 006; 048

EMTAGS:
Infection 0310; Diagnosis 0140; Therapy 0160; Epidemiology 0400; Organization and management 0142; Malignant neoplastic disease 0306; Mammal 0738; Human 0888; Subcutaneous drug administration 0183; Note 0063;

Priority journal 0007; Enzyme 0990; Heredity 0137
DRUG DESCRIPTORS:
*interferon--drug combination--cb; *interferon--drug therapy--dt
alpha2b interferon --drug therapy--dt; alanine aminotransferase
--endogenous compound--ec; virus rna--endogenous compound--ec; alpha2a
interferon --drug therapy--dt; alphan1 interferon--drug therapy--dt; beta
interferon--drug therapy--dt; ribavirin --drug combination--cb; ribavirin
--drug therapy--dt
MEDICAL DESCRIPTORS:
*hepatitis c --diagnosis--di; *hepatitis c --drug therapy--dt; *
hepatitis c --epidemiology--ep
organization; food and drug administration; liver cirrhosis--diagnosis--di;
liver cirrhosis--epidemiology--ep; liver cirrhosis--surgery--su; liver cell
carcinoma--epidemiology--ep; mortality; drug efficacy; liver biopsy; liver
transplantation; human; subcutaneous drug administration; note; priority
journal

13/5/22 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

10335326 EMBASE No: 97117548
Results of hepatitis C treatment with interferon alone or associated
with other drugs
RESULTATS DU TRAITEMENT DE L'HEPATITE C PAR L'INTERFERON SEUL OU EN
ASSOCIATION A D'AUTRES MEDICAMENTS
Serfaty L.
L. Serfaty, Unite d'Hepato-Gastroenterologie, Hopital Saint-Antoine, 184,
Rue du Faubourg Saint-Antoine, F-75571 Paris Cedex 12 France
Gastroenterologie Clinique et Biologique (France) , 1997, 21/1 BIS
(S154-S166) CODEN: GCBID ISSN: 0399-8320
DOCUMENT TYPE: Journal
LANGUAGES: French
SUBFILES: 004; 006; 048
NUMBER OF REFERENCES: 136

EMTAGS:
Infection 0310; Therapy 0160; Etiology 0135; Virus 0761; Malignant
neoplastic disease 0306; Mammal 0738; Human 0888; Major clinical study 0150
; Methodology 0130; Controlled study 0197; Intramuscular drug
administration 0184; Intravenous drug administration 0182; Conference paper
0061; Enzyme 0990
DRUG DESCRIPTORS:
*recombinant alpha2b interferon--clinical trial--ct; *recombinant alpha2b
interferon--drug administration--ad; *recombinant alpha2b interferon
--drug combination--cb; *recombinant alpha2b interferon --drug therapy
--dt; *recombinant alpha2b interferon --pharmacology--pd; *recombinant
alpha2a interferon --clinical trial--ct; *recombinant alpha2a
interferon --drug administration--ad; *recombinant alpha2a interferon
--drug combination--cb; *recombinant alpha2a interferon --drug therapy
--dt; *recombinant alpha2a interferon --pharmacology--pd; *beta
interferon --clinical trial--ct; *beta interferon--drug administration--ad;
*beta interferon--drug combination--cb; *beta interferon--drug therapy--dt;
*beta interferon--pharmacology--pd; *lymphoblast interferon--clinical trial
--ct; *lymphoblast interferon--drug administration--ad; *lymphoblast
interferon--drug combination--cb; *lymphoblast interferon--drug therapy--dt
; *lymphoblast interferon --pharmacology--pd; *alpha interferon
--clinical trial--ct; *alpha interferon --drug administration--ad; *
alpha interferon --drug combination--cb; *alpha interferon --drug
therapy--dt; *alpha interferon --pharmacology--pd; *recombinant gamma
interferon--drug administration--ad; *recombinant gamma interferon--drug
combination--cb; *recombinant gamma interferon--drug therapy--dt; *
recombinant gamma interferon--pharmacology--pd
ursodeoxycholic acid--drug combination--cb; ursodeoxycholic acid--drug
therapy--dt; corticosteroid--drug combination--cb; corticosteroid--drug
therapy--dt; nonsteroid antiinflammatory agent--drug combination--cb;
nonsteroid antiinflammatory agent--drug therapy--dt; ribavirin --drug
combination--cb; ribavirin --drug therapy--dt; alanine aminotransferase

--endogenous compound--ec; aspartate aminotransferase--endogenous compound --ec
MEDICAL DESCRIPTORS:
*chronic hepatitis--drug therapy--dt; *hepatitis c --drug therapy--dt; *hepatitis c --etiology--et; *hepatitis c virus
drug mixture; liver cell carcinoma; drug tolerability; recurrent infection; human immunodeficiency virus; hemodialysis; human; major clinical study; clinical trial; randomized controlled trial; controlled study; intramuscular drug administration; intravenous drug administration; conference paper

13/5/24 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE

10328041 EMBASE No: 97119917
Initial experience with combined treatment of chronic viral hepatitis C (preliminary communication)
PRVNI ZKUSENOSTI S DVOJKOMBINACNI LECBOU CHRONICKE VIROVE HEPATITIDY C (PREDBEZNE SDELENI)
Urbanek P.; Marecek Z.; Brodanova M.
Czech Republic
Ceska a Slovenska Gastroenterologie (Czech Republic) , 1997, 51/2 (52-55)
CODEN: CSGAE ISSN: 1210-7824
DOCUMENT TYPE: Journal
LANGUAGES: Czech SUMMARY LANGUAGES: English; Czech
SUBFILES: 004; 030; 048
NUMBER OF REFERENCES: 7
The authors submit their initial experience with chronic viral hepatitis C by a combination of ribavirin and interferon alpha in the Czech Republic. The results are preliminary and were obtained in a group of patients selected with regard to the effect produced by previous monotherapy with interferon alpha . In three patients rapid normalization of serum transaminase activity was achieved which was associated with the elimination of the virus. In one patient the transaminase activity declined, however, so far without elimination of the virus. The slowest decline of ALT is observed in a patient primarily resistant to interferon alpha , where so far elimination of the virus did not occur. The presented results are consistent with data in the literature and are very promising for patients with chronic hepatitis C .

BRAND NAME/MANUFACTURER NAME: virazole /icn galenika; intron a/schering plough

EMTAGS:
Infection 0310; Therapy 0160; Mammal 0738; Human 0888; Clinical article 0152; Male 0041; Female 0042; Adult 0018; Oral drug administration 0181; Subcutaneous drug administration 0183; Article 0060; Enzyme 0990
DRUG DESCRIPTORS:
*alpha interferon --drug therapy--dt; *alpha interferon --drug combination--cb; *alpha interferon --clinical trial--ct; *ribavirin --drug therapy--dt; *ribavirin --drug combination--cb; *ribavirin --clinical trial--ct; *recombinant alpha2b interferon --drug therapy--dt ; *recombinant alpha2b interferon --drug combination--cb; *recombinant alpha2b interferon --clinical trial--ct
aminotransferase--endogenous compound--ec
MEDICAL DESCRIPTORS:
*hepatitis c --drug therapy--dt; *chronic hepatitis--drug therapy--dt
drug efficacy; human; clinical article; clinical trial; male; female; adult ; oral drug administration; subcutaneous drug administration; article

13/5/26 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE

10222498 EMBASE No: 97028588
A practical guide to the use of interferons in the management of hepatitis virus infections
Saracci G.; Rizzetto M.
Italy
Drugs (New Zealand) , 1997, 53/1 (74-85) CODEN: DRUGA ISSN: 0012-6667
DOCUMENT TYPE: Journal
LANGUAGES: English SUMMARY LANGUAGES: English
SUBFILES: 030; 048
NUMBER OF REFERENCES: 74
The recommended interferon dosage for patients with chronic hepatitis and typical hepatitis B virus (HBV) infection is 10MU 3 times weekly for 4 to 6 months; with such a regimen sustained alanine aminotransferase (ALT) normalisation, liver histology improvement, clearance of HBV DNA and seroconversion from hepatitis B e antigen (HBeAg) to anti-HBe are obtained in about 40% of treated patients. Patients with elevated disease activity (high ALT values, active chronic hepatitis, low HBV DNA level) tend to respond better to therapy; Oriental patients and immunocompromised patients are not ideal candidates for interferon. Patients with chronic hepatitis B and the HBeAg-negative variant should be given intermediate dosages (6 to 9MU thrice weekly) of interferon for prolonged periods (12 months); however, even with this approach, the relapse rate is high (> 60%) during the follow-up. In chronic hepatitis D virus (HDV) infection, therapy with 9 to 10MU of interferon 3 times weekly for 12 months induces a transient remission in disease (ALT normalisation, HDV RNA clearance) in more than 50% of treated patients, but a sustained response is found in less than 20% of patients. In such disease, baseline predictive factors of long term response are still unknown. In chronic hepatitis C , treatment with 3 to 5MU of interferon given 3 times weekly for 6 to 12 months induces a sustained remission in no more than 30% of treated patients. Probable predictive factors of long term response are: low viraemia, genotype other than 1, absence of cirrhosis, low intrahepatic iron content, low nucleotide diversity of the envelope 2 gene of the hepatitis C virus. Prolonged (> 12 months) therapeutic courses seem to enhance the sustained response rate; in nonresponders/relapsers, combined therapy (interferon plus indomethacin, interferon plus ketoprofen, interferon plus ribavirin) is promising but randomised controlled trials are needed in order to establish the real efficacy and safety of such therapeutic regimens.

EMTAGS:
Infection 0310; Therapy 0160; Histology 0330; Heredity 0137; Iatrogenic disease 0300; Mammal 0738; Human 0888; Review 0001; Adverse drug reaction 0198; Enzyme 0990
DRUG DESCRIPTORS:
*interferon--adverse drug reaction--ae; *interferon--drug combination--cb; *interferon--drug dose--do; *interferon--drug therapy--dt
alanine aminotransferase--endogenous compound--ec; virus dna--endogenous compound--ec; hepatitis b(e) antigen--endogenous compound--ec; hepatitis b(e) antibody--endogenous compound--ec; virus rna--endogenous compound--ec; iron--endogenous compound--ec; indometacin--drug combination--cb; indometacin--drug therapy--dt; ketoprofen--drug combination--cb; ketoprofen --drug therapy--dt; ribavirin --drug combination--cb; ribavirin --drug therapy--dt; paracetamol--drug therapy--dt; alpha2b interferon --drug therapy--dt; alpha2a interferon --drug therapy--dt
MEDICAL DESCRIPTORS:
*chronic hepatitis--drug therapy--dt
hepatitis b--drug therapy--dt; liver histology; seroconversion; disease activity; immune deficiency; recurrence risk; delta agent hepatitis--drug therapy--dt; remission; hepatitis c --drug therapy--dt; viremia; genotype; liver cirrhosis; envelope gene; drug efficacy; drug safety; drug contraindication; headache--drug therapy--dt; headache--side effect--si; myalgia--drug therapy--dt; myalgia--side effect--si; asthenia--drug therapy --dt; asthenia--side effect--si; fever--drug therapy--dt; fever--side effect--si; rigor--drug therapy--dt; rigor--side effect--si; fatigue--side effect--si; anorexia--side effect--si; alopecia--side effect--si;

convulsion--side effect--si; psychosis--side effect--si; thyroid disease --side effect--si; kidney failure--side effect--si; myocarditis--side effect--si; human; review

13/5/30 (Item 14 from file: 73)
DIALOG(R)File 73:EMBASE

9468618 EMBASE No: 95029978
Treatment of chronic hepatitis C
LE TRAITEMENT DE L'HEPATITE CHRONIQUE C
Pawlotsky J.M.; Dhumeaux D.
Service de Bacteriologie-Virologie, CHU Henri Mondor, 51, Av. Mal. de Lattre-de-Tassigny, F 94010 Creteil Cedex France
PRESSE MED. (France) , 1995, 24/3 (161-163) CODEN: PRMEE ISSN: 0755-4982
LANGUAGES: French SUMMARY LANGUAGES: English
SUBFILES: 026; 048
The antiviral and immunomodulating properties of alpha interferon have led to its current use for the treatment of hepatitis C . Though there is no established treatment duration, a 6 month regimen is usually prescribed. Taking serum transaminase elevation as the outcome criteria, most clinical trials have reported that 50% of the patients are non-responders or partial responders. It is also clearly established that relapse (renewed rise in transaminase levels) occurs in one half of the complete responders. Thus after a 3-year follow-up, complete long-term response is achieved in only 20% of the patients. Alpha interferon is consequently an undeniable progress in the treatment of chronic hepatitis C , yet raises a number of important questions. Besides chosing the most reliable and informative response criteria to evaluate treatment effectiveness, research is being conducted to isolate factors predicting response and to establish an 'ideal' protocol. The question of who should be treated also still remains to be answered. Alternative combination therapies such as ursodeoxycholic acid or non-steroid antiinflammatory drugs, could also be beneficial. The most promising development are antiviral drugs with a direct and specific action on viral replication and expression. Ribavirine , the only compound available to date, is under study. In the future the clinician will have several treatment protocols to choose from for adapting management to each individual patient. Clinical cure should signify complete elimination of the causative agent both from the serum and hepatic tissue.

BRAND NAME/MANUFACTURER NAME: roferon a/hoffmann la roche; intron a/ schering plough

EMTAGS:
Infectious diseases 0310; Therapy 0160; Mammal 0738; Human 0888; Short survey 0002; Enzyme 0990
DRUG DESCRIPTORS:
*alpha interferon --drug therapy--dt; *nonsteroid antiinflammatory agent --drug therapy--dt; *ursodeoxycholic acid--drug therapy--dt; *ribavirin --drug therapy--dt
aminotransferase--endogenous compound--ec; recombinant alpha2a interferon ; recombinant alpha2b interferon
MEDICAL DESCRIPTORS:
*hepatitis c --drug therapy--dt
drug efficacy; human; clinical trial; short survey

13/5/31 (Item 15 from file: 73)
DIALOG(R)File 73:EMBASE

9391451 EMBASE No: 94345365
Therapy of chronic viral hepatitis
Goeser T.; Theilmann L.
Medizinische Universitatsklinik, Bergheimerstrasse 58, D-69115 Heidelberg Germany
INT. J. CLIN. PHARMACOL. THER. (Germany) , 1994, 32/11 (571-576) CODEN: ICTHE ISSN: 0174-4879
LANGUAGES: English SUMMARY LANGUAGES: English
SUBFILES: 004; 030; 048
Interferon is currently the only established therapeutical option for chronic viral hepatitis. Sustained response can be achieved in approximately 25% of patients with chronic HBV or HCV infection. Results in chronic HDV infection are disappointing. Whether combination of interferon with other lymphokines or antiviral drugs will lead to higher response rates, remains to be established. The argument that interferon will only place spontaneous seroconversion on an earlier date has not been disproved yet. Long-term follow-ups are necessary to show that therapy with interferon will improve survival and reduce the incidence of hepatocellular carcinoma in patients with chronic viral hepatitis.

EMTAGS:
Infectious diseases 0310; Diagnosis 0140; Therapy 0160; Etiology 0135; Virus 0761; Cancer 0306; Epidemiology 0400; Immunological procedures 0102; Mammal 0738; Human 0888; Human experiment 0104; Review 0001; Enzyme 0990; Heredity 0137; Adverse drug reaction 0198; Iatrogenic disease 0300
DRUG DESCRIPTORS:
lymphokine--drug combination--cb; lymphokine--drug therapy--dt; antivirus agent--drug combination--cb; antivirus agent--drug therapy--dt; aminotransferase--endogenous compound--ec; virus dna; alpha interferon --adverse drug reaction--ae; alpha interferon --clinical trial--ct; alpha interferon --drug combination--cb; alpha interferon --drug therapy--dt; alpha interferon --pharmacology--pd; hepatitis b surface antigen--endogenous compound--ec; hepatitis b(e) antigen--endogenous compound--ec; paracetamol--drug therapy--dt; corticosteroid--drug therapy --dt; alpha2b interferon --clinical trial--ct; alpha2b interferon --drug therapy--dt; ribavirin --clinical trial--ct; ribavirin --drug combination--cb; ribavirin --drug therapy--dt
MEDICAL DESCRIPTORS:
*chronic hepatitis--diagnosis--di; *chronic hepatitis--drug therapy--dt ; *chronic hepatitis--etiology--et
patient care; hepatitis b virus; hepatitis c virus; hepatitis delta virus; drug efficacy; seroconversion; follow up; survival; liver cell carcinoma--complication--co; liver cell carcinoma--epidemiology--ep; morbidity; aminotransferase blood level; virus replication; drug effect; influenza--drug therapy--dt; influenza--side effect--si; leukopenia--side effect--si; thrombocytopenia--side effect--si; enzyme linked immunosorbent assay; human; clinical trial; meta analysis; review

13/5/32 (Item 16 from file: 73)
DIALOG(R)File 73:EMBASE

9339170 EMBASE No: 94291101
Therapy for chronic hepatitis C
Davis G.L.; Lau J.Y.N.; Lim H.L.
Section of Hepatobiliary Diseases, JHMHC, University of Florida, PO Box 100214, Gainesville, FL 32610-0214 USA
GASTROENTEROL. CLIN. NORTH AM. (USA) , 1994, 23/3 (603-613) CODEN: GCNAE ISSN: 0889-8553
LANGUAGES: English SUMMARY LANGUAGES: English
SUBFILES: 004; 048
Recombinant interferon alfa -2b , the only approved treatment for chronic hepatitis C in the United States, suppresses rather than eradicates virus and is effective in normalizing serum alanine

aminotransferase levels and improving histology in half of patients. Other interferons show promise as alternative agents and some, including fibroblast (beta) and other alfa recombinants, have been approved for use in other countries. Limited studies with corticosteroids and nucleoside analogues, including acyclovir and ribavirin , have shown little potential for clinical application as single agents.

13/5/33 (Item 17 from file: 73)
DIALOG(R)File 73:EMBASE

9277511 EMBASE No: 94220693
Interferon therapy in chronic hepatitis C virus infection
Weiland O.
Dept. of Infectious Diseases 173, Huddinge Hospital, Karlinska Institute, Huddinge, S-141 86 Huddinge Sweden
FEMS MICROBIOL. REV. (Netherlands) , 1994, 14/3 (279-288) CODEN: FMREE ISSN: 0168-6445
LANGUAGES: English SUMMARY LANGUAGES: English
SUBFILES: 004; 030
Antiviral treatment of chronic hepatitis C with interferon is reviewed. Alpha -interferon , both recombinant alpha -2a. -2b and human lymphoblastoid interferon given at a dose of greater than or equal to 3MU t.i.w. for 6-12 months will result in normalisation of ALT levels (complete response) in some 50-60% of treated patients with chronic hepatitis C virus (HCV) infection. Approximately half of the complete responders to interferon will relapse within 6 months once treatment is withdrawn (non-sustained response). Longer treatment schedules (6 vs. 12 months) seem to diminish the relapse rate and increase the percentage of sustained response. In patients with sustained response to interferon treatment with continuously normal ALT levels greater than or equal to 6 months after treatment stop a concomitant eradication of the viraemia is usually seen. whereas a non-sustained or non-response to interferon usually will indicate a continuous viraemia. Factors predictive of a favourable response are low pretreatment HCV RNA levels in serum, genotypes other than type II according to Okamoto, short disease duration, female gender and less pronounced liver damage, whereas high serum HCV RNA levels, having genotype II and cirrhosis, are predictive of a less favourable response. Patients with a sustained response and eradication of the viraemia will also improve their liver inflammation with diminishing scores for portal inflammation, piecemeal necrosis, lobular inflammation and also fibrosis after treatment. For non-responders and non-sustained responders to interferon, ribavirin especially in combination with interferon will offer some hope for the future.

BRAND NAME/MANUFACTURER NAME: intron a/schering plough; roferon/hoffmann la roche; wellferon/burroughs wellcome

13/5/35 (Item 19 from file: 73)
DIALOG(R)File 73:EMBASE

9257234 EMBASE No: 94216742
Treatment of chronic hepatitis C
Reichard O.
Immunol Microbiol Pathol Infect Dis, Division of Infectious Diseases, Karolinska Hosp, Huddinge Hospital, Huddinge Sweden
SCAND. J. INFECT. DIS. SUPPL. (Norway) , 1994, -/95 (1-56) CODEN: SJISA ISSN: 0300-8878
LANGUAGES: English SUMMARY LANGUAGES: English
SUBFILES: 004; 006; 048
Ribavirin treatment of patients with chronic hepatitis C virus (HCV) infection - Ten patients were treated with oral ribavirin 12 weeks, all anti-HCV positive and HCV RNA positive in serum as detected by PCR prior to treatment. Pretreatment liver histological findings showed chronic persistent hepatitis (CPH) and chronic active hepatitis (CAH) in 5 patients each. The median serum ALT level at enrolment 3.15 microkat/l

(range 1.22-7.79) decreased significantly to 1.25 microkat/l (range 0.78-2.04) at the end of treatment ($p<0.005$). After treatment relapse to pretreatment levels occurred in all patients within 12 weeks. HCV RNA remained detectable during treatment in all patients, a decrease in titer was seen in 4 patients, whereas it remained unchanged in 5 and increased in one. Adverse reactions were mild and fully reversible after treatment cessation. The most apparent side effect was a mild reversible hemolysis. The decrease in s-ALT levels during treatment, the mild side effects and the oral route of administration indicate that ribavirin may be a useful agent for treatment of chronic HCV infections. Interferon (IFN) treatment of patients with chronic HCV infection - Forty patients received recombinant IFN alfa -2b subcutaneously at a dose of 3 MU t.i.w. for an intended 60 weeks regardless of their treatment response. Serum ALT levels normalised in 24/40 (60%) patients during treatment whereas 16 (40%) were nonresponders. The response was sustained during 6 months follow-up after treatment cessation in 15/24 (62.5%) responders. At treatment start 39/40 (97.5%) patients had HCV RNA detectable in serum. At treatment cessation 1 (7%), 6 (67%) and 9 (56%) of biochemical sustained, non-sustained and non-responders, respectively, were HCV RNA positive. Six months post treatment the corresponding figures were 0 (0%), 8 (89%) and 14 (88%). All 14 sustained responders continued to be non-viremic 2 years after treatment cessation. Histological evaluation with a numerical scoring system revealed that sustained responders benefited most from the treatment. They showed a significant decrease in portal inflammation, piecemeal necrosis, spotty necrosis and fibrosis during treatment. A biopsy 2 years post treatment performed in 7 sustained responders showed sustained histological improvement in all scored parameters. Initially, patients with a sustained response had a significantly lower median pretreatment HCV RNA level than the combined group of patients with a non-sustained or non-response, whereas outcome of treatment was not related to the HCV genotype or the pretreatment histological findings. Repeated IFN treatments for non-sustained responders - Nine patients with non-sustained response to repeated IFN treatment courses were evaluated for histological outcome on a long-term basis. The mean follow-up time between the initial biopsy before treatment, and the last biopsy after the final treatment was 44 months (range 34-53). In contrast to previous results in untreated patients, the histological picture in most patients improved or remained unchanged during the follow-up period, during which time the patients received repeated IFN treatment courses. The mean score for the 4 histological necro-inflammatory parameters thus decreased, although not significantly. The results presented seem to indicate that repeated courses of IFN alfa in non-sustained responders will slow down further histological deterioration.

BRAND NAME/MANUFACTURER NAME: introna

EMTAGS:
Infectious diseases 0310; Therapy 0160; Epidemiology 0400; Virus 0761; Diagnosis 0140; Cancer 0306; Mammal 0738; Human 0888; Male 0041; Female 0042; Major clinical study 0150; Human tissue, cells or cell components 0111; Adult 0018; Oral and intragastric drug administration 0181; Subcutaneous drug administration 0183; Human experiment 0104; Priority journal 0007; Article 0060; Adverse drug reaction 0198; Iatrogenic disease 0300

DRUG DESCRIPTORS:
*ribavirin --adverse drug reaction--ae; *ribavirin --drug combination--cb ; *ribavirin --drug therapy--dt; *methisoprinol--drug therapy--dt; * recombinant alpha2b interferon --adverse drug reaction--ae; *recombinant alpha2b interferon --clinical trial--ct; *recombinant alpha2b interferon --drug combination--cb; *recombinant alpha2b interferon --drug dose--do; *recombinant alpha2b interferon --drug therapy--dt antivirus agent--adverse drug reaction--ae; antivirus agent--drug dose--do; antivirus agent--drug therapy--dt

MEDICAL DESCRIPTORS:
*hepatitis c --drug therapy--dt; *hepatitis c --epidemiology--ep; * hepatitis c --therapy--th
hepatitis c virus; prevalence; virus transmission; virus diagnosis; polymerase chain reaction; diagnostic procedure; clinical feature; chronic hepatitis--drug therapy--dt; chronic hepatitis--epidemiology--ep;

chronic hepatitis--therapy--th; liver cell carcinoma; immunotherapy; myalgia--side effect--si; nausea--side effect--si; fatigue--side effect--si ; hair loss--side effect--si; headache--side effect--si; polymyositis--side effect--si; hypothyroidism--side effect--si; human; male; female; major clinical study; human tissue; adult; oral drug administration; subcutaneous drug administration; clinical trial; priority journal; article

13/5/37 (Item 21 from file: 73)
DIALOG(R)File 73:EMBASE

9120180 EMBASE No: 94069137
New approaches to the treatment of chronic viral hepatitis B and C
Regenstein F.
Ochsner Medical Institutions, 1514 Jefferson Highway, New Orleans, LA 70121 USA
AM. J. MED. (USA) , 1994, 96/1 A (1A47S-1A51S) CODEN: AJMEA ISSN: 0002-9343
LANGUAGES: English SUMMARY LANGUAGES: English
SUBFILES: 004; 006; 048
Interferon treatment of hepatitis B and C virus (HBV, HCV) infections has been hampered by overall initial response rates of <50%, a relapse rate that is >50% for patients with chronic HCV , and rare responses in individuals with chronic HBV who are immunosuppressed or immunologically tolerant to the HBV. Because of these difficulties, the efficacy of other therapeutic agents is being vigorously explored. Among the immunomodulatory agents being evaluated, thymosin appears to be a promising new therapy for HBV. Results from an ongoing multicenter trial evaluating thymosin are expected next year. A variety of nucleoside analogues with anti-viral activity against the HBV have also been identified. Several of the more active agents deserve further study in clinical trials. In chronic HCV infection, only interferon therapy has been extensively studied. Ribavirin alone may have some value, but its precise role in the treatment of chronic HCV will require additional testing. Interferon therapy for patients with chronic HBV or HCV infection represents an important first step in the treatment of these disorders. In the absence of an ideal antiviral agent, however, combinations of the available antiviral and immunomodulatory agents or synergistic combinations of antiviral agents need to be studied in order to achieve better therapeutic responses.

EMTAGS:
Infectious diseases 0310; Therapy 0160; Mammal 0738; Human 0888; Nonhuman 0777; Human experiment 0104; Priority journal 0007; Conference paper 0061
DRUG DESCRIPTORS:
*thymosin--clinical trial--ct; *thymosin--drug combination--cb; *thymosin --drug therapy--dt; *alpha2b interferon --drug combination--cb; * alpha2b interferon --drug therapy--dt; *nucleoside analog--drug therapy --dt; *ribavirin --drug combination--cb; *ribavirin --drug therapy--dt; * prednisone--drug combination--cb; *prednisone--drug therapy--dt granulocyte macrophage colony stimulating factor--drug therapy--dt; beta interferon--drug combination--cb; beta interferon--drug therapy--dt; gamma interferon--drug therapy--dt; interleukin 2--drug therapy--dt; levamisole --drug therapy--dt; transfer factor--drug therapy--dt; aciclovir--drug therapy--dt; vidarabine--drug therapy--dt; 2',3' dideoxynucleoside derivative--drug therapy--dt; foscarnet--drug therapy--dt; fialuridine --drug therapy--dt; ganciclovir--drug therapy--dt; suramin--drug therapy --dt; zidovudine--drug combination--cb; zidovudine--drug therapy--dt; ursodeoxycholic acid--drug combination--cb; ursodeoxycholic acid--drug therapy--dt
MEDICAL DESCRIPTORS:
*hepatitis b--drug therapy--dt; *hepatitis c --drug therapy--dt drug response; immunomodulation; human; nonhuman; clinical trial; multicenter study; priority journal; conference paper

13/5/41 (Item 25 from file: 73)
DIALOG(R)File 73:EMBASE

8768523 EMBASE No: 93072238
The clinical significance of hepatitis C viral infection
Weber J.R.; Wright T.L.
Department of Medicine, University of California, San Francisco, CA USA
INFECT. MED. (USA) , 1992, 9/9 (17-24+49) CODEN: INMDE ISSN: 0749-6524
LANGUAGES: English SUMMARY LANGUAGES: English
SUBFILES: 004; 006; 026; 048

EMTAGS:
Virus 0761; Epidemiology 0400; Infectious diseases 0310; Diagnosis 0140; Therapy 0160; Cancer 0306; Immunological procedures 0102; Mammal 0738; Human 0888; Female 0042; Major clinical study 0150; Clinical article 0152; Case report 0151; Adult 0018; Review 0001; Enzyme 0990
DRUG DESCRIPTORS:
*alpha2b interferon --drug therapy--dt; *alpha2b interferon --drug dose--do; *alpha interferon --drug therapy--dt
aminotransferase--endogenous compound--ec; gamma interferon--drug therapy --dt; ribavirin --drug therapy--dt; corticosteroid--drug therapy--dt; beta interferon--drug therapy--dt
MEDICAL DESCRIPTORS:
*hepatitis c virus--epidemiology--ep; *hepatitis--diagnosis--di; * hepatitis--therapy--th; *hepatitis--drug therapy--dt; *liver cell carcinoma ; *chronic liver disease
bone marrow suppression; autoimmunity; blood transfusion; immunoblotting; drug cost; recurrent disease; liver transplantation; virus transmission; liver cirrhosis; human; female; major clinical study; clinical article; case report; adult; review
EMCLAS DRUG CODES:
03700000000; 03800000000

CAS REGISTRY NO.: 99210-65-8; 9031-66-7; 82115-62-6; 36791-04-5

13/5/44 (Item 2 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci

15670469 Genuine Article#: WY319 Number of References: 45
Title: Prophylaxis and treatment of hepatitis C.
Author(s): Poupon R (REPRINT) ; Serfaty L
Corporate Source: HOP ST ANTOINE,SERV HEPATOGASTROENTEROL, 184 RUE FAUBOURG ST ANTOINE/F-75571 PARIS 12//FRANCE/ (REPRINT)
Journal: ANNALES DE GASTROENTEROLOGIE ET D HEPATOLOGIE, 1997, V33, N1 (JAN-MAR), P34-38
ISSN: 0066-2070 Publication date: 19970100
Publisher: EXPANSION SCI FRANCAISE, 31 BLVD LATOUR MAUBOURG, 75007 PARIS, FRANCE
Language: French Document Type: ARTICLE
Geographic Location: FRANCE
Subfile: CC CLIN--Current Contents, Clinical Medicine
Journal Subject Category: GASTROENTEROLOGY & HEPATOLOGY
Abstract: Interferon is the only treatment shown to be effective on hepatitis C in controlled trials. The response to treatment is generally assessed in terms of a return to normal transaminase activity, but also negative PCR testing for viral RNA and histopathological examination of the liver. At a dose of 3 MU three times a week for 6 months, 25 % of patients have a persistent return to normal transaminase activity, 25 % relapse when interferon is withdrawn, and the remaining 50 % have persistently high levels at the and of treatment and are considered resistant. The rate of persistent responses increases to 40 % when treatment is extended to one year. Viral RNA becomes undetectable in the serum of 80 % of these responders. Most also have a histological improvement, but so do a number of patients who relapse or who are resistant. In the longer term, interferon could prevent the onset of liver cancer in patients with viral C cirrhosis. Interferon is generally well tolerated at the doses currently used, most side effects (hematologic, neuropsychiatric and thyroid disorders) resolving when treatment is continued. The following factors are clearly predictive of the response to interferon: young age, short time since onset. absence of cirrhosis, lower-level viremia, and infection by HCV genotypes other than Ib. Interferon is markedly less effective in immunodeficient patients (transplant, HIV infection, etc,). Several add-on treatments have been tried, but ribavirin appears to be the most promising, both during initial interferon therapy and for patients who relapse or are resistant to a first course. Interferon therapy of the acute phase of hepatitis C significantly reduces the risk of chronic liver disease. There is no vaccine against HCV infection.
Descriptors--Author Keywords: viral hepatitis C ; drug therapy ; interferon alfa 2a ; interferon alfa 2b
Identifiers--KeyWord Plus(R): CHRONIC ACTIVE HEPATITIS ; INTERFERON - ALFA ; VIRUS-INFECTION; RANDOMIZED TRIAL; NON -A ; NON -B ; URSODEOXYCHOLIC ACID; ALPHA -INTERFERON ; VIRAL-HEPATITIS ; RECOMBINANT

insert search terms

CAS REGISTRY NO.: 98530-12-2 (recombinant alpha2b interferon); 128-13-2 , 2898-95-5 (ursodeoxycholic acid); 36791-04-5 (ribavirin); 9000-86-6, 9014-30-6 (alanine aminotransferase); 9000-97-9 (aspartate aminotransferase

Division Director's Memorandum

NDA:	**20-903**
Drug and indication:	**ribavirin in combination with interferon alfa-2b (Rebetol™/Intron® A)**
Dose:	**600 mg twice daily/ 3 million units three times weekly**
Applicant:	**Schering-Plough Research Institute**
Submission dated:	**December 3, 1997**
Date of Memorandum:	**June 1, 1998**

In this application, the sponsor requests approval for oral ribavirin in combination with the licensed biologic product, interferon alfa-2b, for treatment of chronic hepatitis C infection in patients with compensated liver disease who have relapsed following alfa interferon monotherapy. The primary source of evidence supporting the safety and efficacy of this combination is the results of two randomized, placebo-controlled clinical trials, conducted in 345 male and female adult patients. Additional information on safety is provided by data from ongoing studies in other patient populations and by open-label experience. In both of the controlled trials, patients randomized to receive ribavirin in combination with interferon had a significantly higher rate of virologic response than did patients in the interferon monotherapy groups. Rates of histologic improvement were also higher in combination therapy recipients than in monotherapy recipients. However, the differences between treatments were less pronounced on the histologic endpoint than on the virologic endpoint.

The safety profile of interferon has been previously well-characterized. Additional serious safety issues raised by combination treatment with ribavirin include the frequent occurrence of hemolytic anemia (which has the potential for more serious complications in patients with cardiovascular disease) and the risk of teratogenicity. Safe use of this product will therefore require a commitment on the part of providers and patients to adhere to the labeled recommendations for close monitoring of clinical and laboratory parameters, and the need for effective contraception during and for six months after a course of therapy. To partially address the need for intensive patient education, a detailed patient package insert has been developed through collaboration with DDMAC.

I concur with the recommendation of the primary reviewers and with the consensus of the Antiviral Drugs Advisory Committee that this application be approved. Hepatitis C is a serious disease without adequate treatment options and the established risks of treatment appear to be appropriately balanced by the potential for clinical benefit, in patients similar to those enrolled in

the submitted trials. However, several questions about the use of this therapy remain unanswered by the information provided. Importantly, there is currently no information on whether short-term improvement (in virology and histology) predicts a reduction in risk for long-term serious sequelae (such as cirrhosis, hepatocellular cancer and death). Additionally, there is currently no information on the safety and efficacy of this therapy in other patient populations (including those with more advanced liver disease, patients coinfected with HIV, pediatric patients, liver transplant recipients, and patients without previous treatment experience). Because dose-finding studies were not conducted prior to initiation of these phase III studies, data is needed to address whether lower doses of ribavirin in combination with interferon might be similarly effective but safer. The applicant has committed to address these issues in phase IV by submitting data from ongoing studies or by conducting new investigations.

Because ribavirin is a known teratogen in animals and interferon has been shown to have abortifacent and other adverse animal reproductive effects, the sponsor has committed to establishment of a pregnancy registry to provide information to women who may have become pregnant during, or following treatment. This registry will also provide a mechanism for prospective monitoring of pregnancy outcomes in exposed women. Additionally, the need for effective contraception in male and female patients is prominently discussed in multiple sections of the package insert (including in a "black box" warning, in *Contraindications*, in *Precautions - Information for Patients*, *Precautions - Impairment of Fertility*, *Precautions - Pregnancy,* and *Dosage and Administration*).

Other phase IV commitments include:

There are no outstanding regulatory issues.

Heidi M. Jolson, M.D., M.P.H.
Director, HFD-530

cc:
NDA20-903
HFD-530/Jolson/Fleischer/Crescenzi

c:\h\20903DD.doc