

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-903

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

In accordance with section 306(k) of the Food, Drug and Cosmetic Act, Schering Corporation certifies that, with respect to this application, it did not and will not knowingly use the services of any persons that have been debarred under the provisions of Section 306(a) or (b) of the Act.

APPEARS THIS WAY
ON ORIGINAL



In accordance with 21 CFR 314.50 (d)(1)(v), Schering Corporation certifies that a true copy of Section 4, Chemistry, Manufacturing and Control Information of this original NDA is being sent to FDA's New Jersey District Office.

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Patent Information Pursuant to 21 CFR § 314.53

RE: COMBINED THERAPY OF INTRON ®A(INTERFERON ALFA-2b, RECOMBINANT)AND TRADENAME(RIBAVIRIN) TO TREAT CHRONIC HEPATITIS C VIRAL INFECTIONS IN INTERFERON RELAPSE PATIENTS

- I. A. Trade Name:** INTRON ®A
Active Ingredient: Interferon alfa-2b, recombinant
Strength: 3 million IU
Dosage Form: Solution for Injection
- I. B. Trade Name:** TRADENAME
Active Ingredient: Ribavirin (1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide)
Strength: 200 mg
Dosage Form: Capsule

Pursuant to the provisions of 21 CFR § 314.53 we are hereby supplying the patent information for the captioned Schering Corporation ("Schering") NDA:

- I. A. U.S. Patent No.** 4,530,901
Expiration Date: July 23, 2002
Type of Patent: Recombinant DNA molecules and hosts transformed with such molecules which produce interferon alfa-2, recombinant, which is one of the active ingredients in the combined therapy for treating chronic hepatitis C viral infections for which approval is currently being sought.
Patent Owner: Biogen N.V.



II. B. U.S. Patent No. 4,211,771
Expiration Date: July 8, 1999
Type of Patent: Method of treating viral infections in viral diseases in humans using ribavirin, one of the active ingredients in the combined therapy for treating chronic hepatitis C viral infections for which approval is currently being sought.
Patent Owner: ICN

The undersigned declares (a) that the above-stated U.S. Patent No. 4,530,901 covers interferon-alfa-2b, recombinant, as a composition of matter per se, and (b) that interferon alfa-2b, recombinant is the active ingredient in INTRON A, which is an active ingredient in the combination therapy for treating chronic hepatitis C viral infections and (c) that the above-stated U.S. Patent No. 4,211,771 covers a method of using ribavirin to treat viral infections in mammals, and that (d) ribavirin is an active ingredient used in the combination therapy.

The undersigned further declares that approval for the combination therapy of INTRON A and ribavirin is being sought under Section 505 of The Federal Food, Drug and Cosmetic Act, 21 USC § 355 and that a claim of patent infringement under U.S. Patent 4,211,771 and 4,530,901 could reasonably be asserted if a person not licensed by the owners of each of the above-stated U.S. patents engaged in the manufacture, use or sale of Intron A or ribavirin for use in the combination therapy.

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EXCLUSIVITY SUMMARY FOR NDA # 20-903

Trade Name **INTRON A/REBETOL**
Applicant Name **Schering Corporation**
Approval Date If Known

Generic Name **interferon alfa-2b, recombinant/ribavirin**
HFD # **530**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES / X / NO / /

b) Is it an effectiveness supplement?

YES / / NO / X /

If yes, what type? (SE1, SE2, etc.)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no").

YES / X / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / X / NO / ___ /

If the answer to (d) is "yes", how many years of exclusivity did the applicant request?

3 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES / ___ / NO / X /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / ___ / NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / ___ / NO / ___ /

If "yes", identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one-never-before-approved active moiety and one previously approved active moiety, answer "yes". (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved).

YES / X / NO / ___ /

If "yes", identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ Interferon alfa-2b, recombinant

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES", GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant". This section should be completed only if the answer to PART II, Question 1 or 2 was "yes".

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies). If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes", then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO / ___ /

IF "NO", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / X / NO / ___ /

If "no", state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / X / NO / ___ /

(1) If the answer to 2(b) is "yes", do you personally know of any reason to disagree with the applicant's conclusion?

YES / / NO / /

If yes, explain: _____

(2) If the answer to 2(b) is "no", are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no", identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES / X / NO / ___ / Explain: _____

Investigation #2

IND # _____ YES / X / NO / ___ / Explain: _____

b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / ___ / Explain _____ NO / ___ / Explain _____

Investigation #2

YES / ___ / Explain _____ NO / ___ / Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest)

YES / / NO / X /

If yes, explain: _____

Signature of
Project Manager

5/15/98
Date

Signature of
Division Director

6/2/98
Date

cc: Orig NDA Div File HFD-85

CLAIM for EXCLUSIVITY

1. Pursuant to the provisions of Sections 505 (c) (3) (D) (iii) and 505 (j) (4) (D) (iii) of the Food, Drug and Cosmetic Act and 21 CFR 314.108 (b) (4), the applicant claims three (3) years of exclusivity for its Combined Therapy of Intron A (Interferon alfa-2b, recombinant) and Tradename (Ribavirin) to treat chronic hepatitis C viral infection in interferon relapse patients.
2. The applicant certifies that to the best of the applicant's knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in 21 CFR 314.108 (a).
3. A list of all published studies and publicly available reports of clinical investigations known to the applicant through a computer-assisted literature search that are relevant to the Combined Therapy for which the applicant is seeking approval is provided as Attachment 1.
4. The applicant certifies that it has thoroughly searched the scientific literature through a computer-assisted search of the ICON (Interferon Communication Network) database and the Dialog database encompassing the subfiles, MEDLINE, BIOSIS, EMBASE and SciSearch, for English and non-English literature relating to clinical studies of Combined Therapy of Intron A (Interferon alfa-2b, recombinant) and Tradename (Ribavirin) to treat chronic hepatitis C viral infection in interferon relapse patients during the period from 11/5/87 to 11/5/97.
5. To the best of the applicant's knowledge, the list of scientific literature pertaining to INTRON A and Tradename (Ribavirin) is complete and accurate and, in the opinion of the applicant, the publicly available information does not provide a sufficient basis, without reference to the new clinical investigations in this application, for the approval of the Combined Therapy of Intron A (Interferon alfa-2b, recombinant) and Tradename (Ribavirin) to treat chronic hepatitis C viral infection in interferon relapse patients. The applicant's opinion that the studies or reports are insufficient is based on the following:
 - The literature does not contain adequate characterization of the safety and efficacy profiles of INTRON A and Tradename (Ribavirin) in this Combined Therapy, which are established by the data from the new clinical investigations conducted by the sponsor under IND 49,923 and are included in this application.
 - The overall clinical program requirements of this application, and the design of the studies were discussed with the Food and Drug Administration's Division of Antiviral Drug Products prior to study initiation. These studies were also reviewed by the Division during a June 30, 1997 pre-NDA meeting. Such studies are not available in the published literature without reference to the sponsor's new clinical investigations.



6. The applicant was the sponsor named in the Form FDA-1571 for IND 49,923 under which the new clinical investigations were conducted.

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Attachment 1

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* Results of Clinical Investigation Included in NDA 20-903



SCHERING-PLOUGH RESEARCH INSTITUTE

ICON Literature Search

Doc. ID. I97129015
Title NIH Expert Panel Discuss Management of Hepatitis C
Journal Lancet, Vol. 349, No. 9057, 1997, P. 1002
Authors Bhattacharya, I.
Summary Since the identification of hepatitis C virus (HCV) in 1989, chronic HCV infection has become a major concern for clinicians. In the USA, 4 million people are infected with HCV and more than 8000 people die from HCV-associated illness each YR. With a large pool of infected but symptom-free individuals and no effective intervention, the death rate from HCV infection will triple in the next 2 decades. With these grim statistics in mind, the US National Institutes of Health convened an expert panel to discuss treatment strategies and related issues. The only effective (and approved) therapy for this disease in the USA is 3 MU of IFN-alfa-2b (IFN) injected TIW for 6 MOS. Less than half of all pts treated have an end-of-treatment response (ETR), as defined by normalization of serum alanine aminotransferase (ALT) values and loss of serum HCV RNA. 6 MOS after the end of treatment, only 10-20% of pts have a sustained response (SR)-ie, normal ALT values and no detectable circulating virus. The panel agreed that there were sufficient data to support IFN treatment for 12 MOS. Longer therapy does not affect ETR, but it does increase SR rates to 20-30% of all treated pts. The panel recognized the future value of combination therapy, preferably in clinical trials, with IFN and ribavirin; small-scale clinical trials have suggested SR rates of up to 50% after 6 MOS of combination treatment. Proper pt selection for treatment was critical, stressed the panel. With IFN therapy, the best results are achieved in pts with a persistently elevated ALT, positive HCV RNA, and a liver biopsy showing active disease without marked cirrhosis. How to manage pts who are HCV positive, but who have no clinical evidence of liver disease and minimal biopsy abnormalities remains unclear. The benefits of trying to eradicate the virus in cirrhotic pts were also left undefined. Because 85% of pts exposed to HCV become chronically infected, the panel established specific guidelines to reduce the risk of transmission, including "safe-sex" practices and endorsement of needle-exchange programs. They recommended that all HCV-infected people receive hepatitis A and B vaccines. Unfortunately, the likelihood of a hepatitis C vaccine in the near future is remote because HCV mutates often into multiple quasispecies. (This summary represents the entire text of the document.)

ICON Literature Search

Doc. ID. I96283093
Title HCV Recurrence After OLT: A Pilot Study of Ribavirin Therapy following Initial Combination with IFN
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. 293
Authors Bizollon, T.; Palazzo, U.; Chevallier, M.; Trepo, C.; et al
Summary The aim of this study was to evaluate the efficacy of post-transplant therapy with IFN in combination with ribavirin, followed by maintenance with ribavirin alone. Methods: 20 HCV RNA positive pts (mean age: 53 YRS, treated for 6 MOS with IFN alfa-2b (3 MU weekly) in combination with ribavirin 1 g/day followed by ribavirin alone for 6 MOS. The interval between OLT and the initiation of therapy was 11 MOS. Mean ALT before treatment was 241 UI/L (range: 78-548). Mean Knodell score was 6.4 (range: 2-12). Mean pre-treatment HCV RNA by bDNA was 125 ge.Eq/mlx10E6. Results: After 6 MOS of combination therapy, all pts normalized ALT and 10 pts (50%) cleared HCV RNA from their serum. Mean bDNA was 3 Eq/mlx10E6 (vs 125 before treatment, $p < 0.05$). Mean histological score was 3.9 (vs. 6.4 before treatment, $p < 0.05$). During ribavirin monotherapy, ALT remained normal in all but one pt while HCV RNA reappeared in 5. Mean bDNA after 12 MOS was 3.5 Eq/mlx10E6 (vs 125 before treatment, $p < 0.53$). Mean Knodell score at 12 MOS was 3 (vs 6.4 before treatment, $p < 0.05$). 3 pts stopped ribavirin because of anemia. They were again treated for 6 MOS by combination therapy and erythropoietin, with successful results and satisfactory tolerance. None of the pts experienced graft rejection during combination therapy. Conclusion: These results confirm the efficacy and the good tolerance (no rejection) of early combination therapy followed by maintenance ribavirin for HCV liver graft reinfection. (This summary represents the entire text of the document.)

ICON Literature Search

Doc. ID. I94295008 -
Title WHAT OPTIONS ARE LEFT WHEN HEPATITIS C DOES NOT RESPOND TO INTERFERON? PLACEBO-CONTROLLED BENELUX MULTICENTRE RETREATMENT TRIAL ON RIBAVIRIN MONOTHERAPY VERSUS COMBINATION WITH INTERFERON
Journal J. HEPATOL. (29TH ANN. MTG. EASL, 7 - 10 SEPT. 1994, ATHENS, GREECE), VOL. 21, SUPPL. 1, 1994, P. 17
Authors BROUWER, J. T.; NEVENS, F.; MICHIELSEN, P.; SCHALM, S. W.; ET AL.
Summary During treatment of hepatitis C with IFN about 40% of pts are complete non-responsive; these pts are not likely to profit from higher dosages or longer duration of IFN alone. To test the hypothesis that they might profit from drugs acting on a different antiviral level, the authors randomly allocated 65 pts to either 24 WKS of placebo monotherapy, Ribavirin monotherapy (1200 mg/day) or to combination of Ribavirin (1200 mg/day) and IFN-alpha-2b (3 MU TIW). All 65 pts had been treated with 3-6 MU of IFN-alpha-2b TIW for at least 24 WKS, and none sustained ALT normalization or HCV-RNA disappearance during therapy. At present 44 pts are evaluable with at least 24 WKS follow-up after treatment. Out of 29 with monotherapy (either Ribavirin or placebo) only two temporarily normalized ALT levels (7%, 95% CI 1-23%). In contrast 13/15 pts on the combination normalized their ALTs during therapy (87%, CI 60-98%), and 3 had a sustained response during follow-up (20%, CI 4-48%, p=0.03), with viral clearance in 2. Side effects were restricted to flu-like symptoms and moderate hemolytic anemia, without additional toxicity in the combination. In conclusion, combination of IFN-alpha-2b and Ribavirin is able to induce biochemical remission in most HCV pts who had a complete non-response to standard monotherapy with IFN. The proportion of sustained response might be further increased by modification of dosage and duration of the combination. (This summary represents the entire text of the document.)

ICON Literature Search

Doc. ID. I97281026 -

Title Genotype 1 Non-Responder Patients Treated with High Daily IFN-alfa 2b Plus Ribavirin (R) Doses Achieve Rapid and Profound Viral Reduction

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. 216

Authors Buti, M.; Olive, G.; Esteban, J.I.; Esteban, R.; Doran, Z.

Summary Less than 10% of hepatitis C pts infected with genotype 1 achieve sustained response with the standard 3 MU TIW IFN therapy. Viral kinetics studies have shown HCV may replicate in <24 HRS generating >10E9 copies/day. Daily administration of IFN has been proposed to achieve a better response.

The aim of this study was to determine the effect of higher and more frequent dosing of IFN-alfa2b on viral load in previously virologically non-responder pts to the standard IFN schedule (3 MU TIW x 24 WKS) and to determine the response rate. 10 pts with CAH, infected with genotype 1 (8 with 1b, 2 with 1a) were allocated to receive IFN-alfa2b 5 MU daily or TIW for 4 WKS then 5 MU TIW until 24 WKS, plus R for the entire treatment period (1,000-1,200 mg/day). HCV RNA was detected using a sensitive PCR with a limit of detection of 100 copies/ml (Superquant, NGI, California) at baseline, 12 HRS, 24 HRS, 72 HRS, 96 HRS, 1 WK and BIW until WK 4.

ALT levels were normalized in 4/5 pts in each group by WK 8. Baseline virology was higher in the QD group, but not significant ($p < 0.13$). The HCV RNA profile of the 2 groups are shown in the table. A 2 log reduction in HCV RNA by WK 4 was achieved in 1/5 TIW pts and 3/5 QD pts. The pts who achieved a 2 log reduction by WK 4 were HCV RNA-negative by WK 8. At 24 HRS after the 1st dose, the combined groups had a reduction of HCV RNA of 1.16 logs ($p < 0.002$) compared with a reduction of 1.43 logs in the QD group and 0.91 logs in the TIW group after 4 WKS. The 4 WK HCV RNA reduction was statistically significant in both groups ($p < 0.03$ for QD and $p < 0.001$ for TIW, t-test 2 side).

Safety and tolerability of the combination was good with the most common adverse event being reversible hemolytic anemia.

In conclusion: Pts previously non-responders virologically can achieve negativity with administration of 5 MU QD of IFN-alfa2b + R. The combination was safe, well tolerated, and because of encouraging results should be further evaluated. (This summary represents the entire text of the document.)

Table Found on next page...

ICON Literature Search

--Continuation Of Doc. No. I97281026 --

HCV RNA (copies/ml)	0 HRS	24 HRS	1 WK	4 WKS
QD	5.1x10E6	4.4x10E5	5.9x10E5	2.2x10E3
TIW	2.7x10E6	1.5x10E5	5.8x10E5	8.2x10E3

ICON Literature Search

Doc. ID. I97281022
Title Differential Effect of IFN Alpha-2B and Ribavirin on the HCV-RNA Level in Primary Cultures of Human Hepatocytes Derived from Chronic HCV Carriers and of Human Hepatocytes Infected in Vitro
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. 215
Authors Clarysse, C.; Nevens, F.; Pirenne, J.; Yap, S.H.; et al.
Summary In order to examine the direct influence of IFN- α 2b and ribavirin, which are currently available drugs for clinical use, on the HCV replication, the HCV RNA level was determined quantitatively (Amplicor HCV Monitor test, Roche) in primary cultures of human hepatocytes derived from explant livers obtained from pts undergoing liver transplantation due to terminal hepatitis C cirrhosis, and in primary cultures of human hepatocytes infected in vitro by overnight incubation with 20% HCV RNA+ plasma. IFN (500 U/ml) or ribavirin (20 ug/ml) were not efficient to suppress the HCV RNA level of human hepatocytes derived from explant liver up to 14 days during the cultures, while IFN (50 U/ml, 1/10th of the former dose) but not ribavirin (20 ug/ml) was sufficient to eliminate HCV (HCV RNA was also not detectable by qualitative assay) from primary cultures of human hepatocytes infected in vitro within 12 days of culture. The level of HCV RNA was obviously lower in human hepatocyte cultures infected in vitro as compared to that of explant livers from chronic HCV carriers. These findings support the concept that treatment with IFN in early phase of HCV infection is efficient. In addition, IFN is more likely to eliminate HCV if the viral load is low. (This summary represents the entire text of the document.)

ICON Literature Search

Doc. ID. I95093004

Title INTERFERON THERAPY OR CHRONIC HEPATITIS C: UPDATE 1995

Journal TREATMENTS IN HEPATOLOGY, (ABSTR. MTG. THERAPY IN LIVER DIS., BARCELONA, MAR. 1995), P. 155 - 160

Authors DAVIS, G. L.

Summary In 1995, the topic of therapy of chronic hepatitis C must be focused on IFN since other therapeutic alternatives remain limited. IFN was 1st considered as an option because of its availability through studies of pts with hepatitis B and D. The 1st report of IFNs activity are from a small pilot study of 10 pts conducted at the NIH Liver Unit by Dr Hoofnagle and colleagues. 8 of the 10 pts normalized their ALT levels, low doses of IFN were required as compared to that of hepatitis B. Relapse commonly occurred with discontinuation of treatment and pts responded to retreatment. Finally Dr Hoofnagle suggested that longer treatment periods might improve the durability of response. Over the next 4 YRS, 4 randomized controlled studies tested the effects of a fixed dose of 3 MU IFN-alfa-2b administered TIW for 6 MOS. All reported studies showed a significant response to treatment. Again, despite differences in the treatment regime and geographic location of the studies, the results were quite similar. Shido and colleagues showed that hepatitis C virus RNA fell in most pts who had a CR to treatment, but not in non-responders to IFN. A large US multicenter study reported by Lindsay and colleagues examined the question of whether higher doses of IFN might increase response. In fact, there was no difference in either initial or sustained response for doses of 3, 5, or 10 MU for 6 MOS. Although higher doses could hardly be recommended by this data, the study did appear to show a higher sustained response in pts initially treated with a high dose and continued at a lower dose for a total of 12 MOS. Several studies have now suggested that a longer treatment period increases the durability of the response. Metreau and colleagues in France showed a doubling of the sustained response rate from 14% - 29% with extension of the 3 MU TIW from 6-12 MOS. There is now clear evidence that response is significantly impacted by the degree of inflammation and fibrosis on liver biopsy, the level of viral replication, viral genotype, and the diversity of the virus in the individual, so called quasispecies. The degree of histologic inflammation determines response to IFN. Several reports have emphasized a higher response in mild disease than in cirrhotic pts. The amount of viral replication in serum affects the response to IFN. Several studies have now shown that pts who achieved a CR and sustained response to IFN, had lower levels of HCV replication. As with liver biopsy findings, viral levels should not be used to exclude pts from treatment, but may give a clue to which pts are less likely to relapse. Certainly, 1 of the most critical determinants of response to IFN is the viral genotype. Pts with genotypes 2 and 3 have a 2- to 4-fold higher response to IFN than do pts with genotype 1. Finally, it has been reported that viral diversity might influence natural history of HCV infections as well as response to treatment. Each pt through

ICON Literature Search

--Continuation Of Doc. No. I95093004 --

mutation of his or her infecting virus, develop minor genomic variations called quasispecies. Response to IFN is more likely in pts with lesser degrees of HCV diversity. Several potential adjuncts to IFN treatment have been proposed. 2 studies with ribavirin in combination with IFN deserve comment. This agent has shown antiviral activity against a number of viruses in vitro, and pilot studies have suggested activity against HCV. Both appeared to increase the initial and sustained responses compared to IFN alone. Future hopes lay in new agents and combinations of these with IFNs. The authors believe that what is done in clinical practice must be based on well designed clinical trials that confirm these fascinating but preliminary data and ideas.

ICON Literature Search

Doc. ID. I97263014
 Title Factors Predictive of a Beneficial Response to Therapy of Hepatitis C
 Journal Hepatology, Vol. 26, No. 3, Suppl. 1, 1997, P. 122 - 127
 Authors Davis, G. L.; Lau, J. Y. N.
 Summary IFN-alpha is the only drug that has been shown to be effective in the treatment of chronic hepatitis C, but only half of pts respond, either transiently or permanently. Pretreatment features that are associated with a greater likelihood of response to short courses of IFN 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 pts is poor. The purpose of this review is to examine how accurately clinical and virological features predict a response to IFN treatment in pts with chronic hepatitis C. Furthermore, the implications of pt selection strategies based on pretreatment characteristics are evaluated. Finally, the practical use and limitations of these predictive factors as they apply to pts and clinicians are discussed. To examine the practical implications of selecting pts by pretreatment criteria, studies were selected in which treatment response could be correlated to the presence or absence of these factors. Eligible articles were reported controlled studies in which either histology, serum HCV RNA levels, or viral genotype could be correlated with the response at the end of treatment or the end of follow-up, or both. Responses to IFN were defined by convention. ETR was defined by normalization of the serum alanine aminotransferase (ALT) level by the end of the treatment period. SR was defined as ETR followed by persistently normal ALT levels for at least 6 MOS after treatment was discontinued.

ETR was more commonly reported in pts with pretreatment HCV-RNA levels less than 1×10^6 genomes/mL. Although the difference in response rates to short course of IFN was marked between those with low or high levels of viremia, the predictive value of a low HCV RNA level for either ETR or SR was low (48% and 71%, respectively). The accuracy of HCV RNA for correctly predicting response was only modest (57% for ETR and 68% for SR). Hepatitis C genotype has also been associated with treatment response. Pts with HCV genotypes 1a and 1b respond poorly to treatment compared with those with genotypes 2 and 3. As with viral levels, viral genotype other than 1 has a low predictive value for response (58% for ETR and 55% for SR), and its accuracy in predicting treatment outcome was poor (58% for ETR and 72% for SR). Other viral characteristics have also been reported to be associated with response to IFN treatment. Response to treatment was more likely in subjects with genotype 1b who had mutations within the ISDR that would be likely to result in a change in the amino acid sequence. Like other viral markers, however, even these expensive and complex viral assays do not allow identification of all responders with confidence. The ability of viral quasispecies and

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ISDR mutation measurements to predict treatment outcome has not yet been confirmed prospectively or in large series. The presence of cirrhosis on the pretreatment liver biopsy specimen has been associated with a lower response to IFN treatment. As with viral levels and genotype, the absence of cirrhosis has a low predictive value for response (58% for ETR and 30% for SR). Individual pretreatment predictive factors accurately predict response to IFN treatment in 40% to 72%. However, the usefulness of this analysis may be limited because these data were derived from studies that used biochemical end points (normal ALT levels alone), whereas most investigators currently define response by decrease of serum ALT levels into the normal range and loss of HCV RNA by the polymerase chain reaction. Second, these studies used short courses of treatment (usually 6 MOS). Treatment with IFN for 12-24 MOS in responding pts is currently the standard of care. Longer treatment does not significantly increase ETR, but reduces relapse and thereby increases SR. Thus, longer treatment will likely reduce the ability of these factors to predict response, making the effect of the factors similar to what has been observed with ETR in the short-term treatment studies reported. Combination of ribavirin with IFN also increases SR and should have a similar effect. Whether these predictive factors will hold up with longer IFN treatment courses or combination with ribavirin remains to be determined. Finally, the changing technology and unpredictability of results with viral testing make it an unreliable method for predicting response. HCV RNA level is probably not a constant, but varies spontaneously. The level of virus in serum at a single point in time reflects many factors. In most cases, there is insufficient data to support clinical confidence in decisions based on a single sample.

Although individual pretreatment features have only limited predictive value, combinations of these factors might prove more useful. Indeed, several studies have suggested that better selection of pts might be possible. The optimal candidate for IFN therapy might be a young pt without cirrhosis, genotype 1, or high levels of viremia. The best predictor of ETR is the normalization of the serum ALT within the 1st 8-16 WKS of treatment. Reduction in serum ALT levels is seen quickly after initiation of IFN treatment, with most of the decrease occurring within the 1st 12 WKS. Indeed, nearly all pts who achieve ETR or SR will normalize the serum ALT level within 8-12 WKS. Early normalization of the serum ALT level is a highly accurate predictor of ETR (92%) and SR (72%) and is considerably more predictive than the pretreatment factors discussed. The high sensitivity of the finding of early normalization of ALT allows the clinician to discontinue treatment with a high degree of confidence that a response would not occur if treatment were continued. Loss of HCV RNA during the initial WKS or MOS of IFN treatment may also provide accurate identification of responders. However, the decline in HCV RNA level is probably dependent on viral load, genotype, and IFN dosing.

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Although pretreatment factors are not sufficiently accurate to exclude pts from treatment or develop pt selection guidelines, they may still have an important role in pt management. First, they may be helpful in counseling pts about the likelihood of response. This information, along with a discussion of the natural history of the disease, infectious risks, liver biopsy results, costs of treatment, and so forth, is essential if the pt and physician are to make an informed decision about the need for therapy. Second, it is possible that these factors may be useful in refining future treatment regimens. As new treatment regimens such as longer duration of therapy and combination with ribavirin reduce relapse rates, these pretreatment factors become even less accurate predictors of treatment outcome. The best indicator of a favorable outcome of IFN treatment is the intitial ALT and HCV RNA response. This change allows an extremely confident identification of pts who will or will not respond to further treatment and provides the physician with the best tool to refine the subsequent management of the pt.

ICON Literature Search

Doc. ID. I97281040

Title * Retreatment of Relapse After Interferon Therapy for Chronic Hepatitis C: an International Randomized Controlled Trial of Interferon Plus Ribavirin vs Interferon Alone

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. 247

Authors Summary Davis, G.L.; Esteban-Mur, R.; Rustgi, V.; Rizzetto, M.; et al.

Relapse occurs in most pts who initially respond to IFN therapy. Previous reports have stated that 80-90% of relapsers respond to retreatment, but sustained response (SR) to the same dose and duration of IFN is rare (0-4%). However, pilot studies have suggested that retreatment with IFN plus ribavirin (RIBA) results in SR in the majority of pts. AIM: To assess the efficacy and safety of combination therapy with IFN and RIBA as compared to IFN alone in pts with chronic hepatitis C who had previously responded to IFN but relapsed after therapy was stopped. METHODS: 349 subjects with chronic hepatitis C who had previously normalized serum ALT by the end-of-treatment (ETR/ALT) but relapsed were enrolled at 52 international sites and randomized to receive recombinant IFN-alfa2b (INTRON A, Schering-Plough) 3 MU SC TIW for 6 MOS concurrent with either RIBA 1000-1200 mg PO daily or a matched placebo. Subjects were followed for 6 MOS after treatment. The study was double-blinded and the code will be broken in August 1997. RESULTS: Features of the study group included: mean age, 43+/-9 YRS; male 65%; Caucasian, 95%; weight, 75+/-14 kg; mean pretreatment HCV RNA (Superquant, NGI), 4.9 x10E6 eq/ml; genotypes 1 (56%), 2 (17%), 3 (24%); and acquisition by transfusion (28%), other parenteral (40%), or sporadic (28%). US and non-US pts were similar except the former were heavier (79 vs 71 kg) and had higher viral levels before therapy (6.3 vs 3.7 x 10E6 eq/ml). Treatment was well tolerated (decreased or temporarily interrupted in 10.6%; permanently discontinued in 2.3%). Platelets and WBC decreased by 22.3% and 10.4%, respectively, during the first WK and remained stable thereafter. Hgb decreased gradually by a mean of 9% over 4 WKS and then remained stable. The early Hgb decrease was accompanied by a slight and transient rise in mean total bilirubin (0.6-0.7 mg/dl). Based on intent-to-treat analysis, serum ALT normalized by the end of retreatment in 211 (60.5%) and HCV RNA became undetectable by PCR in 215 (61.6%). 12 WKS after therapy was stopped, ALT response was sustained in 105 (49.8% of ETR/ALT; 30.1% of all treated) and HCV RNA loss was sustained in 91 (42.3% of ETR/RNA; 26.1% of all treated). SUMMARY: Results are tentative until completion of post-treatment follow-up and unblinding of treatment groups. However, our preliminary data suggest several important findings. First, retreatment of initial responders who relapse is associated with a lower ETR than previously reported. This emphasizes the need to provide optimal treatment during the initial course of therapy. Second, since retreatment of relapsers with IFN alone has a very low sustained response rate, the observed 26-30% SR rate in the overall group suggests that SR in

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the IFN-ribavirin group is high (50-60%). (This summary
represents the entire text of the document.)

ICON Literature Search

Doc. ID. 197263013
 Title Side Effects of alpha Interferon in Chronic Hepatitis C
 Journal Hepatology, Vol. 26, No. 3, Suppl. 1, 1997, P. 112 - 121
 Authors Dusheiko, G.
 Summary

IFN-alfas have been used widely to treat chronic hepatitis C virus infection. These include recombinant IFNs, purified natural leukocyte, and lymphoblastoid IFNs. IFN-alpha is administered by SC or IM injection either daily or TIW for a period of 6 to as long as 24 MOS. This review focuses on adverse events reported in therapeutic trials of IFN, study monitoring databases, specific case series and case reports, and large retrospective analyses in studies of chronic hepatitis C. The side effects of IFN-alpha can be separated into the following 4 categories: 1) mild to moderate adverse side effects that occur commonly and that usually do not require dose modification; 2) mild to moderate side effects that occur uncommonly (in <10% of treated pts) that may or may not require dose modification; 3) severe or life-threatening side effects; and 4) irreversible side effects. It is also important to discuss contraindications to IFN-alpha in the context of treatment of hepatitis C.

Almost all pts who receive IFN-alpha in doses \geq 3 MU per injection experience some adverse side effects. These are usually minor and do not require a reduction in dose. Nevertheless, these side effects are problematic, and in some pts are poorly tolerated and limit the dose or duration of therapy (Table 1). Tolerance in elderly pts and children is usually similar. Later common side effects of IFN-alpha develop after the 1st few days or WKS of therapy. These later side effects include fatigue, malaise, apathy, and cognitive and behavioral changes. Between 10% and 15% of pts find the longterm side effects intolerable and ask to discontinue treatment. Higher doses of IFN-alpha (>5 to 6 MU TIW) tend to cause higher rates of adverse events. Administration of IFN-alpha at night may reduce the frequency or improve tolerance of the common side effects, which regress after discontinuing therapy, albeit after some WKS. Acetaminophen is used commonly to prevent or abate side effects; daily dosing of this analgesic in chronic hepatitis C should be kept below 2.4 g. IFN-alpha may have mild renal effects. Asymptomatic and mild proteinuria is relatively common. Nephrotic syndrome and severe renal injury of IFN are rare.

Fatal and life-threatening side effects from IFN-alpha therapy are rare with the doses used to treat chronic hepatitis C. The best estimate of the frequency of severe adverse events with IFN therapy derives from a large, retrospective survey conducted in 73 Italian centers on a total of 11,241 pts with either chronic hepatitis B or C. Among this large cohort, only 5 pts (0.04%) died because of complications of therapy, all 5 developing either liver failure or sepsis. Life-threatening side effects occurred in another 8 pts (0.07%), which included depression leading to attempted suicide and bone marrow suppression with granulocyte count less than 500/uL or platelet counts less than 25,000/uL.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-903 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-530 Trade and generic names/dosage form: Intron A (interferon alfa-2b recombinant) injection /Rebetol (ribavirin) capsules Action: AP AE NA

Applicant Schering Corporation Therapeutic Class 7030170 Antiviral/Systemic/Hepatitis

Indication(s) previously approved N/A

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate X

Indication in this application Treatment of chronic hepatitis C in patients 18 years of age or older with compensated liver disease who have relapsed following alfa interferon therapy. (For supplements, answer the following questions in relation to the proposed indication.)

- 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
- 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
- 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
 - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
 - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
 - c. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing,
 - (2) Protocols were submitted and approved.
 - (3) Protocols were submitted and are under review.
 - (4) If no protocol has been submitted, attach memo describing status of discussions.
 - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
- 5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

7.1C Regulatory Management Officer 5/28/98
Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 20-903
Div File
NDA/PLA Action Package
HFD-006/ SOImstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

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Serious but not life-threatening side effects occurred in 131 pts (1.2%); these included symptomatic thyroid disease, impotence, systemic autoimmune disease, immune-mediated dermatological diseases, diabetes mellitus, cardiovascular disease, psychosis, seizures, peripheral neuropathy, and hemolytic anemia. Most of these complications were reversible. Thus, serious side effects occurred in 1/100 pts and fatal or life-threatening side effects in 1/1,000 pts. In some pts, the common and predictable influenza-like side effects become severe and necessitate a reduction in dose or stopping treatment. Severe fatigue, marked cognitive and neuropsychiatric changes, including confusion, depression, paranoia or phobic anxiety, can occur. More common and more likely to lead to a reduction in dose are irritability, sadness, emotional lability, and moodiness. Confusion, vertigo, paraesthesias, and tinnitus have been reported. Other relatively common side effects that may require dose reduction include an increase in non-organ-specific antibodies, autoimmune thyroiditis, hyperthyroidism, autoimmune hepatitis, worsening diabetes mellitus, psoriasis, injection site reactions, or pruritus. Cardiac arrhythmias are relatively rare, but have been reported. The neuropsychiatric side effects of IFN can be troublesome and largely unpredictable. The reported frequency of neurotoxicity during IFN therapy ranges from 25% to 33%. A careful psychiatric history before IFN therapy, and careful monitoring and early intervention is important during therapy. Serum aminotransferase may increase during IFN-alpha treatment. These increases are generally mild and resolve with continued treatment in responsive pts. Antithyroid antibodies and autoimmune thyroiditis are perhaps the most frequent side effects of the immunomodulatory properties of IFN-alpha. Thyroid disorders, including either hypothyroidism or hyperthyroidism, have been reported to develop in 2.5% to 20% of pts. Hyperthyroidism or hypothyroidism may not be reversible after stopping therapy. Stopping therapy early may help blunt the severity of the illness. Other autoimmune endocrine diseases have been reported to occur including diabetes, thrombocytopenia, hemolytic anemia, psoriasis, rheumatoid arthritis, systemic lupus-like syndromes, primary biliary cirrhosis, and sarcoidosis. Several renal lesions, including interstitial nephritis, nephrotic syndrome, and acute renal failure, have been described. 3 different types of cardiovascular sequelae have been reported: arrhythmia, ischemic heart disease, and cardiomyopathy. These events seem rare. Dermatological side effects include: rashes, erythema multiforme, pruritis, mild hair loss, local erythema at the site of injection, psoriasis, vitiligo, and lichen planus. Ophthalmologic side effects include retinal hemorrhages or cotton wools spots. The frequency of abnormalities was higher among diabetic and hypertensive pts. Most were asymptomatic and reversible when treatment was stopped. Sudden hearing loss may be associated with IFN therapy. The auditory disability often developed after some MOS of treatment and resolved in all pts

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within 2 WKS after discontinuing IFN. A number of reports of pneumonitis with respiratory symptoms and pulmonary infiltrates have been published. Lung disease may, in part, relate to higher doses of IFN and concomitant toxicity associated with other drugs or herbal preparations. Fatal cases of pneumonitis developing during IFN therapy have been reported. Prompt discontinuation of IFN-alpha and treatment with corticosteroids appeared to be associated with resolution. Antibody to IFN-alpha can develop during therapy.

There are important contraindications to therapy with IFN-alpha. Almost all of these contraindications are relative, but the decision to use IFN-alpha must be weighed carefully. Toxicity can be predicted in pts with low baseline white blood cell counts or thrombocytopenia. Hypertension, diabetes, clinically significant cardiac disease, renal, neurological, and psychiatric disease are factors that may seriously predispose pts to serious adverse events. Long-term therapy with IFN-alpha is increasingly used among pts who have an excellent end-of-treatment response but who relapse when therapy is stopped. The possibility of unexpected side effects from long-term IFN use needs careful study. Finally, the development of moderate to severe side effects generally leads to discontinuation of therapy, even when beneficial responses in the liver disease are occurring. Means of ameliorating or treating side effects of IFN-alpha are needed, particularly the psychiatric effects. The role of antidepressants in ameliorating the depression induced by IFN therapy needs careful prospective trials. Finally, with the development of new agents for combination therapy of hepatitis C, it is particularly important to analyze whether side effects are more or less frequent with these combinations. Indeed, in the case of the combination of ribavirin and IFN, the development of anemia may pose a particularly difficult problem that can be dose limiting and may be severe enough to be threatening. Thus, future basic and clinical research is needed not only on the efficacy but also on the adverse effects of IFN-alpha therapy.

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Table 1. Common Side Effects of IFN-alpha Usually Not
Requiring Dose Modification

Influenza-like: Fatigue, fever, myalgia, poor-appetite,
tachycardia, chills, headache, arthralgias.

Neuropsychiatric: Apathy, irritability, mood changes,
insomnia, cognitive changes.

Miscellaneous: Diarrhea, nausea, abdominal pain, back pain,
pruritis, alopecia, rhinorrhea.

Laboratory: Decrease in granulocytes, platelet counts, and
red blood cell counts, increase in serum triglyceride
concentrations, proteinuria, increases in serum alanine
and aspartate aminotransferases.

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ICON Literature Search

Doc. ID. I95177005
Title MANAGEMENT OF CHRONIC HEPATITIS B AND C
Journal S. AFR. MED. J., VOL. 84, NO. 8, 1994, P. 563 - 570.
Authors DUSHEIKO, G. M.
Summary Chronic viral hepatitis B, C or D may lead to cirrhosis, hepatocellular failure and hepatocellular carcinoma. The morbidity of these diseases has necessitated a prolonged search for effective therapy. IFN-alpha has been widely studied and remains the mainstay of treatment. Interventional treatment of chronic hepatitis B (CHB) is targeted at pts with active disease and viral replication, preferably at a stage before signs and symptoms of cirrhosis or significant injury have occurred. IFN-alpha therapy is indicated in pts with typical CHB who have HBsAg in serum with HBeAg and/or HBV DNA and raised aminotransferase (AT) activity (at least 2X the upper normal limit of normal). Pts with HBsAg without HBV DNA in serum should not be treated, as IFN-alpha has no effect on HBsAg alone. A response to IFN-alpha is defined by a loss of HBV DNA and HBeAg from serum, fall of serum AT activities into the normal range and subsequent improvement in liver histology. About 20% of pts who respond to treatment with clearance of HBeAg will also clear HBsAg within a YR of therapy, and up to 65% may later clear HBsAg after 6 YRS of follow-up. Response is generally associated with histological reduction in inflammation. Parameters that predict responsive pts are: women, AT levels, chronic active hepatitis, lower serum HBV DNA, negative for anti-HIV, history of hepatitis, whites, recent onset of disease, IgM anti-HBc, cytoadhesion molecules and activation of the IFN systems as measured by 2,5-adenylate synthetase. The major early side-effects of IFN include an influenza-like syndrome, chills, fever, malaise, muscle aches and rigors. Later side-effects include malaise, muscle aches, headaches, poor appetite, weight loss, increased need for sleep, psychological effects, (irritability, anxiety, depression) hair loss, thrombocytopenia and leukopenia. Unusual or severe side-effects include seizures, acute psychosis, bacterial infections, auto-immune reactions, thyroid disease, proteinuria, myocardiopathy, skin rashes and IFN antibodies. Neutralizing of antibodies may be 1 variable which affects response to IFN. In some pts, loss of efficacy or breakthrough may correlate with antibodies. Special strategies of treatment are needed for special groups of pts with hepatitis B. Pts with anti-HBe+ chronic hepatitis lose HBcAg and have histologic improvement, however they tend to relapse with time, although response rates are high. Asian children, or other children who are infected perinatally, respond poorly to IFN. In contrast, children with active disease and high serum AT levels respond to IFN therapy similarly to adults and usually accept treatment well. Asian adults have a low rate of response but pts with active disease may respond to corticosteroid withdrawal and IFN (up to 50% of pts with elevated ALT cleared HBeAg). In pts with advanced cirrhosis, multiple, serious side-effects are problematic. Anecdotal experience suggests that IFN has little

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effect in pts with major immune deficiencies. Glomerulonephritis caused by chronic HBV has been treated with recombinant IFN-alpha-2b and glomerulonephritis resolved. Other antiviral agents for chronic hepatitis B include: 2,3-dideoxyguanosine (ddG), 2,3-dideoxyinosine (ddi) and 3'-2'-dideoxythymidine (AZT), ara-AMP, levamisole, and thymosin. These are now being evaluated in larger controlled trials. Prednisolone withdrawal plus IFN (alpha-2b) to IFN alone has not shown any added benefit except in pts with pre-treatment serum ALT < 100 IU/l. Therapy of chronic hepatitis C with IFN-alpha indicated that a proportion of pts may respond to treatment with this agent. after 6 MOS, 1/2 of the responsive pts will promptly relapse. Unfortunately responsiveness to IFN-alpha remains somewhat unpredictable. Factors which predict a greater likelihood of response include cirrhosis, genotypes, and levels of viremia. Some pts have sustained response to treatment; a small proportion (approximately 10-20%) of these pts may be HCV RNA-positive, but appear to have a higher probability of later relapse off therapy. Immunosuppressed pts and pts with HIV may respond although long-term responsiveness is uncertain. In studies of ribavirin in hepatitis C infection, median serum AST levels declined, but rose to pre-treatment levels upon completion and there was a significant decrease in geometric mean titres of HCV RNA. 38% had normal ALT during treatment, but a further 1/3 had only a 50% decline in ALT. Despite the significant improvement in serum ALT, a marked decline in serum HCV was not observed. Studies of ribavirin + IFN-alpha used sequentially indicated that the combination treatment is associated with higher response rates than IFN alone.

ICON Literature Search

Doc. ID. I95285011

Title COMBINATION TREATMENT OF ALPHA INTERFERON-2B (ALPHA-IFN) AND RIBAVIRIN IN CHRONIC HEPATITIS C GENOTYPE 4 PATIENTS RESISTANT TO INTERFERON THERAPY

Journal HEPATOLOGY, AM. ASSOC. STUDY LIVER DIS. (AASLD), POSTGRAD. COURSE + 46TH ANN. MTG., NOV. 3 - 7, 1995, VOL. 22, NO. 4, PT. 2, 1995, P. 152

Authors EL-ZAYADI, A.; SELIM, O.; EL HADDAD, S.; HAMDY, H.

Summary The aim of this study was to evaluate the role of combination therapy of IFN-alpha and ribavirin in chronic hepatitis C (CHC) genotype 4 pts who failed to respond to IFN-alpha 12 WKS after the start of therapy. 24 consecutive chronic hepatitis C pts (all males with a mean age of 43 YRS) who failed to respond to IFN-alpha after 12 WKS of therapy. All pts were positive anti (HCV-ELISA-2 and RIBA-2), serum HCV-RNA PCR. Mean pre-therapy alanine aminotransferase (ALT) level was 116.2 +/- 29.4 IU/l. Liver histology reported chronic persistent hepatitis (CPH) in 2 pts, chronic active hepatitis (CAH) in 9, and CAH+ cirrhosis in 13 pts. Pts were treated with IFN-alfa-2b (Schering-Plough International), 3 MU TIW combined with ribavirin 1,000 mg/day for 24 WKS. Pts treated with IFN in a previous study (submitted for publication) were taken as a reference group. The reference group (No=92) included 77 males and 15 females with a mean age 39.5 YRS. Differences between the 2 groups regarding age, liver histopathology and mean pretreatment ALT levels were statistically insignificant. All pts were followed for at least 6 MOS after discontinuation of therapy. At the end of 6 MOS of combination therapy, ALT was normalized in 16/24 pts (66.7%) compared with 28/92 (30.4%) of the IFN group. The difference was highly significant $P < 0.003$). 6 MOS after the end of the therapy 10/24 (41.7%) pts on combination therapy maintained their normal ALT compared with 18/92 (19.5%) of the IFN group and the difference was highly significant ($P < 0.016$). HCV-RNA was positive in all pts before therapy. 6 MOS after the end of therapy 4/10 (40%) of the sustained responders in the combination therapy cleared the virus compared with 4/18 (22.2%) of the sustained responders in the IFN group. Although loss of viremia was higher in combination therapy than in the IFN group, it did not reach statistical significance ($P < 0.322$). Ribavirin was associated with hemolysis, requiring reduction in 2 pts and a mild decrease in lymphocyte counts (23.00 vs 1,420/CUMM). Combination therapy of IFN-alpha and ribavirin was associated with a significant sustained response in pts with CHC genotype 4, resistant to IFN-alpha treatment.

ICON Literature Search

Doc. ID. I97282019

Title A Prospective, Randomized Controlled Trial of High Dose Interferon-alpha Plus Ribavirin in Interferon-Nonresponders with Chronic Hepatitis C

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. 415

Authors Ferenci, P.; Stauber, R.; Hackl, W.; Steindl, P.; et al.

Summary About 50% of pts of chronic hepatitis C do not respond to IFN-alpha (IFN). In this trial the efficacy of a combination of high-dose IFN with ribavirin to augment response rates was studied. Study protocol: 310 pts with chronic hepatitis C received a 3 MO course of 5 MU IFN-alfa-2b (INTRON A, Schering-Plough)/TIW. Prior to treatment, all had an ALT > 2xULN and were anti-HCV and HCV-RNA (PCR) positive. CR was defined by disappearance of serum HCV-RNA. 157 non-responders were randomized either to continue with IFN (5 MU IFN/TIW for 3 MOS followed by 10 MU/TIW for 3 MOS; total dose: 870 MU) alone (group A) or in combination with ribavirin (1 to 1.2 g/d) (group B). ALT was measured in monthly, HCV-RNA in 3 monthly intervals. After 6 MOS treatment was terminated in all non-responders in group B. Non-responders in group A were offered a combination therapy in an open study. In responders, ribavirin was stopped, and IFN was gradually decreased (10-5-3-2-1 MU/TIW/MO). Pretreatment characteristics of the randomized pts were: group A: n=77; m/f: 55/22; 16% cirrhosis, age: 45.7+/-12 YRS; ATL (U/L): 66+/-35; group B: n=80; m/f: 56/24; 17% cirrhosis, age: 48.2+/-12; ATL: 71+/-40. After 9 MOS of treatment, 10 pts (12.6%) in group A were HCV-RNA neg., 54 HCV-RNA pos., and there were 13 drop-outs. In group B 26 (32.9%, p=0.0066; chi-square test, intent to treat analysis) were HCV-RNA neg., 39 HCV-RNA pos., and there were 14 drop-outs. In addition to the well known side-effects of IFN, no major side-effects were observed in the combination group. The mean hemoglobin concentration dropped by 2 g/l in the combination group. Complete follow-up data are available in 10 responders to combination therapy. 8 became HCV-RNA pos. after ribavirin was stopped and 2 are sustained responders. These data indicate that a combination of high-dose IFN with ribavirin is effective to induce a shortlasting CR in one-third of non-responders to a 3 MO treatment with 5 MU/TIW IFN. Prolonged treatment with IFN/ribavirin may be necessary to obtain a sustained response. (This summary represents the entire text of the document.)

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been shown to be a positive predictor in several studies. Low pre-treatment levels of HCV RNA were associated with a sustained response. In Japanese pts, several studies have demonstrated a higher response to IFN therapy in pts with HCV genotype III, and genotype II was associated with a low response in European pts. Other drugs may be beneficial alone or in combination with IFN. Ribavirin, a nucleoside analog, has been shown in several pilot studies to be associated with ALT response and a decrease in levels of HCV RNA in some pts and combination of IFN-alfa with ribavirin might enhance the response rate.

ICON Literature Search

Doc. ID. I97203008
 Title Modulation of Hepatitis C Virus Quasispecies Heterogeneity by Interferon-alpha and Ribavirin Therapy
 Journal J. Viral Hepat., Vol. 4, No. 2, 1997, P. 99 - 106
 Authors Gonzalez-Peralta, R. P.; Liu, W. Z.; Davis, G. L.; Lau, J. Y. N.; et al.
 Summary Hepatitis C virus (HCV) is a single-strand, positive sense RNA virus that is believed to replicate via a viral encoded RNA-dependent RNA-polymerase. This replication strategy has limited fidelity. Therefore, HCV exists as a highly heterogeneous population of closely related genomes, called quasispecies. HCV quasispecies have been shown to have important pathobiological implications. While both IFN-alpha (IFN) and ribavirin therapy have been associated with reduction in serum transaminase levels in a proportion of pts with chronic hepatitis C infection, only IFN has been demonstrated to have an effect on serum viral RNA levels. Recent data have suggested that IFN exerts a selective pressure on HCV quasispecies. However, the effect of ribavirin on HCV quasispecies heterogeneity is unknown. We have recently developed a rapid and reliable method based on single-strand conformation polymorphism (SSCP) for the study of HCV quasispecies. The aim of this study was to determine the effects of IFN and ribavirin therapy on HCV quasispecies based on SSCP. 14 pts, ages 28-62 YRS, who participated and completed follow-up in a randomized placebo-controlled trial of ribavirin (Virazol, ICN Pharmaceuticals; 1.2 g/day PO for 36 WKS, n=7; placebo, n=7), as well as 15 pts, ages 30-71 YRS, who were subsequently treated with IFN (INTRON-A, Schering Plough; >=3 MU SC TIW for 24 WKS) were studied. All pts were seropositive for antibody to HCV (EIA-2) and HCV RNA (nested RT-PCR), and had abnormal serum ALT levels for at least 6 MOS. Serum HCV RNA was quantified using ddDNA assay. Viral quasispecies was determined using SSCP analysis of the HCV hypervariable region 1 (HVR1). Before therapy, HVR1 was amplified in 14/15 pts who were treated with IFN, in 6/7 pts who received ribavirin and in 6/7 pts given placebo. The median number of SSCP bands per pt was 8, 7, and 3 for those who received IFN, ribavirin, and placebo, respectively. There was no correlation between pretreatment of HCV quasispecies heterogeneity and either age, sex, serum ALT, HCV genotype, HAI or Knodell score. After IFN therapy, complete and sustained response, CR with early relapse, and no response was seen in 4, 3, and 8 pts, respectively. Pts who had a complete and sustained response had lower pretreatment viral quasispecies heterogeneity (median SSCP bands per pt = 3) compared with those who had either a CR with early relapse (median SSCP bands per pt = 8) or no response to IFN-alfa (median SSCP bands per pt = 8) (p<0.05). After IFN-alfa therapy, serum HCV RNA levels decreased in 11/15 pts and 8 pts became HCV RNA 5'UTR negative by RT-PCR. In all of these pts, HCV quasispecies heterogeneity at the end of treatment was lower than pretreatment values; median change = -6 SSCP bands per pt. The amount of amplicon loaded for SSCP gel electrophoresis was controlled in our experiments; this excludes

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the possibility that the reduced number of bands was related to the lower level of viremia after therapy. Serum ALT were decreased more than 50% of pretreatment values in 5/7 pts and in 1/7 pts after ribavirin and placebo therapy, respectively. However, of these, only 3 pts (all of whom received ribavirin) had normal ALT at the end of therapy. Viral quasispecies heterogeneity before therapy was similar in these 3 pts (median SSCP bands per pt = 6), compared with the 3 pts with detectable HVR1 who did not respond to ribavirin (median SSCP bands per pt = 5). After therapy, HCV RNA levels decreased in only 3/7 pts within each ribavirin- and placebo-treated groups; all pts who received ribavirin or placebo remained HCV RNA 5'UTR+ at the end of therapy. HCV quasispecies heterogeneity was lower in 1 and 0/5 pts in whom HVR1 was detected before and after ribavirin and placebo therapy, respectively (median change = 0 and +2 SSCP bands per pt for ribavirin- and placebo-treated pts, respectively). After therapy, the SSCP-band pattern was identical in 3/5 pts within each group treated with ribavirin or placebo. There was no correlation between viral quasispecies and HCV RNA levels. There was also no difference in the detection of HVR1 with respect to HCV genotype. Using an optimized SSCP method to assess HCV quasispecies heterogeneity, 2 important points were demonstrated in this study. First, decreased HCV quasispecies heterogeneity was associated with a subsequent beneficial response to IFN. Second, and more unique, IFN but not ribavirin was shown to exert a selective pressure on viral quasispecies.

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Doc. ID. I97282004

Title * CD4 Positive T Lymphocyte Proliferative Responses in a Cohort of Patients with Chronic Hepatitis C Virus Treated with Ribavirin and Interferon.

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. 406

Authors Grellier, L.; Khakoo, S.; Wells, B.; Dusheiko, G.; et al.

Summary Host immunity may play a role in response to IFN-alpha therapy of chronic hepatitis C virus infection (HCV). We have sequentially analyzed HCV-specific CD4+ proliferative responses in vitro in pts with chronic HCV treated with IFN-alfa2b and ribavirin to examine the relationship between anti-viral response and CD4+ proliferative responses at baseline, or during therapy. 36 pts with chronic HCV were studied. 3 groups of 12 pts were randomized to receive IFN (3 MU SC TIW) or ribavirin (800-1200 mg/day) or combination therapy for 4 WKS during a pharmacokinetic study. Pts were then commenced on combination therapy for 6-12 MOS. These data report the proliferative responses at baseline and at 6 MOS (in those pts who have reached this point). Peripheral blood mononuclear cells (PBMC) were isolated immediately prior to therapy, after 4 WKS of therapy, then every 3 MOS while on combination therapy, and at 3 monthly intervals during follow-up. Stored PBMC were tested in batches in standard CD4+ proliferation assays against a variety of HCV antigens (core, NS3, NS4, and NS5). Initial treatment response was defined as a 2-log decline in HCV RNA at 4 WKS. Treatment response during 6 MOS of therapy was defined as normalization of serum ALT together with negative serum HCV RNA. NS5 was the most commonly recognized HCV antigen at baseline (stimulation index >3 seen in 26/36 pts). Core antigen was the most infrequently recognized at baseline (10/36 pts). There was no significant difference between the magnitude of the baseline HCV-specific CD4+ proliferation and initial treatment response vs non-response (e.g. median stimulation index 4.3 vs 3.6 for NS5). 15 pts have now completed 6 MOS of therapy. Serial proliferation indices in this cohort varied between individuals; however, suppression of proliferation to core (-24%), NS3 (-37%), NS4 (-63%), and NS5 (-57%) was seen in treatment responders. Of those individuals who have reached 3 MOS of follow-up post therapy, 3/4 treatment responders have shown an increase in HCV-specific CD4+ responses. Conclusions: The baseline CD4+ proliferation index does not always predict an early virological response to anti-viral therapy that is seen in some HCV-infected pts. IFN-alpha and combination therapy inhibit antigen-specific in vitro anti-proliferative CD4+ responses. Successful anti-viral treatment of HCV infection may be followed by an induction of HCV-specific CD4+ proliferation; this however, is not observed during treatment, to explain the virological response. (This summary represents the entire text of the document.)

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Doc. ID. I97282037
 Title Induction Dosing With Interferon-Alpha2b: An International Study
 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. 420
 Authors Hadziyannis, S.J.; Tsantoulas, D.; Raptopoulou, M.; Glue, P.; et al.
 Summary Most studies conducted in Western Europe and the United States have investigated the efficacy of IFN-alpha for hepatitis C utilizing a TIW regimen. Reports from Japan indicate that the sustained response rates obtained in that country seem to be higher than the ones obtained in the West. The key difference may be the dosing regimen and the intensity of IFN utilized in Japanese pts. Further, many studies have reported that early viral clearance seems to be a predictor for sustained response. This is an open label study comparing 3 MU, 5 MU and 10 MU of IFN-alfa-2b over a 2 WK period given either in the standard TIW regimen or daily in previously untreated pts. This study also includes a group with 5 MU TIW of IFN-alfa-2b + daily ribavirin (R) (1,000-2,000 mg). The objective of the study is to determine the effects of daily induction therapy as assessed by an increase in viral clearance and/or a reduction in viral load over a 2-WK period. HCV-RNA by quantitative PCR was determined by a single laboratory with a level of quantitation of 100 copies/ml (Superquant, NGI, California, USA). Virology was measured at baseline, 12 HRS, 24 HRS, 48 HRS, 72 HRS, 96 HRS, 1 WK, 10 days and 2 WKS. The HCV-RNA profile (copies/ml) and number of pts HCV-RNA negative per group is shown in the table. Only 1 pt did not complete the study (10 MU IFN QD group) due to administrative reasons, but is included in the analysis. There was no difference in safety or adverse events in any of the groups except mild reversible hemolysis in the 5 MU IFN TIW + R group. Groups had similar baseline viral loads except for 5 MU IFN TIW and 10 MU IFN TIW which were lower. No group on TIW dosing achieved statistically significant reduction in viral load by WK 2. In conclusion: Pts treated with daily doses of IFN had a higher reduction in viral load by WK 2, and it appeared that higher doses achieved viral reduction. More pts in higher daily doses achieved negativity by WK 2. Because of the good tolerability and apparently improved results with daily doses, larger studies should be conducted to determine long-term effect. (This summary represents the entire text of the document.)

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Dose	Baseline	24 HRS	2 WKS
3 MU TIW	1.9 x 10E6	3.0 x 10E5	5.7 x 10E4
3 MU QD	2.3 x 10E6	1.2 x 10E5	5.6 x 10E3
5 MU TIW	1.4 x 10E5	1.7 x 10E4	4.4 x 10E3
5 MU TIW + R	3.6 x 10E6	1.9 x 10E5	1.2 x 10E5
5 MU QD	2.8 x 10E6	1.1 x 10E5	2.9 x 10E3
10 MU TIW	7.7 x 10E5	1.6 x 10E4	2.5 x 10E4
10 MU QD	2.2 x 10E6	4.8 x 10E4	5.0 x 10E2

Dose	# neg. at 2 WK	HCV-NRA red (end vs base)	p (end vs base)
3 MU TIW	2/17	-1.53 log	ns
3 MU QD	3/15	-2.63 log	0.002
5 MU TIW	2/8	-1.53 log	ns
5 MU TIW + R	1/5	-1.47 log	ns
5 MU QD	6/15	-2.98 log	0.0006
10 MU TIW	1/5	-1.49 log	ns
10 MU QD	4/7	-3.63 log	0.03

ICON Literature Search

Doc. ID. I97106012
 Title * Comparison of Reduction of Serum Hepatitis C Levels with Interferon Alpha Alone on in Combination with Ribavirin
 Journal J. Hepatol., (32nd Ann. Mtg. Eur. Assoc. Study Liver, EASL, London, UK, Apr. 9-12, 1997), Vol. 26, Suppl. 1, 1997, P. 84
 Authors Khakoo, S. I.; Wells, B.; Glue, P.; Dusheiko, G. M.; et al.
 Summary The mechanism of improved responses in pts with chronic hepatitis C with ribavirin and IFN-alpha combination therapy is uncertain. We have measured serum HCV RNA levels after 4 WKS of therapy with either or both drugs to examine whether combined treatment with IFN-alpha and ribavirin is related to a more rapid decline in viral load than with IFN-alpha (or ribavirin) monotherapy. Twenty-three pts (16 males, 7 females, mean age 38.2 YRS) with chronic hepatitis C were treated with IFN-alfa2b 3 MU TIW (8 pts), ribavirin 1g-1.2g daily (7) or both (8 pts) for 4 WKS as part of a pharmacokinetic study. HCV RNA levels were determined by quantitative PCR (National Genetics Institute, USA). Mean baseline HCV RNA levels were similar amongst the groups (10E6.67 copies/ml vs 10E6.81 vs 10E6.77 respectively). Seven out of 8 combination pts, compared with 4/8 IFN-alpha pts and 0/7 ribavirin treated pts had a 1 log decline in serum viral load by the end of 4 WKS of therapy. The declines in serum viral concentrations between the combination and IFN-alpha treated groups at the following time points are shown in the Table. These data show that the combination of IFN-alpha and ribavirin causes a significantly more rapid decline in serum HCV titre than IFN-alpha alone. The enhanced efficacy of Ribavirin-IFN-alpha may result from both an improved initial response as well as reduction in relapse. The clinical relevance of this observation is being tested in pts treated for 6 to 12 MOS. (This summary represents the entire text of the document.)

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Mean (+/-SD) log ₁₀ decline in viral titre (copies/ml)			
	IFN-alpha	IFN-alpha + ribavirin	
Week 1	0.47 +/- 0.51	0.89 +/- 0.83	p>0.1
Week 2	0.65 +/- 0.82	1.70 +/- 1.66	p<0.1
Week 3	1.02 +/- 0.96	2.84 +/- 2.24	p<0.05
Week 4	1.12 +/- 0.94	2.97 +/- 2.24	p<0.025

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Doc. ID. I97263010
 Title Therapy of Hepatitis C: Interferon Alfa-2a Trials
 Journal Hepatology, Vol. 26, No. 3, Suppl. 1, 1997, P. 89 - ,95
 Authors Lee, W. M.
 Summary

IFN-alfa2a (Roferon A; Hoffmann-La Roche) is a recombinant alpha IFN made by recombinant techniques in *Escherichia coli*. It has both antiviral and immunomodulatory effects demonstrated both in vitro and in vivo. This review summarizes the results of therapeutic trials of IFN-alfa2a in the treatment of chronic hepatitis C, focusing on the effect of dose, length of treatment, and other factors that determine initial and sustained response to this agent. Diagnosis of chronic hepatitis C included clinical histories suggesting disease for greater than 6 MOS, a liver biopsy consistent with the diagnosis of chronic hepatitis, abnormal alanine aminotransferase (ALT) levels (>1.5 times the upper limit of normal), and in most instances, the presence of anti-HCV. Pts were adults between the ages of 18-81 YRS. Histological findings included chronic active hepatitis in 58% and chronic active hepatitis with cirrhosis in 27%. The primary measure of efficacy was a biochemical response, based on ALT measurements. A biochemical end-of-treatment response was defined when ALT levels were normal on 2 consecutive occasions at least 21 days apart at the end of the treatment period, and a sustained response was the same at least 6 MOS after cessation of therapy.

2 fixed dose regimens were used in the initial 3 randomized trials of IFN-alfa2a, in which 842 pts completed the studies. Doses ranging from 0 (placebo) to 1, 3, 4.5, and 6 MU TIW were used for 6 or 12 MOS, with 6 MOS of follow-up. The overall results demonstrated a significant dose-response curve for induction of response as well as end-of-treatment and sustained biochemical responses ($P < 0.001$). The overall data suggest that fixed doses of <3 MU TIW are of no value, but that 3, 4.5, or 6 MU TIW for at least 6 MOS has clear benefits in eradicating HCV infection. Whether there are significant benefits from doses >3 MU is unclear. 325 pts were enrolled in 5 randomized trials comparing different and varying doses during treatment; 3 compared de-escalating doses, beginning with 6 MU and decreasing to 3 MU at 3 MOS. In these studies, total duration of treatment also varied from 6-12 MOS. Taken together, the de-escalation regimens led to sustained biochemical responses in 27% to 49% of pts, results slightly better than those observed with other 12-MO protocols. Higher starting doses of IFN-alfa2a used longer periods of treatment than the conventional 6 MOS, either through the use of a fixed dose or by induction with a higher dose and de-escalation. The overall results suggest an improvement in efficacy with longer treatment for a given IFN-alfa2a dose. A dose-response effect was demonstrated when fixed doses were used in longer treatment programs. Taken together, there was a marginal improvement in sustained responses with 12-MO compared with 6-MO courses of therapy. As already noted, the use of a high initial induction dose of IFN-alfa2a, followed by dose reduction

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or de-escalation, has been associated with slight improvement in sustained response rates, but it is difficult to compare the findings across studies. 2 direct comparisons of induction regimens with fixed doses have been performed. In a study of 174 pts, Chemello et al. randomized pts to receive 1 of 3 regimens: 6 MU TIW for 4 MOS followed by 3 MU TIW for 9 MOS, a fixed dose of 3 MU TIW for 12 MOS, or a fixed dose of 6 MU TIW for 6 MOS. Sustained biochemical responses 1 YR after therapy were 49%, 31%, and 28%, respectively, suggesting that induction and the use of longer therapy periods were more effective. In a study by Alberti et al., a direct comparison of induction and fixed-dose treatment likewise favored induction therapy, although the total dose of IFN was greater when compared with that received by the group treated with 3 MU for 12 MOS. In studies analyzing factors that correlated with response outcome, the presence of cirrhosis and genotype 1b were associated with significantly lower sustained response rates. However, the predictors of response varied considerably among the studies reviewed. These included lower viral titer before treatment, HCV genotype, younger age, shorter duration of disease, and genotypes 2 and 3 were independent predictors of a sustained response. In a retrospective analysis, pts with a sustained response tended to be younger and had a lower body surface area than those without a response. For the 2 earliest IFN-alfa2a clinical studies, analysis of virological and histological data available revealed that an end-of-treatment virological response occurred in 33% of those whose baseline biopsy specimen revealed chronic persistent or lobular hepatitis, 27% of those with chronic active hepatitis without cirrhosis, and 20% of those with chronic active hepatitis and cirrhosis. There was a significant reduction in the HAI for all pts who demonstrated a virological response, and with a mean decrease in end-of-treatment HAI score from baseline of 2.8 compared with 0.6 for those who did not respond. In another study, virtually all pts who had a combined biochemical and virological sustained response showed histological evidence of improvement, and 48% of this group were shown to have a normal biopsy or minimal changes on follow-up an average of 9 MOS after completion of therapy. From the original Roche IFN-alfa2a study database, information was available on 364 pts (78%) regarding long-term follow-up for up to 4.5 YRS. Of 58 pts with a sustained biochemical response as defined in the original study, 52 (90%) had durable responses at least 3 YRS after completion of an initial 3-6 MOS of observation off therapy. HCV RNA results were available on 19 sustained biochemical responders. 95% of long-term biochemical responders to therapy with IFN-alfa2a are HCV RNA negative and presumed free of viremia. Pts are occasionally identified in whom the biochemical response to therapy does not correlate with HCV RNA results. A combination of HCV RNA and ALT testing is probably optimal for clinical management. As has been observed with IFN-alfa2b, ribavirin appears to enhance the durability of

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responses in those whose serum ALT and HCV RNA levels return to normal during therapy.

The overall experience with IFN-alfa2a suggests that it is equivalent in efficacy to alfa2b, lymphoblastoid and consensus IFN, and has a similar safety profile. More detailed experience with induction therapy and with prolonged therapy using IFN-alfa2a suggests that both induction therapy using higher doses for the initial phase of treatment (typically 3 MOS) as well as extension of therapy to 12 MOS in toto are beneficial. Nevertheless, the presence of histological evidence of cirrhosis, and in some studies, high HCV RNA titers limit the eventual outcome. No simple algorithm has yet been devised to predict response to treatment using IFN-alfa2a or to any other IFN-alpha.

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Doc. ID. I97283037

Title Combination of Interferon Alpha 2b Plus Ribavirin for the Treatment of Chronic Hepatitis C: Preliminary Results of an Open-Labeled Community Trial

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. 548

Authors Lewis, J. H.; Gallagher, J. G.; Gibbs, L.; Epstein, M. E.

Summary The combination of IFN-alfa2b (INTRON A) plus oral ribavirin is currently being studied as a means to improve the sustained response rate in chronic HCV pts with a previous non-response or non-sustained response (relapse) to IFN alone. This trial was initiated among 24 university-based and community gastroenterology/hepatology groups to reflect clinical practice. Non-cirrhotic HCV pts were screened and eligible initial non-responder pts were randomized to receive 3 or 5 MU TIW INTRON A with 1000-1200 mg ribavirin based on body weight for an initial 12 WK period. Pts who had previously relapsed received the combination with the INTRON A dose starting at 3 MU TIW. QOL questionnaires and safety data were obtained at regular intervals according to the protocol.

Results: A total of 129 pts have been entered as of June 1, 1997 with 8 having completed the initial 12 WK phase of Tx; 5 men, 3 women; mean age 45.3 YRS (range 38-60 YRS). For these 8 individuals to date, all have shown a >50% reduction in HCV RNA from pre-treatment baseline (National Genetics, Inst.). Mean pre-treatment RNA level was 2.6 million copies/ml (range 343K - > 5 M) and post-treatment was 334K copies (<100-1.8 million). 2/8 individuals had HCV RNA levels <100 copies/ml and normalized ALT. Of the remaining 6 pts, 3 have normalized ALT. Mean pre-treatment ALT for the entire group was 257 IU/l (49-620) and post-treatment was 42.8 IU/l (range 17-66). Genotypes of these 8 individuals are 1a (n=4), 1b (2), 2b (1) and 4c/d (1). No serious or new adverse events have been observed with INTRON A. Mild to moderate anemia developed in all 8 pts (mean fall in Hct from 44% to 36.3%).

Conclusions: These preliminary results of our ongoing study of INTRON A plus ribavirin Tx for HCV pts who previously did not respond or relapsed after IFN Tx alone are favorable and the combination is well tolerated. QOL and safety data collection are ongoing. (This summary represents the entire text of the document.)