Randomized, Double-Blind, Placebo-Controlled Trial of Interferon Alfa2a With and Without Amantadine as Initial Treatment for Chronic Hepatitis C

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Although the antiviral effects of amantadine sulphate (1-aminoadamantan sulphate) have not been characterized for the hepatitis C virus (HCV), previous pilot studies have suggested promising results in patients with chronic hepatitis C. The aim of the present study was to compare the efficacy, safety, and health-related quality of life (HRQOL) of interferon alfa (IFN-α) alone or in combination with oral amantadine for treatment of chronic hepatitis C. One hundred nineteen previously untreated patients with chronic hepatitis C were randomly allocated to treatment with IFN-α2a at a dose of 6 megaunits 3 times a week subcutaneously for 24 weeks, followed by 3 megaunits thrice weekly for an additional 24 weeks plus amantadine sulphate administered orally 100 mg twice a day for 48 weeks or the same IFN regimen plus a matched placebo. The primary endpoint was undetectable serum HCV RNA (<1,000 copies/mL) at week 24 after treatment. At the end of treatment and the 24-week follow-up period serum HCV RNA was undetectable in 20 (33%) and 6 (10%) of the 60 patients treated with the combination IFN-α plus amantadine and in 20 (33%) and 13 (22%) of the 60 patients treated with IFN-α alone, respectively (P = n.s.). Discontinuation of therapy for adverse events was similar in both treatment groups. Although treatment with IFN-α worsened HRQOL, combination with amantadine showed a substantial trend to improve fatigue and vigor. In conclusion, combination therapy IFN-α plus amantadine is as effective as IFN-α monotherapy in previously untreated patients with chronic hepatitis C. (Hepatology 2000;32:835-841.)

Hepatitis C virus (HCV) infection often progresses to chronic hepatitis, cirrhosis, and possibly hepatocellular carcinoma.1 Chronic hepatitis C infection is a leading cause of chronic liver disease and the most common indication for liver transplantation. Treatment of HCV-infected patients with interferon alfa (IFN-α) can achieve viral clearance and improve histology and prognosis. However, the overall sustained virologic response to IFN-α monotherapy is less than 20%.2,3 Recent studies investigating the efficacy of combination therapy with IFN-α and ribavirin in patients with chronic hepatitis C, showed improved sustained virologic response rates of approximately 40%.4-5 Nevertheless, further improvements in the treatment of chronic hepatitis C are still needed.

Amantadine (1-aminoadamantan) is a tricyclic amine with antiviral activity against toga-, myxo-, arena-, flavi-, and coronaviruses.6-10 Inhibition of influenza A virus replication by amantadine is clinically well characterized.11 The molecular mechanisms include inhibition of an early step in viral replication, most likely viral uncoating and interaction with the viral M2 protein, which is a membrane-bound protein thought to be important in virus budding.12,13 Although antiviral effects of amantadine have not been characterized for the hepatitis C virus, promising results have been reported in several pilot studies of HCV-infected patients treated with amantadine alone14-16 or in combination with IFN-α.6-17 The aim of this study was to compare efficacy, safety, and health-related quality of life (HRQOL) of therapy with IFN-α2a alone and in combination with oral amantadine sulphate, administered for 48 weeks for the treatment of chronic HCV infection in patients who have not previously been treated with IFN, ribavirin, and/or amantadine.

PATIENTS AND METHODS

Patients. Men and women aged 18 to 70 years with compensated chronic HCV infection not previously treated with IFN, ribavirin, and/or amantadine were eligible for enrollment. Eligible patients tested positive for anti-HCV (second-generation enzyme immunoassay) and HCV RNA by reverse transcription-polymerase chain reaction (RT-PCR), had a liver biopsy within a year of study entry showing chronic hepatitis, and had elevated serum alanine transaminase (ALT) levels for at least 6 months before initiation of treatment. Entry leukocyte counts had to be at least 2,500/µL; the platelet counts greater than 70,000/µL.

Patients with the following criteria were excluded: any other cause of liver disease or other relevant disorders, including human immunodeficiency or hepatitis B virus coinfection; evidence or history of autoimmune disease; clinically significant hematologic, hepatic, metabolic, renal, rheumatologic, anaphylactic reactions, neurologic or psychiatric disease; clinically significant cardiac or cardiovascular abnormalities, organ grafts, systemic bacterial or fungal infection; clinically significant bleeding disorders; evidence of malignant neoplastic disease within 5 years; average daily intake of alcohol exceed-
ing 50 g of ethanol; or drug abuse within the previous year. Further exclusion criteria were pregnancy and lactation period.

Study Design. This study was a randomized, double-blind, placebo-controlled trial conducted at the university hospitals of Berlin and Frankfurt, Germany. The patients were assigned to treatment with either the combination of IFN-α2a plus amantadine sulphate or IFN-α2a plus placebo. Randomization was performed with a random number generator in fixed blocks of 4 with a ratio of 1:1. All patients received IFN-α2a (Roferon A; Hoffmann-La Roche AG, Grenzach-Wyhlen, Germany) at a dose of 6 megaunits 3 times per week subcutaneously for 24 weeks, followed by 3 megaunits 3 times per week for an additional 24 weeks. Amantadine sulphate (Inflex; Merz + Co. GmbH Co., Frankfurt a.M., Germany) or a matched placebo was administered orally twice a day with a total dose of 200 mg for 48 weeks. Treatment was prematurely discontinued in patients with detectable HCV RNA 20 weeks after initiation of therapy. The study was approved by the ethics committees at the participating centers and performed according to the Declaration of Helsinki, the German Drug Law, and the ICH/CPMP guidelines “Good Clinical Practice.” All patients gave written informed consent before enrollment.

All patients were evaluated as outpatients for safety, tolerance, and efficacy at weeks 1, 2, 4, 8, and subsequently every 4 weeks during treatment. When treatment was completed, patients were assessed at weeks 4, 12, and 24. Hematologic and biochemical testing were performed by local laboratories. Pretreatment serum HCV RNA was quantified by a standardized RT-PCR assay (Amplicor Monitor HCV version 2.0; Roche Diagnostic Systems, Branchburg, NJ). Qualitative detection of HCV RNA was performed by RT-PCR (Amplicor HCV; Roche Diagnostic Systems) in serum samples obtained at treatment weeks 4, 12, 20, 36, and 48, as well as in week 24 of the follow-up period. The lower detection limit of the qualitative assay is 1,000 copies/mL. Genotyping of HCV was performed by reverse hybridization assay (Inno LiPA HCV II; Innogenetics, Gent, Belgium). A second liver biopsy was scheduled at the end of the 24-week follow-up period.

Instruments Used for Assessment of HRQOL. Emotional and psychologic states were measured at baseline, at weeks 24 and 48 of treatment, and at the end of the 24-week follow-up period by a German adapted and validated “Profile of Mood States scale,” which measures 4 factor scores for depression, fatigue, vigor, and anger. Furthermore, quality of life was assessed at the same time points by the “Everyday Life” questionnaire (EDLQ), a German validated questionnaire adapted to the SF-36 Health Survey. The EDLQ assesses the following 6 subscales of the HRQOL or subjective health: body (e.g., make demands on body, concentrate on a task); mind (e.g., cope with illness, accept oneself); everyday life (e.g., solve daily problems, perform personal hygiene); social activity (e.g., get along with family, count on partner’s help); zest of life (e.g., enjoy life); and medical treatment (e.g., believe in success of treatment). For every patient a sum score of all items of the subscale was used; missing items were replaced by the mean of the nonmissing items of the subscales. However, missing questionnaires were not replaced.

Study End Points. The primary efficacy endpoint for this study was defined as undetectable serum HCV RNA levels 24 weeks after treatment. Patients who did not have a week-24 follow-up assessment for serum HCV RNA were classified as nonresponders in the analysis. Secondary efficacy parameters were the virologic response during and at the end of treatment. As additional secondary endpoints, biochemical and histologic responses were analyzed as well as changes in adverse event load and HRQOL. Liver biopsy specimens were assessed by an experienced pathologist who was unaware of clinical and biochemical data as well as of treatment regimen and response. Histologic results were classified according to internationally standardized criteria.

Statistical Analysis. The required number of patients was estimated as n = 120 (60 in each group). The sample size estimation was based on a type I error rate of α = .05 and a type II error rate of β = .05. The sustained virologic response rate as primary end point was expected to be 40% for combination treatment with IFN-α2a plus amantadine and 12.5% for IFN-α2a monotherapy. The primary statistical analysis of efficacy data is based on the intention-to-treat population of 119 patients, who were randomly assigned to treatment and received at least one dose of medication. The differences between virologic response rates were tested with a one-tailed Fisher exact test on a significance level of α = .05. Analysis of biochemical response rates was performed by two-tailed Mann-Whitney U test (α = .05). All tests, except those for HRQOL, were done by SAS procedures (version 6.12, SAS Institute Inc, Cary, NC). For HRQOL analysis, the differences of sum scores at weeks 24 and 48 during treatment and week 24 after treatment to baseline were tested by Wilcoxon rank sum test using StatXact4 (Cytel Software Corp, Cambridge, MA).

RESULTS

Between March and October 1997, 120 patients were randomized; however, one patient did not receive treatment (Fig. 1). Analysis is based on 59 and 60 patients assigned to IFN-α2a plus amantadine sulphate or IFN-α2a plus placebo, respectively, who received at least one dose of medication. The baseline characteristics of the patients are summarized in Table 1.

Biochemical and Virologic Response. An initial virologic response with serum HCV RNA less than the detection limit of 1,000 copies/mL at week 4 of therapy was seen in 21 (36%) and 22 (37%) patients treated with IFN-α and amantadine or placebo, respectively. At week 20 the respective virologic response rates were 32 (54%) and 31 (52%). Treatment of pa-
Table 1. Demographic, Biochemical, Serologic, Molecular, and Histologic Profile of Patients With Chronic Hepatitis C at Baseline

| Characteristics               | IFN-α2a Plus Amantadine | IFN-α2a Plus Placebo |
|-------------------------------|-------------------------|----------------------|
| Demography                    |                         |                      |
| No. (M/F)                     | 59 (37/22)              | 60 (36/24)           |
| Body weight (kg)*             | 75.5 ± 16.9             | 71.7 ± 11.4          |
| Mean age (yr)*                | 42.1 ± 12.9             | 41.6 ± 10.3          |
| Risk factor for transmission |                         |                      |
| Transfusion-related           | 17                      | 10                   |
| Intravenous drug abuse        | 21                      | 24                   |
| Other (sexual, tattoo, occupational) | 4  | 5  |
| Unknown                       | 17                      | 21                   |
| Biochemistry*†                |                         |                      |
| ALT (U/L)                     | 57.5 ± 39.0             | 59.6 ± 36.0          |
| AST (U/L)                     | 29.5 ± 18.4             | 31.3 ± 19.3          |
| γ-GT (U/L)                    | 30.1 ± 19.9             | 52.0 ± 63.1          |
| Bilirubin (μmol/L)            | 11.6 ± 4.6              | 11.6 ± 5.6           |
| Prothrombin time (%)         | 102.0 ± 11.0            | 106.2 ± 12.4         |
| γ-Globulin (g/L)              | 19.2 ± 3.7              | 18.7 ± 3.4           |
| Serology                      |                         |                      |
| HBsAg                         | 0                       | 0                    |
| Anti-HBc                       | 21                      | 32                   |
| Anti-HCV                      | 59                      | 60                   |
| Anti-HIV-1 and -2             | 0                       | 0                    |
| Molecular                     |                         |                      |
| HCV genotype (1;2;3;4)‡       | 42; 3; 13; 1 40; 3; 15; 1 |                      |
| Pretreatment HCV RNA*‡        | (10⁶ copies/mL)         | 7.8 ± 8.5            |
| Histology                     |                         |                      |
| Inflammatory activity (mild; moderate; severe) | 39;18;2 36;24;0         |
| Fibrosis (none; mild; moderate; severe) | 8;23;18;8 2;28;22;8     |

Table 2. Virologic and Biochemical Responses During Treatment, End of Treatment (Week 48), and End of Follow-Up Period (Week 24 After the End of Treatment)

| Virologic response          | IFN-α2a Plus Amantadine | IFN-α2a Plus Placebo |
|-----------------------------|-------------------------|----------------------|
| Wk 4                        | 21 (36%)                | 22 (37%)             |
| Wk 12                       | 25 (42%)                | 32 (53%)             |
| Wk 20                       | 32 (54%)                | 31 (52%)             |
| Wk 24 of follow-up period   | 6 (10%)                 | 13 (22%)             |
| Wk 24                       | 37 (63%)                | 34 (57%)             |
| Wk 12                       | 49 (72%)                | 43 (62%)             |
| Wk 20                       | 36 (61%)                | 31 (52%)             |
| End of treatment (week 48)  | 20 (34%)                | 20 (33%)             |
| Wk 24 of follow-up period   | 12 (20%)                | 15 (25%)             |
| Wk 24                       | 37 (56%)                | 34 (57%)             |

NOTE. Responses are defined as undetectable HCV RNA by RT-PCR and normalized ALT, respectively.

Table 3. Sustained Virologic Response to Different Regimens According to Baseline Characteristics

| Characteristics | All Patients | IFN-α2a Plus Amantadine | IFN-α2a Plus Placebo |
|-----------------|--------------|-------------------------|----------------------|
| Genotype*       |              |                         |                      |
| HCV-1           | 7/82 (9%)    | 2/42 (5%)               | 5/40 (13%)           |
| HCV non-1       | 12/36 (33%)  | 4/17 (24%)              | 8/19 (42%)           |
| Mean HCV RNA    |              |                         |                      |
| ≤1 × 10⁶ copies/mL | 17/96 (18%) | 4/45 (9%)               | 13/51 (25%)          |
| >1 × 10⁶ copies/mL | 2/23 (9%)   | 2/14 (14%)              | 0/9 (0%)             |
| Age             |              |                         |                      |
| ≤40 yr          | 14/61 (23%)  | 4/30 (13%)              | 10/31 (32%)          |
| >40 yr          | 3/58 (9%)    | 2/29 (7%)               | 3/29 (10%)           |
| Sex             |              |                         |                      |
| Male            | 12/73 (16%)  | 2/37 (5%)               | 10/36 (28%)          |
| Female          | 7/46 (15%)   | 2/42 (18%)              | 3/24 (13%)           |
| Fibrosis at baseline |         |                         |                      |
| None/mild/moderate | 17/103 (17%) | 6/51 (12%)             | 11/52 (21%)          |
| Severe          | 2/16 (13%)   | 0/8 (0%)                | 2/8 (25%)            |

* Genotyping was indeterminate in one patient treated with IFN-α plus placebo.

A variety of virus- and host-related variables that have recently been shown to predict virologic response* were analyzed (Table 3). In the group of patients treated with IFN-α and amantadine, only 2 of 42 patients (5%) infected with HCV-1 and 4 of 17 patients (24%) infected with HCV non-1 achieved a sustained virologic response. In the IFN-α monotherapy group a sustained virologic response was observed in 5 of 40 (13%) and 8 of 19 patients (42%) infected with HCV-1 and HCV non-1, respectively. In relation to pretreatment viremia, the sustained virologic response in patients treated with IFN-α plus amantadine was 9% (=1 × 10⁶ copies/mL) and 14% (>1 × 10⁶ copies/mL) and in patients treated with IFN-α alone 25% (=1 × 10⁶ copies/mL) and 0% (>1 × 10⁶ copies/mL). Using logistic regression analysis for variables genotype, viremia, age, sex, and fibrosis at baseline adjusted for medication and center, only HCV genotype was associated with sustained virologic response (odds ratio [95% CI]: 4.9 [1.5; 15.8]; P = .01).
**Histology.** Paired pre- and posttreatment liver biopsy specimens were available in 16 of 59 patients treated with IFN-α plus amantadine and in 11 of 60 patients treated with IFN-α plus placebo. Pre- and posttreatment inflammatory activity was mild in 13 and 14 and moderate in 3 and 2 of 16 patients treated with combination therapy, respectively. Fibrosis was absent (n = 1), mild (n = 10), moderate (n = 4), or severe (n = 1) before therapy and absent (n = 1), mild (n = 10), or moderate (n = 5) after combination treatment. In the group of patients with IFN-α monotherapy 8 patients showed mild and 3 of 11 patients moderate inflammatory activity in the pretreatment biopsy, whereas in the posttreatment biopsy all patients had only mild inflammatory activity. Fibrosis was mild (n = 7), moderate (n = 3), or severe (n = 1) before and mild (n = 6) or moderate (n = 5) after IFN-α monotherapy. Histologic improvement of inflammatory activity was observed in 4 patients, of whom 1 patient was a sustained virologic responder (monotherapy) and 3 patients who became negative for HCV RNA during treatment, but relapsed after treatment was discontinued (1 and 2 patients with combination and monotherapy, respectively).

**Adverse Events.** According to the protocol, treatment was discontinued at week 24 in 23 and 21 patients treated with IFN-α with and without amantadine, respectively, because of detectable HCV RNA by RT-PCR 20 weeks after initiation of therapy. In addition, 10 patients treated with combination therapy and 7 patients treated with IFN-α monotherapy discontinued treatment (Fig. 1). In 6 of 17 patients treatment discontinuation was related to adverse effects (concentration impairment, weight loss, general flu-like symptoms in 3 patients receiving combination treatment; alcohol abuse and recurrent infections in 2 patients of the monotherapy group); a 71-year-old male patient treated with IFN-α and amantadine experienced a serious adverse event. In week 31 of therapy the patient developed angina and subsequently a myocardial infarction. After angioplasty the patient recovered uneventfully; however, antiviral therapy was permanently discontinued. All other adverse events reported in the combination and the monotherapy group were mild or moderate. Overall, less adverse events were reported by patients treated with than without amantadine (327 vs. 405). However, the type and relative frequency of adverse events were similar in both groups and reflect the known safety profile of IFN-α (Table 4).

In patients treated with IFN-α plus amantadine or IFN-α alone, leukocytes decreased from baseline to week 4 from 6.6 ± 2.0/μL to 4.6 ± 1.1/μL and from 6.1 ± 2.0/μL to 4.4 ± 1.4/μL, respectively. At the end of the follow-up period leukocyte counts returned to normal in both groups (6.1 ± 1.5/μL and 6.1 ± 2.1/μL, respectively). Hemoglobin and platelets decreased from baseline to week 4 from 14.5 ± 1.3 g/dL to 14.1 ± 1.4 g/dL, and from 211 ± 60/μL to 161 ± 44/μL, respectively. At the end of follow-up hemoglobin and platelets returned to baseline levels (14.1 ± 1.4 g/dL and 211 ± 54/μL, respectively) with no significant differences between treatment groups. Hyperthyroidism developed in one patient under combination therapy and in 3 patients treated with IFN-α alone, while in both treatment groups hypothyroidism was observed in 3 patients.

**HRQOL.** The mean of the differences between the sum scores of the POMS scale during therapy and follow-up period compared with baseline are shown in Fig. 2A for the intention-to-treat population. In patients who were treated with IFN-α plus amantadine compared with patients treated with IFN-α alone, a significantly better depression (P < .05) and fatigue score (P < .05) was observed at the end of the follow-up period. Although, treatment with IFN-α worsened all items, combination with amantadine showed a trend to improve fatigue and vigor scores during therapy compared with patients receiving IFN-α monotherapy. Similarly, in the EDLQ a substantial trend for improving HRQOL during the treatment period was observed for all subscales in patients treated with IFN-α plus amantadine compared with patients receiving IFN-α alone (Fig. 2B).

**DISCUSSION**

At the beginning of infection many viruses are taken into endosomes, where their fusion glycoproteins are activated at low pH to fuse virus and endosomal membranes, allowing the genome-transcriptase complex to enter the cell. Later, newly synthesized fusion glycoproteins and other virus membrane
proteins are transported to the cell surface through the acidic trans-Golgi. Evidence suggests that the M2 protein of the influenza A virus functions as a channel in 2 stages: initially as a virus membrane component, which allows acidification of the virus core; subsequently as a trans-Golgi membrane component, which relieves the pH gradient in this compartment. By blocking M2 protein function, amantadine inhibits virion core disassembly and maintains the trans-Golgi at its normally low pH.25 The molecular mechanisms of amantadine against other viruses are less well defined.6–10 Because of the lack of appropriate in vitro models, potential (pH-dependent) mechanisms of HCV entry into cells, replication, and processing are largely unknown.

Preliminary studies suggested that amantadine inhibits dose-dependently HCV RNA content in cultured peripheral blood mononuclear cells from hepatitis C virus infected patients.26 Recently, Smith14 reported promising results in a small cohort of HCV-infected patients treated with amantadine. In this trial, 22 patients with chronic hepatitis C, who had previously failed a 24-week course of IFN-α, were treated...

Fig. 2. Mean differences between the sum scores of (A) the “Profile of Mood States” scale and (B) the EDLQ during therapy (week 24 and 48) and week 24 of the follow-up period compared with baseline (intention-to-treat collective). ( ■) and ( □) represent patients treated with IFN-α2a plus amantadine and IFN-α2a plus placebo, respectively. The numbers above and below the bars represent the SD of the mean. *P < .05.
with 200 mg amantadine orally per day for 24 weeks. After a follow-up period of 24 weeks after cessation of amantadine therapy, normalization of ALT levels and reduction in HCV-RNA concentration to less than the detectable limit of the branched DNA assay (200,000 genome equivalents per mL) were observed in 6 of 22 patients (27%). Similar studies also showed biochemical or virological responses of amantadine in patients with chronic hepatitis C. These results were challenged by other pilot trials showing no effect of amantadine or rimantadine on transaminase or HCV RNA levels in patients previously not responding to IFN-α. Additional data suggested that combination therapy of chronic hepatitis C with IFN-α and amantadine may be superior to IFN-α monotherapy.

The present study is a double-blind, randomized, placebo-controlled multicenter trial comparing the efficacy of combination therapy IFN-α plus amantadine with IFN-α monotherapy in previously untreated patients with chronic hepatitis C. The patients' characteristics were similar among groups. In both treatment groups no significantly different biochemical and virologic response rates were observed at any investigated time point during treatment and at the end of the follow-up period. Almost identical virologic response rates were observed in both groups at week 4, indicating no effect of amantadine on initial viral kinetics. Thus, amantadine did not reinforce the antiviral activity of IFN-α in patients with chronic hepatitis C.

The number of adverse events reported was approximately 20% less in patients treated with than without amantadine. In the "Profile of Mood States" scale, combination therapy IFN-α plus amantadine showed a trend to improve fatigue and vigor scores during therapy compared with patients receiving IFN-α monotherapy. Similarly, in the SF-36 Health Survey related EDLQ a trend for improving HRQOL during the treatment period was observed for all subscales in patients receiving combination therapy compared with patients treated with IFN-α alone. Similar to the results of the present trial, amantadine has previously also been shown to reduce fatigue in patients with central nervous disease.

An open pilot study in IFN-α nonresponders showed significantly higher biochemical and virologic end-of-treatment response rates in patients treated with IFN-α, ribavirin, and amantadine compared with combination treatment IFN-α and ribavirin. Six months after therapy a trend for the triple therapy remained. These results were confirmed in a larger open trial of 60 IFN-α nonresponders, in which 65% and 43% of the triple therapy arm had virologic response at the end of 12-months treatment and a 6-months follow-up period, respectively, compared with 10% and 5% in the double therapy group. The data of the present study do not support IFN-α synergistic antiviral activity of amantadine, and it appears unlikely that this may be modified by the addition of ribavirin. However, it is tempting to speculate that the enhanced virologic response rates observed in these triple therapy trials may be related to amantadine-induced improvement of HRQOL during treatment leading to less side effects, higher patient compliance, and better adherence to the trial regimen. Further randomized and placebo-controlled trials, including assessment of compliance and HRQOL, are required to address this hypothesis.

When compared with IFN-α monotherapy, the combined treatment of IFN-α plus amantadine does not improve biochemical, virologic, or histologic responses in patients with chronic infection with HCV, but it appears beneficial to reduce IFN-α related adverse effects and may improve HRQOL in patients with chronic hepatitis C undergoing IFN-α therapy. However, at present, the use of amantadine to impair IFN-related side effects should not be encouraged unless further studies support efficacy and safety of the drug in this setting.

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REFERENCES

1. van der Poel CL, Cuypers HT, Reesink HW. Hepatitis C virus six years on. Lancet 1994;344:1475-1479.
2. Poyward T, Leroy V, Cohard M, Thevenot T, Mathurin P, Opolon P, Zarski JP. Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. Hepatology 1996;24:778-789.
3. Lindsay KL. Therapy of hepatitis C: overview. Hepatology 1997;26(Suppl 1):71-77.
4. Poyward T, Marcellin P, Lee S, Niederau C, Minuk GS, Ido G, Bint V, et al. The International Hepatitis Intervventional Therapy Group (IHT). Randomised trial of interferon α2b plus ribavirin for 48 weeks or for 24 weeks versus interferon α2b plus placebo for 48 weeks for treatment of chronic hepatitis C infection with hepatitis C virus. Lancet 1998;352:1426-1432.
5. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, et al. for the Hepatitis Intervventional Therapy Group (IHT). Interferon α2a plus a combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 1998;339:1485-1492.
6. Oxford JS, Schild GC. In vitro inhibition of rubella virus by 1-adaman
tamine hydrochloride. Arch Gesamte Virusforsch 1965;17:313-329.
7. Kato N, Eggers HJ. Inhibition of uncoating of fowl plague virus by l-
adaman
tamine hydrochloride. Virology 1969;37:632-641.
8. Pfla C, Trowbridge RS, Welsh RM, Staneck OL, O’Connell CM. Arena
viruses: inhibition by amantadine hydrochloride. J Gen Virol 1972;14:209-211.
9. Koff WC, Elm JL, Jr, Halstead SB. Inhibition of dengue virus replication by amantadine hydrochloride. Antimicrob Agents Chemother 1980;18:125-129.
10. Lebowitz JL, Reneker SJ. The effect of amantadine on mouse hepatitis virus replication. Adv Exp Med Biol 1993:342:117-122.
11. Dolin R, Reichman RC, Madore HP, Maynard R, Linton PN, Webber-Jones J. A controlled trial of amantadine and rimantadine in the prophylaxis of influenza A infection. N Engl J Med 1992;327:580-584.
12. Hay AJ, Wolstenholme AJ, Skelhel JJ, Smith MH. The molecular basis of the specific anti-influenza action of amantadine. EMBO J 1985:4:3021-3024.
13. Wang C, Takeuchi K, Pinto LH, Lamb RA. Ion channel activity of influenza A virus M2 protein: characterization of the amantadine block. J Virol 1993;67:5585-5594.
14. Smith JP. Treatment of chronic hepatitis C with amantadine. Dug Dis Sci 1997;42:1681-1687.
15. Younossi ZM, Perrillo RP. The roles of amantadine, rimantadine, ursode
oxycholic acid, and NSAIDs, alone or in combination with alpha interferons, in the treatment of chronic hepatitis C. Semin Liver Dis 1999;19(Suppl 1):93-102.
16. Tabone M, Ercole E, Zaffino C, Sallio Bruno F, Pera A, Bonino F. Amantadine hydrochloride decreases serum ALT activity without effects on serum HCV-RNA in chronic hepatitis C patients. Ital J Gastroenterol Hepatol 1998;30:611-613.
17. Caronia S, Crosse M, Murray-Lyon I, Lysyni D, Main J, Thomas HC, Foster G. A pilot study of interferon plus amantadine and interferon alone in the treatment of chronic hepatitis C. [Abstract]. J Hepatol 1999;30(Suppl 1):138.
18. Zeuzem S, Ruester B, Roth WK. Clinical evaluation of a new polymerase chain reaction assay (Amplicor HCV) for detection of hepatitis C virus. Z Gastroenterol 1994;32:342-347.
19. Lee J-H, Roth WK, Zeuzem S. Evaluation and comparison of different hepatitis C virus genotyping and serotyping assays. J Hepatol 1999;28:1001-1009.
20. McNair DM, Lorr M, Droppleman LF. Profile of Mood States. San Diego: Educational and Industrial Testing Service, 1971.
21. Bullinger M, Heinisch M, Ludwig M, Geier S. Skalen zur Erfassung des Wohlbefindens: Psychometrische Analysen zum “Profile of Mood States” (POMS) und zum “Psychological General Wellbeing Index” (PGWI). Zeitschrift für Differentielle und Diagnostische Psychologie 1990;11:53-61.
22. Gandek B, Ware JE. SF-36 Health Survey Manual and Interpretation Guide. Boston: New England Medical Center, The Health Institute, 1993.
23. Bullinger M, Kirchberger I, von Steinbüchel N. Der Fragebogen Alltagsleben—ein Verfahren zur Erfassung der gesundheitsbezogenen Lebensqualität. Zeitschrift für Medizinische Psychologie 1993;2:121-131.
24. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 1994;19:1513-1520.
25. Skehel JJ. Amantadine blocks the channel. Nature 1992;358:110-111.
26. Martin J, Navas S, Fernandez M, Rico M, Pardo M, Quiroga JA, Zahm F, et al. In vitro effect of amantadine and interferon alpha-2a on hepatitis C virus markers in cultured peripheral blood mononuclear cells from hepatitis C virus-infected patients. Antiviral Res 1999;42:59-70.
27. Fong TL, Fried MW, Clarke-Platt J. A pilot study of rimantadine for patients with chronic hepatitis C unresponsive to interferon therapy. Am J Gastroenterol 1999;94:980-993.
28. Krupp LB, Coyle PK, Doscher C, Miller A, Cross AH, Jandorf L, Halper J, et al. Fatigue therapy in multiple sclerosis: results of a double-blind, randomized, parallel trial of amantadine, pemoline, and placebo. Neurology 1995;45:1956-1961.
29. Brillanti S, Foli M, Di Tomaso M, Gramantieri L, Masi C, Bolondi L. Pilot study of triple antiviral therapy for chronic hepatitis C in interferon alpha non-responders. Ital J Gastroenterol Hepatol 1999;31:130-134.
30. Brillanti S, Levantesi F, Foli M, Di Tomaso M, Bolondi, L. Amantadine and Rebetron™ exert a synergistic antiviral effect on HCV replication in interferon-α non-responders with chronic hepatitis C [Abstract]. Gastroenterology 1999;116(Suppl 1):212.