

Neutropenia During Combination Therapy of Interferon Alfa and Ribavirin for Chronic Hepatitis C

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Interferon therapy of hepatitis C causes a decrease in neutrophil counts, and neutropenia is a common reason for dose adjustment or early discontinuation. However, it is unclear whether neutropenia caused by interferon is associated with an increased rate of infection. In this study, we assessed factors associated and clinical consequences of neutropenia before and during interferon therapy of chronic hepatitis C. A total of 119 patients with chronic hepatitis C treated with the combination of interferon alfa and ribavirin were analyzed. In these studies, neutropenia was not used as an exclusion or dose modification criterion. In multivariate analysis, only black race was associated with baseline neutropenia. During treatment, neutrophil counts decreased by an average of 34%. Among 3 blacks with baseline neutropenia without cirrhosis or splenomegaly, there was little or no decrease in neutrophil counts (despite typical decreases in platelet and lymphocyte counts). Documented or suspected bacterial infections developed in 22 patients (18%), but in no patient with neutropenia. United States population estimates suggest that 76,000 blacks with hepatitis C have neutrophil counts below 1,500 cells/ μ L and might be denied therapy if this exclusion criterion was generally applied. In conclusion, neutropenia is frequent during treatment of hepatitis C with interferon and ribavirin, but it is not usually associated with infection. Constitutional neutropenia, which is common among blacks, should not exclude patients from therapy with interferon as these patients usually have minimal further decreases in neutrophil counts on therapy and are not excessively prone to bacterial infections. (HEPATOLOGY 2002;36:1273-1279.)

Chronic hepatitis C is one of the most common chronic viral infections worldwide and is a major cause of cirrhosis, end-stage liver disease, and hepatocellular carcinoma.¹ Treatment with a 24- to 48-week course of interferon alfa with or without ribavirin can lead to a sustained eradication of the virus, which is associated with a long-term improvement in liver histology² and, probably, a reduction in the risk of cirrhosis and liver cancer.³ However, treatment with interferon is not

without shortcomings. Side effects are common, and many patients have contraindications to therapy.

A common side effect of interferon alfa therapy is bone marrow suppression and particularly a reduction in white blood cell counts. Absolute neutrophil and lymphocyte counts typically decrease by 30% to 50% of baseline during therapy with the doses of interferon required to treat hepatitis C.⁴ Neutrophil counts can fall to levels that are associated with an increase in risk of bacterial infections and sepsis. Indeed, in the recent large randomized controlled trials of pegylated or standard interferon combined with ribavirin neutropenia was listed as the most common reason for dose reduction (18% of patients) and was a reason for early drug discontinuation in 1% of patients.⁵ Furthermore, most studies have excluded patients with preexisting neutropenia ($< 1,500$ cells/ μ L). This exclusion criterion has major implications for select population groups with hepatitis C. Neutropenia is more common among black patients than whites⁶ and a larger proportion of blacks are excluded from trials of therapy of hepatitis C for this reason. Whereas the consequences of neutropenia are believed to be substantial, there is little evidence for

Abbreviations: NHANES 3, Third National Health and Nutrition Examination Survey; HCV, hepatitis C virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus.

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adverse clinical implications of neutropenia induced by interferon particularly in patients with preexisting low white cell counts. At the Clinical Center of the National Institute of Health, clinical studies of therapy of hepatitis C have not used neutropenia as an exclusion criterion. We retrospectively have analyzed neutrophil counts during therapy of hepatitis C and occurrence of bacterial infections. The effect of using neutropenia to exclude potential patients from treatment was determined among white and black participants in the Third National Health and Nutrition Examination Survey (NHANES 3).

Patients and Methods

Study Design. This analysis was based on all patients treated at the Clinical Center of the National Institutes of Health with the combination therapy of interferon alfa (alfa-2b) and ribavirin for chronic hepatitis C between July 1998 and January 2002. Two cohorts of patients were analyzed. One-hundred and eight patients were participating in a randomized, placebo-controlled trial of continuing long-term ribavirin therapy in patients who failed to respond to the combination of interferon alfa and ribavirin. In this study, all patients were initially treated with interferon alfa (3 million units 3 times weekly) and ribavirin (1,000 to 1,200 mg daily) for 24 weeks. Patients who became HCV-RNA-negative by 24 weeks continued therapy for a full 48 weeks, whereas those who remained positive stopped interferon therapy and were offered randomization to continue to receive ribavirin or placebo for the next 48 weeks. During this same period, another 22 patients were treated outside of this clinical trial, either because they did not fulfill the inclusion and exclusion criteria or were treated after enrollment was complete. All patients were followed in a similar fashion with visits to the outpatient clinic at 2- to 4-week intervals during the first 24 weeks of treatment and at 8-week intervals thereafter. At each visit patients were asked about symptoms and side effects of therapy and had blood drawn for complete blood counts, routine liver tests and HCV-RNA.

Patients were all above the age of 18 years and had elevations in either alanine or aspartate aminotransferase activities, presence of anti-HCV and HCV-RNA in serum, evidence of chronic hepatitis on liver biopsy performed within the previous 12 months and written informed consent. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Exclusion criteria included decompensated liver disease, alanine aminotransferase levels greater than 1,000 U/L (>25 times the upper limit of normal), pregnancy or inability to practice adequate contraception, significant

systemic or major illnesses other than liver disease, preexisting anemia (hematocrit <36% for men and <34% for women) or known history of hemolytic anemia, antiviral, or immunosuppressive therapy within the last 6 months, evidence of coronary artery disease or cerebral vascular disease, and active substance abuse. Baseline total white blood cell, neutrophil, or lymphocyte counts were not exclusion criteria.

Side effects and toxicity of therapy were classified as grade 1 (acceptable, not requiring dose modification), grade 2 (requiring dose modification), and grade 3 (requiring discontinuation of therapy) according to usual standards,⁷ except that the dose of interferon was not modified based on a specific leukocyte, neutrophil, or lymphocyte count.

Neutropenia was defined as a peripheral absolute neutrophil count below 1,500 cells/ μ L. During therapy, neutropenia was assessed at levels of 1,000, 750, and 500 cells/ μ L, the usual thresholds for dose reduction of interferon or discontinuation in therapy of hepatitis C. Episodes of infection were defined if there was a confirmed (by bacteriologic cultures or positive radiograph) or suspected infection, which led to either oral or parenteral antibiotic therapy during or within 4 weeks of stopping therapy. Infections were categorized as mild if not requiring hospital admission, intravenous antibiotics, bed rest, or discontinuation of antiviral treatment. Constitutional neutropenia was defined as the presence of an absolute neutrophil count of less than 1,500 cells/ μ L before starting treatment in the absence of cirrhosis histologically, splenomegaly (on the basis of abdominal ultrasound) or thrombocytopenia (< 150,000 platelets/ μ L) or other known cause of neutropenia.

NHANES 3. The NHANES 3 was used to determine the prevalence of neutropenia in the United States population. Conducted in the United States from 1988 through 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC), NHANES 3 consisted of interview, examination, and laboratory data collected from a complex multistage, stratified, clustered probability sample of the civilian, noninstitutionalized population aged 2 months and older, with oversampling of the elderly, non-Hispanic blacks, and Mexican-Americans.⁸ The study was approved by the CDC Institutional Review Board and all participants provided written consent to participate. Granulocytes and total white blood count were measured by Coulter Counter.⁹ Neutrophil count was calculated as granulocyte count - (0.045 \times total white blood count) to adjust for the small proportion of eosinophils and basophils that contribute to the granulocyte count.¹⁰

Statistical Analysis. Univariate analyses were performed using Fisher's exact and the Student's *t* test. A *P* value of less than .05 was considered statistically significant. All statistical tests were 2-tailed. Variables included in the multivariate models were those considered significant with a *P* value less than .10 in univariate analysis. Multiple linear and logistic regression analyses were used for continuous and nominal outcomes, respectively. For the purposes of the multivariate analysis, nominal variables were transformed into multiple categorical variables. Statview software version 5.0.1 was used to analyze data (SAS Institute, Cary, NC). Analysis of NHANES 3 data incorporated sample weights, stratification, and clustering using SUDAAN software (Research Triangle Institute, Research Triangle Park, NC).¹¹

Results

Patients. Between July 1998 and January 2002, 130 patients were treated with the combination of interferon alfa and ribavirin at the Clinical Center of the National Institutes of Health. For this analysis of neutropenia, 11 patients were excluded because of immunoglobulin deficiency (1 patient), HIV positivity (1 patient), use of pegylated interferon (1 patient), initiation of combination therapy in patients already receiving long-term interferon or ribavirin monotherapy (7 patients), or drop-out within the first week of therapy (1 patient).

Baseline characteristics of the 119 patients are summarized in Table 1. Absolute neutrophil counts ranged from 855 to 6,159 cells/ μ L, with 5 having baseline neutrophil count below 1,500 cells/ μ L. Factors that correlated with baseline neutrophil count were analyzed in both univariate and multivariate analysis (Table 2). Lower neutrophil counts correlated significantly with lower weight, hematocrit, and lymphocyte and platelet counts, as well as higher total bilirubin and iron saturation, prolonged prothrombin time, and black race. In the multivariate analysis only black race ($P < .0001$) was significantly associated with lower neutrophil counts after adjusting for lymphocyte and platelet counts.

Baseline lymphocyte counts were analyzed similarly in univariate and multivariate analysis. Lower baseline lymphocyte counts correlated with higher age, lower body mass index, lower hematocrit, platelet and neutrophil counts, lower total protein, and having a normal rheumatoid factor (P all $< .01$), but not with black race ($P = .6$). In the multiple regression analysis, only 3 variables remained associated with lower baseline lymphocyte counts: lower hematocrit, lower neutrophil counts, and having a normal rheumatoid factor (P all $< .01$).

Table 1. Baseline Characteristics

N	119
Age (mean, range in y)	47 (27-63)
Male sex (N, proportion)	75 (63%)
Weight (mean, range in Kg)	83 (53-143)
Body mass index (mean, range in Kg/m ²)	28 (18-48)
Duration of infection (mean, range in y)	23 (1-46)
Race (N, proportion)	
White	91 (76%)
Black	16 (13%)
Asian	8 (7%)
Hispanic	4 (3%)
Source of infection (N, proportion)	
Injection drug use	58 (49%)
Transfusion	20 (17%)
Medical procedures	7 (6%)
Sexual contact	2 (2%)
Unknown	32 (27%)
Genotype 1 (N, proportion)	88 (75%)
Viral load > 2 million copies/mL (N, proportion)	78 (68%)
Cirrhosis (N, proportion)	18 (15%)
Ishak score (mean, range)	2.6 (0-6)
White blood cell count (mean, range in cells/ μ L)	6,024 (2,300-9,600)
Neutrophil count (mean, range in cells/ μ L)	3,181 (855-6,159)
Hematocrit (mean, range in volume %)	44 (36-54)
Platelet count (mean, range in thousands/ μ L)	200 (58-438)

Changes in White Blood Cell Counts During Therapy. The changes in neutrophil and lymphocyte counts during treatment are shown in Fig. 1. In these analyses, results for patients who had dose modification were included, but those from patients who discontinued therapy early were censored once interferon was stopped. Neutrophil counts changed by an average of -34% (range, $+31$ to -74%) during therapy, and lymphocyte counts by -33% (range, $+21$ to -71%). The majority of patients (63%) had at least 1 neutrophil count below 1,500 cells/ μ L, but only 32 patients (27%) had a neutrophil count below 1,000 cells/ μ L, 11 (9%) below 750 cells/ μ L, and 2 (2%) below 500 cells/ μ L during the 24- to 48-week course of therapy. Five patients had an average neutrophil count below 1,000 cells/ μ L during therapy.

Variables that were associated with having at least 1 neutrophil count below 1,000 cells/ μ L during treatment are shown in Table 3. After adjusting for baseline neutrophil count, the only variable that was associated with developing neutropenia during therapy was lower body weight (OR, 0.94; 95% CI, 0.89-0.99; $P = .0045$).

The correlation between total white blood cell and neutrophil counts was good in patients with neutrophil counts higher than 1,000 (adjusted r^2 , 0.711; $P < .0001$), but it was poor in patients with neutrophil counts below 1,000 (adjusted r^2 , 0.1; $P = .043$). In multivariate analysis, only lower baseline lymphocyte count ($P < .0001$) and longer duration of treatment ($P < .0001$) were significantly associated with development of low lymphocyte counts during therapy.

Table 2. Factors That Were Associated With Initial Neutrophil Count (Univariate Analysis)

Variable	Correlation Coefficient (r)	P Value
Age (y)	-0.16	.078
Male sex	-0.12	.180
Weight (Kg)	0.19	.037
Black race	-0.36	< .0001
Alanine aminotransferase (IU/L)	-0.061	.51
Aspartate aminotransferase (IU/L)	-0.17	.058
Bilirubin (mg/dL)	-0.18	.048
Albumin (g/dL)	0.14	.13
Total protein (g/dL)	0.15	.11
Prothrombin time (sec)	-0.35	< .0001
Creatinine (mg/dL)	0.09	.32
Hematocrit (volume %)	0.20	.029
Platelet count (1,000/ μ L)	0.48	< .0001
Baseline lymphocyte count (1,000/ μ L)	0.45	< .0001
Abnormal rheumatoid factor	0.09	.34
Abnormal antinuclear antibody	-0.06	.54
TSH (μ IU/mL)	0.04	.70
Iron saturation (%)	-0.20	.03
Ferritin (μ g/L)	-0.15	.11
HCV RNA > 2 million copies/mL	-0.09	.35
HCV genotype 1	-0.15	.10
Ishak score (U)	-0.13	.17
Presence of cirrhosis	-0.09	.33
Presence of splenomegaly	-0.06	.53

Table 3. Pretreatment Factors and Odds Ratios for Developing at Least 1 Neutrophil Count <1,000 Cells/ μ L During Treatment (Univariate Analysis)

Variable	OR (95% CI)	P Value
Age (y)	0.99 (0.95-1.04)	.87
Male sex	0.97 (0.42-2.24)	.94
Black race	2.43 (0.82-7.19)	.11
ALT (IU/L)	1.002 (0.99-1.007)	.32
AST (IU/L)	1.009 (1.001-1.017)	.024
Bilirubin (mg/dL)	2.93 (0.97-8.92)	.058
Albumin (g/dL)	0.70 (0.22-2.21)	.54
Total protein (g/dL)	1.23 (0.55-2.75)	.61
Prothrombin time (sec)	2.54 (1.51-4.27)	.0004
Creatinine (mg/dL)	0.49 (0.039-6.051)	.58
Weight (Kg)	0.96 (0.93-0.99)	.0049
Hematocrit (volume %)	0.94 (0.84-1.045)	.24
Platelet count (1,000/ μ L)	0.98 (0.97-0.99)	< .0001
Abnormal rheumatoid factor	0.90 (0.39-2.079)	.81
Iron saturation (%)	30.86 (1.88-507.2)	.016
Ferritin (μ g/L)	1.002 (0.99-1.004)	.25
HCV RNA > 2 million copies/mL	1.18 (0.48-2.90)	.72
HCV genotype 1	2.097 (0.72-6.076)	.17
Ishak score (U)	1.26 (0.99-1.60)	.056
Presence of cirrhosis	2.50 (0.89-7.053)	.083
Presence of splenomegaly	1.79 (0.72-4.49)	.21
Baseline neutrophil count (1,000/ μ L)	0.13 (0.057-0.29)	< .0001
Baseline lymphocyte count (1,000/ μ L)	0.30 (0.14-0.67)	.0031

Five patients had preexisting neutropenia (neutrophil counts lower than 1,500 cells/ μ L). Three out of the 5 met the criteria for constitutional neutropenia (absence of cirrhosis, splenomegaly, or thrombocytopenia). These patients had baseline neutrophil counts of 855, 1,145, and 1,399 cells/ μ L and were all black. During treatment, neutrophil counts changed minimally in these 3 patients, and none had neutrophil counts of less than 750 cells/ μ L

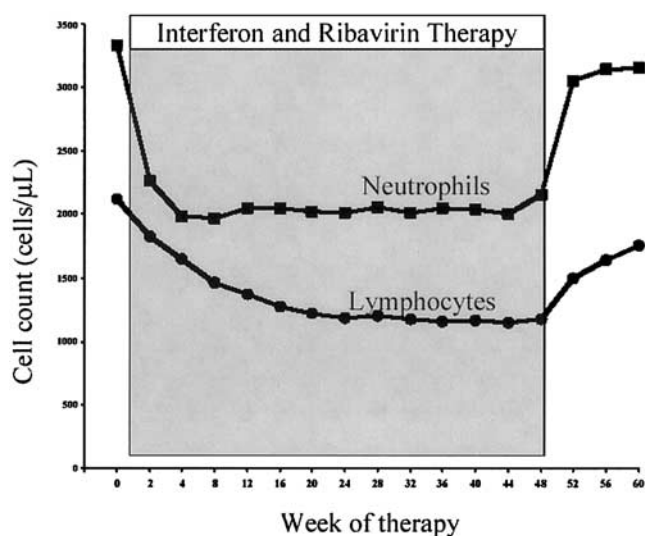


Fig. 1. Temporal evolution of neutrophil and lymphocyte counts during interferon and ribavirin combination therapy.

during 48 weeks of therapy. Indeed, average neutrophil counts on therapy increased by 25% in 1 patient and decreased by only 9.6% and 4.7% in the other 2. Nevertheless, lymphocyte counts decreased in these 3 patients to the same degree as nonneutropenic patients, averaging -40% on therapy. In contrast, the remaining 2 patients with preexisting neutropenia were not black, and both had advanced fibrosis and thrombocytopenia. Both patients developed significant decreases in neutrophil counts with therapy, average neutrophil counts being 439 and 878 cells/ μ L during treatment.

The dose of interferon was modified in 16 patients (13%) for the following reasons: psychiatric problems or persistent fatigue (7 patients), angina pectoris (3 patients), anemia (2 patients), and other symptoms (4 patients). No patient had a dose modification because of neutropenia. Among the analyzed patients, 50 (42%) had a sustained virologic response and were HCV-RNA-negative 6 months after stopping therapy. The sustained response rate was similar in patients who developed significant neutropenia (45%) compared with those who did not (42%; $P > .9$).

Infections. Twenty-two patients (18%) developed bacterial infections during or immediately after stopping therapy (Table 4). Only 1 patient required hospital admission: a 72-year-old man with Child's Class A cirrhosis developed cellulitis and edema of the lower extremities associated with high fever and prostration after 28 weeks

Table 4. Infections Occurring Among the 119 Patients Treated With Interferon and Ribavirin

Infection	n
Sinusitis	5
Pharyngitis	4
Gingivitis	1
Otitis media	2
Bronchitis	2
Pneumonia	1
Urinary tract infection	4
Prostatitis	1
Cellulitis	2
Total	22

of combination therapy. He required intravenous antibiotics, and both interferon and ribavirin were discontinued. He had not had significant neutropenia before therapy (1,670 cells/ μ L) or while on therapy (mean neutrophil count was 1,118 cells/ μ L) and recovered with treatment. All other episodes of infection were classified as mild.

No patient who developed infection had a preexisting neutropenia (below 1,500 cells/ μ L) and none developed neutropenia of less than 750 cells/ μ L at any point during treatment. Comparison of patients with and without infections showed no differences in baseline neutrophil counts or in degree of decrease in neutrophil counts during therapy (Table 5). There was no correlation between the week of infection and the week of the lowest neutrophil count. In univariate analysis, variables associated with infection included lower baseline reticulocyte count (OR, 0.15; 95% CI, 0.039-0.55; $P = .0044$) and lower ferritin levels (OR, 0.99; 95% CI, 0.98-0.99; $P = .04$). Older age did not reach statistical significance (OR, 1.05 per year; 95% CI, 0.99-1.10; $P = .057$). In the multiple logistic regression analysis, lower reticulocyte counts was associated with infection (OR, 0.19 per percent increase; 95% CI, 0.053-0.72; $P = .014$). The other variables evaluated in this analysis were unrelated to infection, including ferritin ($P = .12$), black race ($P = .51$), initial immunoglobulin levels ($P > .14$), baseline neutrophil or lymphocyte counts or their average value during therapy ($P > .4$).

NHANES 3. The average total white blood cell and granulocyte counts and estimated neutrophil counts in the United States general population aged 20 to 64 years as assessed in NHANES 3 is shown according to non-Hispanic white and black ethnicity in Table 6. Estimated mean neutrophil counts were significantly lower in blacks than whites. Overall, neutropenia was present in 5% of blacks compared with only 0.3% of whites. Among persons with anti-HCV, neutropenia was present in almost 12% of blacks, but only 1.4% of non-Hispanic whites.

With these results, an estimated 76,000 blacks have hepatitis C and neutrophil counts below 1,500 cells/ μ L. Other ethnic groups had results similar to non-Hispanic whites.

Discussion

The treatment of chronic hepatitis C has steadily improved since the initial demonstration that interferon alfa had an effect on the biochemical and virologic features of disease.¹² At present, optimal combinations of pegylated interferon alfa and ribavirin yield rates of response of approximately 55%.⁵ However, it should be stressed that these excellent results were achieved in cohorts of patients that had uncomplicated hepatitis C, without comorbidities or contraindications to therapy. In studies on unselected patients with chronic hepatitis C presenting to referral centers, only a third of patients were found to qualify for therapy with the usual inclusion and exclusion criteria used in the pivotal controlled trial.¹³ As advances are made in therapy of chronic hepatitis C, advances also must be made in the ability to apply this therapy to wider groups of patients.

Among the exclusion criteria for therapy, low white blood cell and neutrophil counts are seemingly appropriate in view of the myelosuppressive actions of interferon alfa. The safety concern is that interferon-induced neutropenia may predispose to severe bacterial infection. However, the association of drug-induced neutropenia and infection has been shown largely in studies of chemotherapy, such as in oncology patients undergoing severe immune system and bone marrow suppressive therapy.¹⁴ In patients without immune suppression and no other predisposing factor for bacterial infections, it is not clear whether drug-induced neutropenia carries an excess risk for severe bacterial infection. Indeed, in a pooled analysis among 2,089 patients in the pivotal studies of combination therapy of hepatitis C,¹⁵⁻¹⁷ neutropenia was not as-

Table 5. Differences Among Baseline and On-Treatment Leukocyte Counts Between Patients Who Developed Infection Compared With Those Who Did Not Develop Infection

Variable	No		<i>P</i>
	Infection	Infection	
n	97	22	
Baseline neutrophil count	3,171	3,226	.83
Neutrophil count decrease (%)	34.1	33.7	.92
Average neutrophil count during treatment	2,036	2,103	.72
Lowest neutrophil count during treatment	1,392	1,536	.32
Baseline lymphocyte count	2,090	2,020	.63
Lymphocyte count decrease (%)	33.9	26.3	.03
Average lymphocyte count during treatment	1,379	1,477	.41
Lowest lymphocyte count during treatment	955	1,016	.52

Table 6. United States Estimates of Total White Blood Cell Count, Granulocytes, Neutrophils, and Neutropenia (<1,500 Cells/ μ L) in Unselected and Anti-HCV-Positive Population for Whites and Blacks From Third National Health and Nutrition Examination Survey (1988-1994)

General Population	Non-Hispanic Whites (Standard Error)	Non-Hispanic Blacks (Standard Error)	P Value
Total white blood cell count (cells/ μ L)	7,310 (50)	6,620 (20)	<.00001
Granulocytes (cells/ μ L)	4,650 (40)	3,790 (20)	<.00001
Estimated neutrophils (cells/ μ L)	4,440 (40)	3,590 (20)	<.00001
Percentage with neutrophils < 1,500 cells/ μ L	0.32 (0.09)	5.11 (0.38)	<.00001
Estimated total number in the population	105,634,000	15,749,000	
Estimated number with neutrophils < 1,500 cells/ μ L	338,000	804,773	
Anti-HCV Positive			
Total white blood cell count (cells/ μ L)	7,710 (290)	6,300 (190)	<.00001
Granulocytes (cells/ μ L)	4,820 (230)	3,360 (160)	<.00001
Estimated neutrophil count (cells/ μ L)	4,470 (220)	3,080 (150)	<.00001
Percentage with neutrophils < 1,500 cells/ μ L	1.39 (1.36)	11.74 (2.43)	.0006
Estimated total number in the population	2,066,000	651,000	
Estimated number with neutrophils < 1,500 cells/ μ L	28,000	76,000	

sociated with infection. Only 1 of the 23 deaths reported from these studies was caused by infection. However, patients with baseline neutrophil counts below 1,500 cells/ μ L were excluded and the dose of interferon was reduced to 50% if neutrophil count fell below 750 cells/ μ L.¹⁸

In this analysis of neutrophil counts among 119 patients treated at a single referral center, neutropenia was not used as an exclusion criterion and therapy was safely accomplished despite decreases in neutrophils below the usual levels that lead to dose reduction or drug interruption. Bacterial infections did not occur in neutropenic patients, and the only severe infection that was identified occurred in an elderly patient with preexisting cirrhosis. Of potential interest, the only baseline measure that predicted subsequent infection was low reticulocyte count. We are unaware of other information linking reticulocyte count to subsequent infections. Nevertheless, the association was strong and deserves further investigation.

There was poor correlation between total white blood cell count and neutrophil count in patients with neutropenia, indicating that measurement of absolute neutrophil count instead of total white blood cell count is necessary in monitoring therapy. Of greatest importance, 3 patients were treated who appeared to have constitutional neutropenia, marked by persistently low neutrophil counts (below 1,500 cells/ μ L) without other evidence of bone marrow suppression or splenomegaly. Constitutional neutropenia is common, affecting roughly 800,000 blacks, of whom 76,000 also are anti-HCV-positive. Almost 12% of blacks with hepatitis C would be excluded from therapy if a neutrophil criterion of 1,500 cells/ μ L were required for treatment. Constitutional (ethnic) neutropenia is a benign condition and is not associated with an increased risk of bacterial infection.¹⁹ Indeed, these

patients develop typical increases in neutrophils during bacterial infections and have normal responses to hydrocortisone.^{19,20} The cause of constitutional neutropenia is not known, but is probably related to differences in the release of mature granulocytes from the bone marrow storage pool to the circulating blood and not to a decrease in production. Normal cellularity and maturation of all cell lines have been found in healthy blacks with neutropenia.²⁰ In the current study, patients with constitutional neutropenia had minimal decreases (or actual increases) in neutrophil counts during interferon therapy, while having typical interferon-induced decreases in lymphocyte and platelet counts. Thus, patients with low neutrophil counts without bone marrow compromise, cirrhosis, or splenomegaly can probably be safely treated with interferon and need not be excluded from therapy or treated with growth factors to increase white cell counts before starting therapy.

A separate argument could be used for caution in treating patients with neutropenia caused by cirrhosis and hypersplenism. Virtually all published studies on use of interferon in patients with cirrhosis have excluded patients with preexisting neutropenia, and even in these selected patients dose modification for neutropenia is common (up to 14%).²¹ In our study, patients with cirrhosis and preexisting neutropenia had typical decreases in white blood cell counts during therapy. Furthermore, because of the presence of cirrhosis, these patients are likely to have an increase in susceptibility to bacterial infections. The fact that the 2 patients in this study with preexisting neutropenia and cirrhosis did not suffer a bacterial infection argues only that bacterial infections are not invariable during interferon-induced neutropenia. Patients with neutropenia caused by cirrhosis are best closely

monitored and given growth factors or reduced dosages of interferon in the event of severe neutropenia.

In conclusion, neutropenia is frequent during treatment of hepatitis C with interferon and ribavirin, but it is not commonly associated with infections. These results suggest that patients with constitutional neutropenia probably can be treated safely and may not require dose modification. These findings support a revision of current criteria for exclusion and dose modification based on white blood cell counts in the treatment of hepatitis C. These modifications would expand the proportion of patients who could receive interferon-based therapy for hepatitis C. Because this was a descriptive study of limited sample size, it did not allow for identification of a specific cutoff value for neutrophils that can be considered safe. However, in the absence of other risk factors for bacterial infection, neutrophil counts of as low as 500 cells/ μL are likely to be safely tolerated during interferon therapy. These criteria need to be validated in larger, prospective clinical trials.

References

- Alter MJ, Mast EE. The epidemiology of viral hepatitis in the United States. *Gastroenterol Clin North Am* 1994;23:437-455.
- Lau DT, Kleiner DE, Ghany MG, Park Y, Schmid P, Hoofnagle JH. Ten-year follow-up after interferon-alpha therapy for chronic hepatitis C. *HEPATOLOGY* 1998;28:1121-1127.
- Camma C, Giunta M, Andreone P, Craxi A. Interferon and prevention of hepatocellular carcinoma in viral cirrhosis: an evidence-based approach. *J Hepatol* 2001;34:593-602.
- Wong S, Kaita K, Gauthier T, Jones S, Minuk GY. A comparative trial of recombinant interferon alpha 2a versus alpha 2b on myelosuppression in healthy adult volunteers. *Hepatogastroenterology* 1996;43:301-305.
- Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;358:958-965.
- Reed WW, Diehl LF. Leukopenia, neutropenia, and reduced hemoglobin levels in healthy American blacks. *Arch Intern Med* 1991;151:501-505.
- Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207-214.
- Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94. Series 1: programs and collection procedures. *Vital Health Stat* 1994;1:1-407.
- U.S. Department of Health and Human Services (DHHS), National Center for Health Statistics. Third National Health and Nutrition Examination Survey, 1988-1994, Reference Manuals and Reports: Manual for Medical Technicians and Laboratory Procedures Used for NHANES III (CD-ROM). National Health and Nutrition Examination Survey III, 1988-94 (NCHS CD-ROM). In: Centers for Disease Control and Prevention; 1996.
- Elin RJ. Laboratory reference range values of clinical importance. In: Wyngaarden JB, Smith LH, Jr, eds. *Cecil Textbook of Medicine*. 18th ed. Philadelphia: Saunders, 1988; 2394-2404.
- Research Triangle Institute. SUDAAN user's manual release 7.0, 1996.
- Hoofnagle JH, Mullen KD, Jones DB, Rustgi V, Di Bisceglie A, Peters M, Waggoner JG, et al. Treatment of chronic non-A, non-B hepatitis with recombinant human alpha interferon. A preliminary report. *N Engl J Med* 1986;315:1575-1578.
- Muir AJ, Provenzale D. A descriptive evaluation of eligibility for therapy among veterans with chronic hepatitis C virus infection. *J Clin Gastroenterol* 2002;34:268-271.
- Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med* 1966;64:328-340.
- Davis GL, Esteban-Mur R, Rustgi V, Hoefs J, Gordon SC, Trepo C, Shiffman ML, et al. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. International Hepatitis Interventional Therapy Group. *N Engl J Med* 1998;339:1493-1499.
- McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, Goodman ZD, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. *N Engl J Med* 1998;339:1485-1492.
- Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, Bain V, et al. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). *Lancet* 1998;352:1426-1432.
- Maddrey WC. Safety of combination interferon alfa-2b/ribavirin therapy in chronic hepatitis C-relapsed and treatment-naive patients. *Semin Liver Dis* 1999;19 (Suppl 1):67-75.
- Haddy TB, Rana SR, Castro O. Benign ethnic neutropenia: what is a normal absolute neutrophil count? *J Lab Clin Med* 1999;133:15-22.
- Mason BA, Lessin L, Schechter GP. Marrow granulocyte reserves in black Americans. Hydrocortisone-induced granulocytosis in the "benign" neutropenia of the black. *Am J Med* 1979;67:201-205.
- Heathcote EJ, Shiffman ML, Cooksley WG, Dusheiko GM, Lee SS, Balart L, Reindollar R, Reddy RK, et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *N Engl J Med* 2000;343:1673-1680.