Treatment of HCV in HIV/HCV Coinfection: What Are the New Questions?

there are a number of potential benefits tied to the treatment of chronic hepatitis C virus (HCV) infection in HIV-infected individuals. The most desired outcome of treatment—which is possible in both HCV-monoinfected and HIV/HCV-coinfected patients—is viral eradication. Additional but unproven benefits of anti-HCV therapy may be a reduction in inflammatory hepatic damage with regression of fibrosis and/or the risk of hepatocellular carcinoma, or to improve tolerability of antiretrovirals. There is also the public health component of HCV treatment: to render patients aviremic, thus reducing their chances of passing the virus on to others.

Over the past year, the results of several pivotal studies evaluating pegylated interferon and ribavirin—the standard-of-care drug combination for the treatment of chronic hepatitis C—in HIV/HCV-coinfected patients have been completed and published. Across the board, the results were encouraging, illustrating a clear-cut therapeutic advantage of pegylated interferon and ribavirin over conventional interferon-alpha and ribavirin. However, there are important design and population differences between the studies, raising some questions as to how best to translate these data into clinical practice.

Treatment Basics

Until recently, daily or three-times-weekly injections of interferon-alpha, combined with daily oral doses of ribavirin, was the only treatment option available, with sustained response rates well below 20% in HCV-monoinfected patients. While interferon-alpha remains a vital component of anti-HCV combination therapy, attention has now shifted to the pegylated interferons—formulations of interferon-alpha that have been covalently bonded to polyethylene glycol (PEG)—that inhibit destruction of interferon by polymerases, reduce immunogenicity, and improve exposure by slowing renal clearance. With a half-life of 80 hours, pegylated interferons ensure sustained antiviral effects without added toxicity.

Schering-Plough’s 12 kDa branched-pegylated IFN-alpha-2b (Peg-Intron) was approved in January 2001 and Hoffmann-La Roche’s 40 kDa branched-pegylated IFN-alpha-2a (Pegasys) was approved in October 2002.

Both pegylated interferons are approved for use in combination with ribavirin, a guanosine nucleoside analogue. Schering-Plough markets Rebetol-brand ribavirin and Roche markets Copegus-brand ribavirin. Doses of Peg-Intron (weight-dependent dose) and Pegasys (fixed dose) are administered, via subcutaneous injection, once a week. Ribavirin is taken orally, usually twice a day.

In HCV-monoinfected (HIV-negative) patients, combinations of pegylated interferon and ribavirin were associated with sustained virologic response rates of up to 46% in those with genotype 1 and up to 80% in those with genotype 3. In HIV/HCV-coinfected patients, a number of studies have been completed and the results of four pivotal clinical trials published in peer-reviewed medical journals have emerged. While the rates of sustained virologic responses in coinfected patients appear to be lower than those obtained in HCV-monoinfected patients, these new data clearly indicate that pegylated interferon and ribavirin is the combination of choice that affords a significant improvement over regimens containing conventional interferon-alpha.

The Studies

The French Ribavic (ANRS HC02) study was an open-label, randomized, controlled comparison of conventional interferon/ribavirin and pegylated interferon/ribavirin (Carrat, 2004). Four-hundred twenty-one patients were randomized to receive either pegylated interferon/ribavirin—using Schering-Plough’s Peg-Intron formulation of pegylated interferon (1.5 µg/kg/week) along with a fixed dose of ribavirin (800 mg/day)—or conventional interferon-alfa 3 MIU three-times weekly plus fixed-dose ribavirin (800 mg/day). Treatment was continued for 48 weeks, with an additional 24 weeks of follow-up incorporated into the study.

There was also a randomized, single-center, open-label clinical trial—colloquially dubbed the Laguna study—conducted in Barcelona (Laguno, 2004). Ninety-five patients were randomized to receive either Peg-Intron (1.5 µg/kg/week) plus ribavirin (800 to 1,200 mg/day, dependent on body weight) or conventional interferon-alfa (3 MIU TIW) plus ribavirin (800 to 1,200 mg/day). Patients with HCV genotype 1, or genotypes 2 or 3 with high HCV viral loads, were treated for 48 weeks, while patients with HCV genotypes 2 or 3 and low HCV viral loads were treated for 24 weeks.

The AIDS Clinical Trials Group (ACTG) 5071 study was a randomized, open-label clinical trial of Roche’s Pegasys/ribavirin vs. conventional interferon/ribavirin (Chung, 2004). One-hundred thirty-three coinfected patients were randomized to 180 µg/weekly pegylated interferon plus escalating doses of ribavirin, starting with 600 mg/daily for the initial four weeks, 800 mg daily for the next four weeks, and subsequently to a maximum of 1,000 mg/day (most patients were maintained on 800 mg/day). Patients randomized to receive conventional interferon began therapy with 6 MIU three times weekly, and then decreased to 3 MIU three times weekly after 12 weeks, along with dose-escalating ribavirin.

But last not least is the AIDS Pegasys Ribavirin International Coinfection Trial (APRICOT), by far the largest and only international HCV/HIV-coinfection treatment trial conducted to date (Torriani, 2004). The study enrolled 868 patients from 91 sites in 19 countries. Two-hundred eighty-five patients were randomized to receive conventional interferon (3 MIU TIW) plus ribavirin (800mg/daily), 283 were randomized to receive Pegasys (180 mg/weekly) plus ribavirin placebo, and 289 were randomized to receive pegylated interferon and ribavirin.

Demographic Data

Among the patients in these four studies randomized to receive pegylated interferon plus ribavirin, there were a number of demographic similarities. Between 68% and 80% of the pegylated interfer-
on/ribavirin recipients in these four studies were male. Average baseline CD4+ count data were also similar, with a low of 477 cells/mm³ in the RIBAVIC study to a high of 560 cells/mm³ in the Laguno study. HIV infection was well controlled: between 82% and 88% of patients were receiving potent antiretroviral therapy and between 60% and 70% of the patients had HIV-RNA levels below the level of quantification.

There are some important demographic differences as well. A5071 enrolled a sizeable percentage of African Americans: 33% received pegylated interferon/ribavirin. In APRICOT, 11% of pegylated interferon/ribavirin recipients were African American. Not surprisingly, in the European studies, very few (if any) were of African descent.

The Laguno study had the smallest percentage of patients with HCV genotype 1—the most recalcitrant of the HCV genotypes—with 49% randomized to pegylated interferon/ribavirin, compared to 52% in RIBAVIC, 77% in A5071, and 61% in APRICOT. Importantly, 53% of patients receiving pegylated interferon/ribavirin in the Laguno study had HCV viral loads below 800,000 IU/mL, compared to an average of 940,000 IU/mL among pegylated interferon/ribavirin recipients in RIBAVIC, 6.2 million IU/mL in A5071, and 5.6 million IU/mL in APRICOT. In A5071 and in APRICOT, 82% and 72% of patients had a pretreatment HCV viral load above 800,000 IU/mL. Dr. Torriani also pointed out that 40% of patients receiving pegylated interferon/ribavirin in RIBAVIC had bridging fibrosis or cirrhosis, compared to 30% in the Laguno study, 11% in A5071, and 15% in APRICOT.

“These demographic differences are worth noting,” Dr. Torriani explained. “They are important when interpreting the results of these four studies.”

Sustained Virologic Responses: A Comparison

A SUSTAINED VIROLOGIC RESPONSE (SVR) IS DEFINED AS AN UNDETECTABLE HCV-RNA TITER SIX MONTHS AFTER COMPLETING TREATMENT. SVRs were reported using the stringent intent-to-treat analysis (see Figure 1).

In RIBAVIC, SVRs were documented in 27% of all patients receiving pegylated interferon/ribavirin, compared to 21% of patients receiving conventional interferon/ribavirin. In the Laguno study, SVRs were reported in 44% of patients receiving pegylated interferon/ribavirin, compared to 21% of patients receiving conventional interferon/ribavirin. In A5071, SVRs were reported in 27% of patients in the pegylated interferon/ribavirin group and 12% of patients in the conventional interferon/ribavirin group. Finally, in the APRICOT study, SVRs were achieved in 40% of patients randomized to the pegylated interferon/ribavirin group, 20% of the pegylated interferon/placebo recipients, and 12% of those randomized to the conventional interferon/ribavirin group.

Predictors of SVR

OF CENTRAL CONCERN IN ALL OF THE CONFECTION TREATMENT TRIALS reported to date are the significant relapse rates. In APRICOT, for example, the end-of-treatment (EOT) response—defined as HCV-RNA levels below 50 IU/mL at the completion of therapy—was 38% in the patients with HCV genotype 1 receiving pegylated interferon/ribavirin. However, within six months after completing therapy, the rate of SVRs among HCV genotype 1 patients receiving pegylated interferon/ribavirin dropped to 29%. “The relapse rate was less than 20%,” Dr. Torriani said. “But relapses were present and pose the question of whether a higher dose of ribavirin may decrease the relapse rate.”

In all studies, genotypes 2 or 3 emerged as the strongest independent predictor of SVR, followed by low HCV viral loads for genotypes 1 and 4. In the RIBAVIC study, younger age and ALT levels three times the upper limit of normal were additional predictors of SVR. Unlike the very high baseline HCV-RNA levels in A5071, RIBAVIC, and APRICOT, baseline HCV viral loads in the Laguno study were below 800,000 IU/mL in 53% of patients randomized to receive pegylated interferon/ribavirin. It is not surprising that overall SVR in that group reached 44%, including 37% of patients with HCV genotypes 1 or 4. As explained by Dr. Torriani, in APRICOT, HCV genotype 1 patients with low HCV viral loads had a 61% SVR compared to 18% of those with genotype 1 and high viral loads (see Figure 2).

“What these four studies showed is that pegylated interferon plus ribavirin is significantly superior to conventional interferon plus ribavirin,” Dr. Torriani summarized. “However, these overall sustained virologic response rates are lower than the ones we’ve observed in HCV-monoinfected patients.”

As for the HCV genotype, the RIBAVIC data yielded SVRs of 17% among patients receiving pegylated interferon/ribavirin with genotypes 1 or 4, compared to 44% of patients with genotypes 2 or 3. In the Laguno study, the SVR was 38% among patients with HCV genotype 1 or 4 treated with pegylated interferon/ribavirin, compared to 53% of patients with HCV genotypes 2 or 3. In A5071, 14% of HCV genotype 1 patients treated with pegylated interferon/ribavirin had SVRs, compared to 73% of patients with genotypes 2 or 3 receiving these two agents. And in APRICOT, SVRs were reported in 29% of genotype 1 patients treated with pegylated interferon/ribavirin, compared to 62% of patients with genotypes 2 or 3 receiving pegylated interferon/ribavirin.
IU/mL, we can treat him for a year and expect a sustained response,” Dr. Torriani said. “On the other hand, if we have patients with HCV viral loads of greater than 800,000 IU/mL—which, unfortunately, is what we see with most of our genotype 1 patients—we can probably expect a sustained response rate of approximately 18%. The ribavirin dosing used in the Laguno study suggests that higher doses may result in a better initial response, as well as a decrease in relapses. However, this needs to be studied in a larger randomized trial. Additional studies looking at this have been requested by the FDA.”

Neither Ribavirin nor Apricot determined that the baseline CD4+ cell count (greater than 200 cells/mm³), lower body weight, or absence of cirrhosis were predictive of SVRs.

Ribavirin, Apricot, and As071 all confirmed that the absence of an early virologic response (EVr)—defined as a 2 log₁₀ reduction or more in HCV viral load by week 12—has a very strong negative predictive value (NPV) with respect to sustained responses. Therefore, if a patient has not achieved an EVr by week 12, the chances of an SVR are practically nonexistent. Only 2% or less of the patients in each treatment group who did not have an EVr went on to have a sustained response.

Also of interest are analyses of the positive predictive value (PPV) of sustained responses by EVRs. Four weeks after beginning treatment, HCV genotype 1 patients who had undetectable HCV viral loads had an 82% chance of achieving an SVR. Among genotype-2 or -3 patients with undetectable HCV-RNA levels at four weeks, 94% achieved an SVR. “This positive predictive value is very suggestive,” Dr. Torriani confided. “If you have a patient who is having a difficult time with side effects and is discouraged by his or her therapy, seeing undetectable HCV-RNA at week 4 should really give the patient and his or her provider a strong incentive to stay on therapy, given that the chance of sustained response is very high.”

Adverse Events

In Apricot, the proportion of patients who withdrew from therapy differed among the three treatment groups and was lowest in the pegylated interferon/ribavirin group (see Figure 3). Overall, 39% of patients withdrew from treatment with conventional interferon/ribavirin, 31% withdrew from treatment with pegylated interferon/ribavirin, and 25% withdrew from pegylated interferon/ribavirin. However, the number of patients reporting adverse events or serious adverse events was generally similar among the treatment groups. Serious events judged to be related to treatment were more frequent in the two groups that received pegylated interferon.

There were ten deaths in the study, but only two were concluded to be treatment-related. The death of one patient who received conventional interferon/ribavirin was attributed to respiratory failure; the death of the second patient who received pegylated interferon/ribavirin was attributed to suicide.

Fatigue, fever, headache, myalgia, nausea, diarrhea, insomnia, asthenia, and depression were all relatively common adverse events, affecting 20% to 45% of patients.

With respect to psychiatric side effects, Dr. Torriani pointed out that most patients experience a peak in symptoms of depression and anxiety around the fourth month of treatment. “This is good news in the sense that we often have a strong indication as to how well the patient is responding to therapy by the end of month 4,” she said. “In patients with symptoms of psychiatric side effects, this is likely a good time to decide whether or not therapy should be stopped or continued, based on what we know about early virologic responses. On the other hand, signs of depression have to be searched at each visit, and treatment with appropriate antidepressants started without delay since the effects will be often begin within two to four weeks.”

Weight loss was another adverse effect of therapy seen in all trials. “In HCV-monoinfected patients, a loss of five kilograms is typical during treatment,” Dr. Torriani pointed out. “In our coinfected patients, we see similar reductions in body weight. This may aggravate lipoatrophy. Indeed, we saw many of our patients melting away. Fortunately, they recuperated from their weight loss after stopping therapy. This certainly isn’t a side effect that should be underestimated.”

Neutropenia is a common adverse effect of pegylated interferon/ribavirin therapy. A neutrophil count of less than 1,000 cells/mm³ has been documented in as many as 50% of patients receiving this combination; a neutrophil count of less than 500 cells/mm³ has been documented in 2% to 11% of patients. “While this can be corrected with G-CSF,” Dr. Torriani noted, “there haven’t been any randomized studies looking at its use in coinfected patients undergoing HCV therapy.” In most clinical trials, the incidence of severe bacterial infections, as a result of treatment-induced neutropenia, is less than 2%. In Apricot, the incidence was approximately 3% in the pegylated interferon groups compared to 7% in the conventional interferon group.

As for CD4+ count changes, Apricot noted a decrease of 131 cells/mm³ in the conventional interferon/ribavirin group, a decrease of 135 cells/mm³ in the pegylated interferon/ribavirin group, and a decrease of 157 cells/mm³ in the pegylated interferon/ribavirin group. The drop was attributable to the overall decrease in leukocytes. However, there was a small increase in the percentage of CD4+ counts during treatment. “In addition,” Dr. Torriani added, “by the end of the follow-up period, the patients’ CD4+ cell counts had returned to pre-treatment levels and we did not observe any increases in opportunistic infections.”

In Apricot, hepatic decompensation occurred in 14/860 (1.6%) patients who received at least one dose of study medication. Decompensation occurred mostly within the first six months of therapy, only in patients with cirrhosis, and was evenly distributed among the three treatment groups.

To identify the risk factors associated with hepatic decompensation, members of the Apricot safety monitoring group based in Germany— independent of the study sponsor and investigators—performed multiple logistic regression analysis comparing the baseline characteristics of those cirrhotic patients who experienced decompensation with those of the other cirrhotic patients enrolled (Mauss, 2004). The incidence of hepatic decompensation in the cirrhotic subgroup of the study was 10.4%, with six patients dying during the study. The
risk factors associated with hepatic decompensation were increased bilirubin, decreased hemoglobin, increased alkaline phosphatase or decreased platelets, and treatment with didanosine (Videx). Markers of viral replication, histological activity, cellular immune status, or the anti-HCV regimen were not associated with hepatic decompensation.

“Patients with markers of advanced cirrhosis should be monitored very, very carefully during the first several weeks of therapy because they are at risk of hepatic decompensation,” Dr. Torriani commented. “Treatment with antiretrovirals such as didanosine may increase the risk further. Didanosine should be avoided.”

In finishing up her discussion of adverse events, Dr. Torriani reviewed some of the possible techniques of managing the most relevant complications. Flu-like symptoms, for example, can be managed using non-steroidal anti-inflammatory drugs. Anemia requires monitoring hemoglobin every two weeks during the first eight weeks. Replacing zidovudine and correcting anemia with erythropoietin are treatment options. Reducing the dose of ribavirin is another possibility, although this may be associated with reduced efficacy.

As for depression, starting antidepressant therapy in high-risk patients should be considered before initiating pegylated interferon/ribavirin therapy. Clinicians should consistently ask about symptoms of depression and start antidepressant therapy as needed.

Avoiding didanosine is an important issue to consider in patients with cirrhosis at risk for hepatic decompensation. “Cirrhotic patients should also be monitored, every two weeks, during the entire treatment period to watch for signs of worsening liver disease.”

**Markers of Disease Progression**

**THE PRIMARY ROLE OF THE LIVER BIOPSY IN INDIVIDUALS WITH CHRONIC HCV INFECTION IS TO STAGE LIVER FIBROSIS. BIOPSES ARE FIRMLY RECOMMENDED BY U.S. TREATMENT GUIDELINES, WHEREAS IN OTHER COUNTRIES THEIR USE IS A BIT MORE CONTROVERSIAL.** "One of the problems I have with liver biopsies is the risk to the patient and the cost," Dr. Torriani said. “Few of our patients have proper reimbursement. In turn, one of the questions on the minds of many clinicians is, do we have noninvasive markers of fibrosis available that we can use?”

Dr. Torriani noted a recent study reported by Dr. Mark Sulkowski and his colleagues at the 12th Conference on Retroviruses and Opportunistic Infections (Sulkowski, 2005). A total of 67 HCV/HIV-coinfected patients underwent two liver biopsies. The paired biopsies were simultaneously evaluated by a single pathologist—blinded to the Ishak criteria, from F0 (no fibrosis) to F6 (cirrhosis). Among the 61 evaluable patients, the median time between the first biopsy and the second biopsy was 2.84 years. Fibrosis increased two stages or more in 17 (28%) patients, whereas a one-stage decrease occurred in only four (7%) patients. Among patients with mild fibrosis at the first biopsy, 26% had evidence of two-stage progression. “These data indicate that waiting to do a second biopsy, five years after an initial biopsy is performed showing little or no fibrosis, may be too late in HCV/HIV-coinfected patients,” Dr. Torriani commented. “Either we start bringing patients in more frequently for biopsies or we start thinking about non-invasive markers.”

Examples of noninvasive tests include FibroSpect from Prometheus Laboratories, a diagnostic panel employing serum markers to assist in the detection of liver fibrosis. The FibroSpect11 uses a combination of components in the fibrogenic cascade, such as hyaluronic acid, TIMP-1 (tissue inhibitor of metalloproteinase), and alpha-2-macroglobulin. The French FibroTest and the ActiTest, marketed in the U.S. by LabCorp as the HCV-FibroSure Test, are the most comprehensively studied serum marker assays for the assessment of fibrosis and necroinflammatory activity. The HCV-FibroSure Test includes the following five markers, as well as age and gender: alpha2-macroglobulin, haptoglobin, gamma-glutamyl transpeptidase (GGT), total bilirubin, apolipoprotein A1, plus alanine aminotransferase (ALT).

“There are multiple confounders that need to be dealt with when using these tests,” Dr. Torriani said. “Antiretroviral therapy, hemolysis, the use of other medications, and the use of alcohol can all affect the accuracy of these assays.”

Also from France comes transient elastography, marketed as FibroScan, a noninvasive and rapid bedside method of assessing liver fibrosis by measuring liver stiffness correlating with fibrosis scores. “However, among the concerns we have about this test is the influence of lipodystrophy seen in HIV on the accuracy of elastography.”

Dr. Torriani reviewed the results of a cross-sectional study of 130 French HIV/HCV-coinfected patients who received liver biopsies and had serum samples available for retrospective testing (Myers, 2003). A five-marker index was used, similar to the FibroSure Test; it was found that the PPV for septal fibrosis (F2, F3, or F4) for scores greater than 0.6 was 86%, whereas the NPV for scores less than 0.2 was 93%. These data suggest that serum fibrosis markers could obviate liver biopsies in 55% of patients,” Dr. Torriani said. “These findings are similar to those observed in HCV-monoinfected patients. However, there are limitations to consider, including the retrospective design of the study and the relatively small numbers. While biochemical markers are useful in differentiating between a patients with no/little fibrosis and patients with advanced fibrosis, they don’t do a good job of discerning between intermediate biopsy scores, such as F2, F3, or F4.”

At the 12th CROI, investigators reported the results of an APRICOT substudy evaluating the utility of another serum marker test dubbed f1b-4 and employing the following relatively basic equation: F1b-4 = age (years) x AST (iu/mL) / platelets (x 1,000) x ALT(iu/mL)1/2. The test was initially devised using data from 555 patients’ biopsies and serum markers, and was further validated in a separate group of 277 patients (Sterling, 2005). F1b-4 results range from 0.2 (mild fibrosis) to 10 (cirrhosis). A result of less than 1.45 had a sensitivity of 70%, a specificity of 74%, a PPV of 42%, and an NPV of 90%; A result of greater than 3.25 had a sensitivity of 22%, a specificity of 97%, a PPV of 65%, and an NPV of 82%. The APRICOT investigators concluded that liver biopsy could have been avoided in 71% of these HCV/HIV-coinfected patients assessed for HCV therapy. And while serum marker testing was useful in differentiating between low, intermediate, and advanced grades of liver fibrosis, it wasn’t effective in terms of differentiating between the intermediate fibrosis scores (e.g., F2-F4).

**Treatment of Non-Responders and Relapsers**

THE DEFINITION OF A TREATMENT NONRESPOUNDER IS SOMEONE WHO FAILS TO ACHIEVE AN EARLY VIROLOGIC RESPONSE AT 12 WEEKS (< 2 log10 decline in HCV-RNA) OR AT 24 WEEKS (UNDETECTABLE HCV-RNA). “Sustained virologic responses in patients who are virologic non-responders at weeks 12 or 24 are not likely using current therapies,” Dr. Torriani said. “Management strategies in these patients depend on fibrosis stages. In patients with minimal disease, it’s probably better to wait before restarting therapy. In patients with significant disease, treating is the best approach. Retreatment strategies include high-dose induction of pegylated interferon/ribavirin for sustained virologic responses. Another option includes long-term maintenance therapy using pegylated interferon to delay or prevent additional liver disease.”
Lessons Learned and Future Questions

“When it comes to the treatment of HCV in HIV-infected patients,” Dr. Torriani explained, “higher HCV viral loads, defects in HCV-specific immunity, and unknown race effects may be factors contributing to the lower SVRs we see in clinical trials and in clinical practice.” Based on these observations, she emphasized that treatment with pegylated interferon/ribavirin should be continued for 48 weeks—regardless of the genotype (HCV-monoinfected patients with genotypes 2/3 may discontinue treatment after 24 weeks)—with monitoring of early virologic responses at four and 12 weeks.

Central questions regarding the treatment of HIV/HCV-coinfected patients remain. Should clinicians be prescribing higher doses of ribavirin—between 1,000 and 1,200 mg/daily—to enhance early kinetics and decrease relapses? While there have been limited data on the safety and efficacy of ribavirin doses above 800 mg/day, the Laguno study employed weight-based ribavirin dosing at 800, 1,000, and 1,200 mg/daily without additional safety concerns. What’s more, clinical trials evaluating interferon/ribavirin in HCV-monoinfected patients have demonstrated that 1,000 to 1,200 mg/daily ribavirin is more effective than 800 mg/daily ribavirin for HCV genotype 1.

“Another strategy worth considering is the role of higher-dose pegylated interferon to improve SVRs in coinfected patients,” Dr. Torriani suggested. “This may be particularly useful in patients with HCV genotype 1. It might also be useful to extend therapy in patients with early virologic responses. Instead of the recommended 12 months, it might be best to extend therapy for a total of 18 months or more. This is being studied right now.” She also commented that individualized HCV treatment may be a thing of the future, with optimal dosing and treatment duration decisions being made in accordance with various patient characteristics, including HCV genotype, pre-treatment HCV-RNA levels, viral kinetics, and cellular immune status.

Much work also needs to be completed in terms of better understanding how best to manage nonresponder patients. “Maintenance or long-term pegylated interferon therapy may be a suitable option, while waiting for new options to come along,” Dr. Torriani said. “We also need to be more proactive in managing psychiatric and hematologic adverse effects of therapy, while at the same time focusing on the development of less toxic treatment options. Finally, the search is still on for clinical useful noninvasive markers of liver disease.”

References


