

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Response-guided Therapy for HCV

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G&H What is response-guided therapy?

PK Response-guided therapy is a paradigm for treating chronic hepatitis C infection in which treatment decisions are based on how rapidly hepatitis C virus (HCV) responds to treatment. With response-guided therapy, patients who rapidly clear virus from their bloodstream are eligible to receive a shorter duration of therapy, while slower responders receive standard or extended durations of therapy. Use of response-guided therapy is already well reported in easier-to-treat genotypes of HCV, specifically genotypes 2 and 3; over the upcoming year, response-guided therapy for genotype 1 HCV infection will also be a commonly used option with direct-acting antiviral agents. This approach would allow many patients to be treated with just 24–28 weeks of therapy instead of the standard 48 weeks of treatment. Although response-guided therapy has not yet been incorporated into practice guidelines, preliminary studies suggest that the addition of telaprevir or boceprevir to pegylated interferon will allow preservation of sustained virologic response rates while reducing treatment durations for patients who respond rapidly. By treating HCV for a shorter period of time when patients respond quickly, or for a longer period of time if patients respond more slowly, clinicians can potentially improve the treatment's efficacy rate.

G&H Why is response-guided therapy superior to a fixed 48-week course of therapy?

PK Response-guided therapy is a move away from one-size-fits-all medicine. Instead of giving all patients the

same treatment, response-guided therapy allows for a tailored approach that takes into account both viral and host factors when determining treatment for HCV. In the United States, the current standard of care for genotype 1 HCV infection is 48 weeks of treatment. With response-guided therapy, in contrast, genotype 1 patients who clear virus quickly can be treated for just 24 or 28 weeks. Currently, HCV treatment consists of pegylated interferon and ribavirin, but a direct-acting antiviral agent will be added to this regimen in the near future, and the phase III results in treatment-naïve patients suggest that one half or more of individuals with genotype 1 HCV infection, which is the hardest genotype to treat, can receive therapy for just 6 months as opposed to 48 weeks.

The ILLUMINATE study, which was presented at the 2010 Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), showed that if patients treated with pegylated interferon, ribavirin, and telaprevir cleared virus at Weeks 4 and 12, then their sustained response rates were the same whether the total treatment duration was 24 or 48 weeks. This finding means that clinicians can treat for a shorter duration and spare patients the side effects and expense associated with an extra 24 weeks of therapy, without affecting overall treatment efficacy. Similar findings were also found with boceprevir. Clinicians should therefore be able to successfully shorten the duration of therapy in a significant number of patients while preserving efficacy rates when using either of these direct-acting antiviral agents.

G&H What is the risk if response-guided therapy fails?

PK The risk is that patients who receive a shortened treatment regimen will relapse. For patients who receive a shortened duration of therapy but then relapse, clinicians could either wait for additional agents to be added to their treatment armamentarium or re-treat patients with a longer duration of therapy. More studies will be needed to determine how to best manage these patients.

The good news is that response-guided therapy appears to be a paradigm that will become the standard of care over the next several years.

G&H Which patients are candidates for response-guided therapy?

PK All patients are candidates for response-guided therapy, and clinicians do not lose anything by using this approach. Under a response-guided therapy paradigm, patients with disease characteristics that make them more difficult to treat will simply be treated for a longer duration rather than a shorter duration. Patients who are more likely to require a longer duration of therapy include black patients; those with advanced fibrosis; patients who are less responsive to pegylated interferon, particularly if they have interleukin (IL)-28B genotypes CT or TT; and patients who previously failed treatment.

G&H Which patients would be likely to receive a shorter duration of therapy under a response-guided therapy paradigm?

PK The shorter duration of therapy would most likely be appropriate for patients who have the IL-28 CC genotype, patients with minimal fibrosis, patients who are younger and/or non-black (white or Asian), and those with a low viral level.

G&H Does the patient's HCV genotype impact whether response-guided therapy can be used?

PK Response-guided therapy is already used by some clinicians in patients with genotype 2 or 3 HCV infection, although currently the standard of care is to treat all genotype 2 or 3 patients for 24 weeks. Several studies have suggested that patients with genotype 2 or 3 HCV infection who clear virus by Week 4 can be successfully treated with 12–16 weeks of pegylated interferon and weight-based ribavirin. Response-guided therapy is less frequently used for genotype 1 patients, at present, but this may soon change. In fact, genotype 1 patients will stand the most to gain from the introduction of the new, direct-acting antiviral agents that will be launched in the coming year, and these agents will facilitate greater use of response-guided therapy.

G&H How soon must patients respond to treatment in order to be eligible for a shortened course of therapy?

PK The point at which clinicians have to decide about treatment duration depends on which treatment regimen

is being used. For patients who are being treated with pegylated interferon and ribavirin, which is the current standard of care, response at Week 4 is a key milestone. With pegylated interferon, ribavirin, and telaprevir—which should soon become another treatment option—the first milestone will also be Week 4. With pegylated interferon, ribavirin, and boceprevir, patients are treated with pegylated interferon and ribavirin alone for 4 weeks, after which boceprevir is added; the milestone for determining whether a shortened treatment duration is appropriate is 4 weeks after boceprevir is added to the treatment regimen (ie, Week 8 of treatment).

G&H Which studies support the use of response-guided treatment?

PK To date, studies that support response-guided therapy include the ILLUMINATE study and the SPRINT-2 study. Results from both of these studies were presented at the 2010 AASLD meeting.

G&H How will the development of new drugs impact the use of response-guided therapy for HCV treatment?

PK Multiple studies have looked at response-guided therapy among patients treated with pegylated interferon and ribavirin. These studies compared the standard treatment duration of 48 weeks with treatment durations of 6 months, 9 months, or even 18 months for slow responders. Thus far, no studies have consistently shown that response-guided therapy is superior to standard therapy when treatment is limited to pegylated interferon and ribavirin.

As new agents are added to HCV drug regimens, however, sustained response rates should improve. I believe that response-guided therapy will therefore become much more widely used in the future, and this approach has a high probability of becoming the standard of care. With current treatment regimens, relatively few individuals are able to clear virus rapidly; with the addition of new agents in 2011, however, far more individuals should be able to clear virus rapidly. As a result, response-guided therapy should become much more widely used over the upcoming year, so it is important that clinicians learn to become comfortable with this approach.

G&H How common is response-guided therapy now?

PK Some clinicians are using a response-guided therapy approach, but it is not yet widely accepted. The main reason this approach has not gained greater acceptance

is that few patients qualify for the shortened treatment duration. With current medications, only approximately 10% of genotype 1 HCV patients can achieve rapid virologic response. With the newer agents that will soon be available, however, rapid virologic response rates are going to be much higher in clinical practice, hopefully in the range of 50–80%. As a result, more patients will be candidates for shortened therapy per a response-guided therapy paradigm.

G&H Do you expect response-guided therapy to become more common in 2011?

PK Yes, absolutely. Clinicians will need time to make this change, but I think that response-guided therapy will be adopted fairly quickly for genotype 1 patients. If shorter therapy is just as effective as a 48-week course of treatment, then HCV patients will naturally opt for the shorter treatment duration, as it allows them to avoid 6 months of exposure to pegylated interferon, ribavirin, and other agents. This change not only reduces the period during which patients must tolerate drug-related side effects but also spares them the expense associated with the extra 6 months of therapy.

Suggested Reading

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