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SPECIAL ARTICLE

Direct-Acting Antiviral Drug Approvals for Treatment of Chronic Hepatitis C Virus Infection: Scientific and Regulatory Approaches to Clinical Trial Designs

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Therapeutic options for treatment of chronic hepatitis C have improved substantially since the approval of direct-acting antiviral agents (DAAs). Several interferon (IFN)-free or IFN- and ribavirin (RBV)-free treatment regimens with shorter durations and improved efficacy and safety profiles are now available. The U.S. Food and Drug Administration (FDA) used several scientific approaches and regulatory mechanisms, such as (1) use of a "validated" surrogate (sustained virological response) for a primary endpoint, (2) shortening the time point for measuring the surrogate by 12 weeks, (3) use of historical controls when clinically appropriate, and (4) use of modeling when scientifically sound to extend treatment indications to subpopulations not fully evaluated in clinical trials, which had an impact on DAA development and subsequent approvals. This article intends to provide increased transparency to various stakeholders about the FDA's scientific approaches and regulatory processes that supported drug development and marketing approval of DAAs for treatment of hepatitis C, a serious, life-threatening infection. (HEPATOLOGY 2015; 00:000-000)

Hepatitis C virus (HCV) infection is a major public health problem and a leading cause of chronic liver disease. The natural history of chronic hepatitis C (CHC) involves progression to cirrhosis, hepatocellular carcinoma (HCC), liver failure, and death. The ultimate goal of CHC treatment is to reduce the occurrence of end-stage liver disease and its complications, including decompensated cirrhosis, liver transplantation (LT), and HCC.

CHC treatment success has improved substantially over the past 4 years. Before the approvals of the first direct-acting antiviral agents (DAAs) in 2011, standard CHC treatment was pegylated interferon (Peg-IFN) and ribavirin (RBV) for 24-48 weeks based on HCV genotype.[1,2] Peg-IFN plus RBV yielded sustained virologic response rates (sustained virological response; SVR) in less than half (40%-45%) of treatment-naïve patients infected with genotype 1 infection, the most common genotype in the United States (70%-75%).[1,2] In addition, Peg-IFN and RBV have many adverse reactions associated with use that were a major reason for patients declining or stopping HCV therapy altogether.[1,2]

In May 2011, the U.S. Food and Drug Administration (FDA) approved two HCV nonstructural (NS)3/4A protease inhibitors (PIs), boceprevir and telaprevir, for use in combination with Peg-IFN and RBV, for treatment of chronic HCV genotype 1 infection, followed by a third PI, simeprevir (SMV), approved in November 2013.[3-6] The addition of a PI to Peg-IFN and RBV substantially increased SVR rates (60%-80% in treatment naïve) and allowed shorter treatment durations in some patients based on response-guided therapy, but added adverse reactions, such as skin reactions, and worsened anemia.[3-6] FDA approval of sofosbuvir (SOF), a nucleotide analog inhibitor of HCV NS5B polymerase (first-in-class) in December 2013, further transformed the landscape of CHC treatment for genotype 1 infection.[7] SOF in combination with Peg-IFN

Abbreviations: CHC, chronic hepatitis C; DAAs, direct-acting antiviral agents; DDIs, drug-drug interactions; FDA, U.S. Food and Drug Administration; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; LDV, ledipasvir; LT, liver transplantation; NI, noninferiority; NS, nonstructural; Peg-IFN, pegylated interferon; PIs, protease inhibitors; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virological response; SVR12, SVR 12 weeks after the end of treatment; SVR24, SVR 24 weeks after the end of treatment.

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and RBV allowed a shorter duration (12 weeks) of interferon (IFN)-based treatment, with SVR rates approaching 90% and improved tolerability.[7] In 2014, the FDA approved several IFN-free regimens for treatment of CHC with genotype 1 infection, including: (1) the first IFN-/RBV-free, once-daily regimen consisting of a fixed-dose combination of SOF and ledipasvir (LDV), an NS5A inhibitor; (2) SMV in combination with SOF; (3) a copackaged triple-DAA regimen consisting of ombitasvir, paritaprevir/ritonavir, and dasabuvir (an NS5A inhibitor, a PI boosted with ritonavir, and a nonnucleoside NS5B polymerase inhibitor, respectively) used with and without RBV (depending on genotype subtype and presence of cirrhosis).[6,8,9]

The field has progressed toward simpler IFN-free or IFN- and RBV-free regimens with shorter treatment durations and improved efficacy and safety profiles. This article intends to provide increased transparency to the various stakeholders about the FDA's decisional approaches and processes that supported drug development and marketing approval of DAAs. Stakeholders include health care professionals, professional organizations/societies, health insurance plans/third-party payers, patients/patient advocacy groups, and state/federal regulatory bodies and agencies. Some stakeholders have been concerned about the adequacy of data obtained from the clinical trials leading to marketing approvals. For example, some groups have questioned the use of historical trials instead of active-controlled trials. This issue has been used to cast doubt on efficacy and even to question treatment or deny reimbursement of some of these new regimens. Some have also been concerned that SVR will not be durable for all DAA regimens.

To address these concerns, this report provides a brief overview of the FDA's regulatory approaches to accelerate the development and approval of promising drugs to treat a serious, life-threatening infection and a brief rationale for the clinical trial designs that supported these approvals.

Evolution of FDA Guidance on Hepatitis C Drug Development

In October 2006, in response to a growing number of hepatitis C DAAs in development, the FDA convened a meeting of the Antiviral Drugs Advisory Committee to discuss clinical trial design issues of novel CHC treatments.[10,11] Committee recommendatons and scientific advances helped the FDA to issue its first draft guidance (September 2010) addressing the development of new treatments for CHC, entitled "Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment." Based on additional rapid scientific advances, comments received from various stakeholders, and input from a meeting convened by The Forum for Collaborative HIV Research in October 2011, the guidance was further revised and a second draft was released in October 2013.[12] Although the revised guidance discusses the development of DAAs with and without IFN, the main focus is the development of DAAs as part of IFN-free regimens for multiple patient populations.[12] The FDA used several scientific approaches and regulatory mechanisms that had an impact on DAA development and subsequent approvals. Specifically, these approaches included: (1) use of a "validated" surrogate (SVR) for a primary endpoint; (2) shortening the time point for measuring the surrogate by 12 weeks; (3) use of historical controls, when clinically appropriate; and (4) use of modeling when scientifically sound to extend treatment indications to subpopulations not fully evaluated in clinical trials.[13-15]

Primary Endpoint in HCV Trials

Obtaining clinical outcomes from prospective, randomized, controlled clinical trials in drug development programs for chronic HCV infection is challenging and not feasible for most CHC populations because of the difficulty of maintaining patients on a randomized arm without intervening therapy for a sufficient duration (many years) to identify late-occurring clinical events, such as hepatic decompensation or HCC. Therefore, for many years and many approvals, a virological surrogate (SVR) has been used to measure treatment success in clinical trials supporting approval. SVR is an objective endpoint that signifies long-term clearance of hepatitis C and is generally regarded as a "virological cure." Based on numerous observational cohorts showing strong correlations between SVR and multiple

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clinically important outcomes, such as development of HCC, end-stage liver complications, and mortality, the FDA considers SVR a "validated" surrogate efficacy endpoint in CHC clinical trials.[16-19]

SVR or virological response measured after the end of treatment has been assessed at various time points in clinical trials. Peg-IFN and RBV were evaluated using SVR24, which assessed response 24 weeks after the end of treatment. However, FDA scientists and others noticed that most viral relapses occurred early in the post-treatment period. This observation led to further assessment of whether SVR at an earlier time point, such as week 12 (SVR12), could be used as a primary efficacy endpoint. The FDA examined the correlation between SVR12 and SVR24 in over 13,000 subjects pooled from multiple clinical trials of Peg-IFN-based regimens and found a high rate of concordance between SVR12 and SVR24; sensitivity and specificity for SVR12 were 99% and 98%, respectively.[13]

The FDA observed similarly high concordance between SVR12 and SVR24 in IFN-free regimens from phase II and III trials across multiple drug development programs. In addition, the product labeling for the fixed-dose combination of SOF plus LDV notes a strong correlation between SVR12 and SVR24.[8] Among subjects with available SVR12 and SVR24 data (206 of 218) in a clinical trial in treatment-experienced patients (with our without cirrhosis), all subjects who achieved SVR12 also achieved SVR24.[8] As another example, product labeling for the recently approved triple-DAA copackaged product states that 99% of subjects achieving SVR12 (n = 526) after receiving various combinations of the DAAs included in the copackaged product maintained their response through 48 weeks post-treatment.[9] Therefore, SVR12 signifies a durable virological response and is now used as the primary efficacy endpoint in all HCV registrational trials. This allows for earlier approvals of highly effective, well-tolerated therapies, facilitating access to those in need.

Clinical Trial Designs

Phase III trial designs recommended in FDA draft guidance and used in recent HCV drug development programs include placebo-controlled trials and historical-controlled trials with or without comparisons of treatment duration or the addition of RBV to a regimen. The placebo-controlled design randomized participants to either immediate treatment with a regimen containing one or more investigational DAA or placebo. At the end of treatment, subjects randomized to the placebo arm receive the DAA-based regimen. Deferred treatment designs can be an option in subjects who do not need immediate treatment. The purpose of the deferred treatment, placebo-controlled design is primarily to collect comparative safety data; however, it also demonstrates the efficacy of the entire regimen compared to placebo or no treatment. The contribution of each new investigational drug to the effect(s) of the combination regimen is often demonstrated in early-phase trials and confirmed, as needed, in other phase III trials comparing multiple regimens.

Code of Federal Regulations Title 21 Section 314.126 on "Adequate and well-controlled studies" lists historical controls as a type of adequate, well-controlled trial. ICH* Efficacy Guidelines document E10 entitled, "Choice of Control Group in Clinical Trials," notes: "In unusual cases, the course of illness is in fact predictable in a defined population and it may be possible to use a similar group of patients previously studied as a historical control." There were multiple reasons why historical controls for trials evaluating HCV treatments were appropriate at this time in drug development: (1) Investigators and patients were not enthused about active controlled trials because the approved standard would have included cumbersome, poorly tolerated IFN-based regimens, and data from phase II trials of IFN-free regimens were already showing SVR rates markedly exceeding approved IFN-based regimens. Avoiding the many toxicities and longer duration of IFN-based therapy was a major safety concern for trial participants; (2) IFN is contraindicated or intolerable for a substantial subset of patients. For these patients, there were no approved standard regimens to use as an active control; (3) because the treatment effect of the investigational regimens was known to be so much larger than placebo, choosing a noninferiority margin for an active controlled trial or historical control was mostly a matter of clinical judgment. A DAA regimen that was somewhat inferior to an approved IFN-based regimen could still be an acceptable treatment option from a clinical perspective if it shortened treatment duration and avoided many or most of the toxicities caused by IFN; and (4) SVR is an objective endpoint with rates that are fairly consistent across trials of IFN-based regimens, particularly when controlling for genotype and patient population.

For example, a historical comparison was used in the trial (NEUTRINO) supporting approval of SOF in combination with Peg-IFN and RBV for treatment of

*The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities and pharmaceutical industry of Europe, Japan, and the United States to discuss scientific and technical aspects of drug registration (www.ich.org).

genotype 1 HCV infection. Although not an IFN-free regimen, it was a step forward in the quest for better-tolerated and shorter IFN-based treatment regimens. The rationale for a single-arm trial design considered the factors of shorter Peg-IFN treatment duration when used with SOF, no requirement for response-guided therapy compared with a control regimen of Peg-IFN, RBV, and a PI, and the approximately 90% SVR12 rate observed with Peg-IFN, RBV plus SOF in an earlier phase II trial. In addition, NEUTRINO enrolled other genotypes, in addition to genotype 1, for which there were no approved IFN-based controls.[20] In the design of NEUTRINO, a SVR rate exceeding 60% was considered clinically meaningful based on the upper limit of the 95% confidence interval for the highest SVR rate for Peg-IFN/RBV treatment observed in historical trials. In addition to shortening the treatment duration of an IFN-based regimen, which is an advantage in itself, exceeding this target would demonstrate that SOF added efficacy to a regimen of Peg-IFN/RBV alone. SVR12 for genotype 1 patients receiving Peg-IFN/RBV/SOF in NEUTRINO was 89% with a 95% lower confidence bound of 85%, clearly exceeding historical rates for Peg-IFN/RBV regimens without or even with a PI.[20] In addition, treatment duration was cut in half (at least), with less toxicity related to duration of the regimen or use of a PI. Despite limitations of cross-study comparisons, the efficacy and advantages of the regimen and contribution of SOF was obvious. A unanimous FDA advisory committee vote for approval of this regimen supports this assertion.[21]

For more recent DAA regimens in development, higher estimates of historical SVR rates were used and based on responses of Peg-IFN/RBV plus a PI. For the triple-DAA copackaged product, specific thresholds for subpopulations based on previous treatment history (treatment-naïve or treatment-experienced), genotype subtype (1a/1b), and presence or absence of cirrhosis were determined.[22] In brief, the 95% upper confidence bound for the SVR point estimate from pooled analyses of historical data was calculated and used as a superiority threshold. Approximately 10% from this threshold was subtracted to be used as the noninferiority threshold. SVR estimates in this range would all be supportive of efficacy that was dramatically better than placebo. Therefore, as stated above, noninferiority margin choices were based on clinical judgment regarding how much loss in SVR was acceptable for a regimen that had the advantages of not including IFN, had a shorter duration, or, potentially, a better tolerability profile. For treating a specific patient, clinicians appreciate the availability of range of treatment options with varied product profiles and sometimes even trade small reductions in SVR for other clinical advantages when making risk-benefit decisions for individual patients.

The recent approvals of SOF/LDV and the triple-DAA copackaged regimen used historical controls for drug efficacy comparisons.[22,23] In addition, two placebo-controlled trials (those randomized to placebo were allowed delayed treatment) also supported efficacy for the triple-DAA combination. High SVR rates ranging from 94% to 99% were observed in registrational trials for both products.[8,9] Moreover, high SVR rates were seen across subpopulations with baseline characteristics that have been traditionally known as poor predictors of response, such as cirrhosis, high baseline viral load, and non-CC interleukin-28B status. For the triple-DAA combination, lower confidence bounds of SVR results in the phase III trials were generally 10%-20% greater than the superiority thresholds demonstrating that there were no borderline results that would be impacted by small changes in the thresholds based on the historical control SVR estimates.

Recently issued HCV Treatment Guidelines, "Recommendations for Testing, Managing, and Treating Hepatitis C," developed by American Association for the Study of Liver Diseases and Infectious Diseases Society of America (http://www.hcvguidelines.org), no longer recommend INF-based regimens as first-line treatment of genotype 1 infection.[24] Oral DAA regimens (with or without RBV) are now preferred initial treatment regimens.[24]

Postmarketing Evaluation and Collaboration With Partners

We strive to bring safe, effective therapies to patients in need in a timely manner. There is growing criticism that patients enrolled in clinical trials do not represent real-world patients. Sometimes there is an underrepresentation of women, the elderly, and various racial/ethnic subgroups in clinical trials. We remain cognizant that not only is the demonstrated efficacy of the drugs in phase III clinical trials important, but also the effectiveness of drugs and treatment outcomes in clinical care settings after a drug's approval.

Fine-tuning the exact regimen/duration for specific patient subgroups (according to baseline factors, such as gender, body mass index, and so on) could be answered in a postmarketing trial. Our approvals have shown robust efficacy, but tailoring an optimal regimen for all patient populations with various genotypes as a premarket strategy may unnecessarily delay access to life-saving treatments; identifying shorter treatment regimens or

providing data on other populations, such as patients undergoing transplantation, could be addressed in the postmarketing setting.

The FDA signed a Memorandum of Understanding with the Hepatitis C Therapeutic Registry and Research Network, or HCV-TARGET group—an international research consortium (academic and community providers), in 2013.[25] The HCV-TARGET group has "established a common research database and is conducting a longitudinal observational post-marketing study to answer important questions about HCV therapy with direct acting antiviral agents."[25] This group monitors observational data collected in real-world settings postmarketing—safety evaluation in larger cohorts and in subpopulations that might have been underrepresented in clinical trials or may not have been evaluated in registrational trials. The Center for Drug Evaluation and Research recognizes that: "This collaboration will not only strengthen our ongoing efforts to monitor the safety and effectiveness of existing hepatitis C treatment regimens, it will also provide opportunities for FDA scientists to apply their research expertise in studying existing data held by HCV-TARGET to identify areas for improvement in clinical trial design that may help improve the future of HCV drug development programs."[25]

Comparative effectiveness trials are also important and informative to compare the safety profile and effectiveness of the various regimens, but they are not required under the FDA's regulations. Data from these trials may provide helpful information to health care providers, third-party payers, and government agencies as they make their treatment and policy decisions.

Future Directions

Regulatory bodies have a public health responsibility of making sure that safe, effective drugs are available to the public in a timely manner. A fine balance needs to be struck between providing sufficient data for drug development and labeling and providing patient access to therapies as soon as possible. A valid, evidence-based approach was used in our approach to the approval of therapies to treat CHC.

Feasibility of active control design in this rapidly evolving field of HCV drug development needs to be reassessed periodically and carefully. Controlled trials allow for direct safety comparisons and will be very informative and important for distinguishing two DAA regimens. As more IFN-free regimens are approved, having comparative data in phase III trials using the approved regimens as controls would be helpful for distinguishing differences in efficacy, particularly in patient populations where SVR rates are still considered less than optimal. Comparative trials can also provide data needed for treatment guidelines and reimbursement decisions.

Subsequent to approval of SOF and RBV for genotypes 2 and 3, we have recommended using control arms for future clinical trials in subjects with genotype 2 and 3 HCV infection, depending on the specific population. It is evident that sample sizes will not be prohibitive in conducting comparative trials to support registrational trials needed for marketing approvals in the future. For example, for a noninferiority (NI) trial in genotype 1 infection with assumed SVR point estimates of 97% for both control and invstigational regimens and an NI margin of 6%, the estimated sample size is approximately 150 subjects per arm (90% power, alpha 5%). Similarly, for an NI margin of 8%, the estimated sample size is even smaller. Alternatively, given the expected high SVR rates of 95% or greater, there may be limited value of a control arm for efficacy comparisons. Therefore, some have proposed trials without active controls and instead setting a stringent efficacy hurdle (e.g., trials powered such that lower bounds of SVR estimates can be shown to exceed 92%). Some investigators have voiced the opinion that the sample size spent on including an active control could be better used investigating differences in treatment durations between specific subpopulations or investigating other differences with the investigational regimen.

In summary, we are at an exciting phase in hepatitis C drug development. With the availability of more potent drugs and efficient trial designs, treatment options are rapidly reaching the marketplace. Historically, in the era of IFN-/RBV-based regimens, clinical trial enrollment was restricted to patients who had minimal comorbidities or those with less-advanced liver disease. With the availability DAAs with improved tolerability and decreased potential for drug-drug interactions (DDIs), clinical trials have now included subjects with human immunodeficiency virus type 1 infection, those with decompensated liver disease, patients with HCC, as well as pre-/post-LT patients.

Recent approvals of IFN- and RBV-free regimens with higher efficacy and improved safety profiles provide health care systems with better options to treat most of their hepatitis C patients, including patients with cirrhosis. Safer, more effective treatment options will have a greater impact on this major public health problem. Clinical trials contained in a marketing application do not cover all patient populations. Future efforts should focus on optimizing treatment regimens in harder-to-

treat subpopulations, including those that might have been under-represented in the clinical trials. Ideally, postmarketing studies should address data gaps in the marketing applications. In addition, difficult-to-treat patients, including those with decompensated liver disease, post-transplant patients, and so on, should be included in the late phases of clinical development after adequate assessment of pharmacokinetics based on host factors and pertinent DDIs.

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