

SPECIAL ARTICLE

Preparing for the Uncertain Yet Inevitable: Off-Label Combinations of Antiviral Agents in Hepatitis C Virus

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The next generation of direct-acting antiviral agents (DAAs) will change the landscape of hepatitis C virus (HCV) therapy. Approval of complimentary oral agents will also introduce new opportunities for off-label treatment. Off-label therapy in HCV will include (1) combinations of approved drugs, used for the approved indication in an unapproved combination, such as combining two DAAs in an interferon (IFN)-sparing regimen, and (2) combinations of approved drugs used in an unapproved combination for an unapproved indication, such as using two available DAAs to treat patients post-LT (liver transplantation). Both providers and patients might find off-label combinations attractive; however, there may be limited data to support safety and efficacy. These treatment choices may also go against the recommendations published in therapeutic guidelines.

This article will address anticipated issues regarding off-label use of HCV medications, including the role of the U.S. Food and Drug Administration (FDA), consumer pressure, medical society guidelines, and third-party payers. Off-label issues specific to the United States will be described; however, many con-

cepts, such as uncertainties of cost, label regulation, and reimbursement, can be applied to health care systems globally.

The FDA

Regulation of Off-Label Use. The FDA regulates market entry for all new prescription drugs in the United States. Once approved, physicians are not bound to prescribe according to the label—in many cases, off-label prescriptions may be part of best practice or standard of care. Off-label prescribing is legal and has been shown to occur in over one fifth of office-based prescriptions.¹ Upcoming generations of DAAs represent robust therapeutic innovation, which will likely outpace the breadth and capacity of the FDA-approved label. Prescribing already approved agents in an off-label combination may be desired to improve efficacy. In addition, safety may also be improved using these combinations by potentially eliminating drugs with toxicity, such as IFN. FDA approval for these combinations would require a new and unique application for the combined regimen, which would be costly and would require partnership between separate manufacturers. As a result, although the FDA will not regulate a provider's ability to prescribe off-label HCV treatment as they see fit, appropriate applications of use may be ambiguous because they will ultimately be based on a combination of opinion and potentially limited available data.

Defining the Need for Off-Label Combinations

Over 185 million people are infected with HCV worldwide.² It has surpassed human immunodeficiency virus (HIV) as a cause for mortality and has been linked to higher all-cause mortality and diminished quality of life.^{3,4} Despite data showing that sustained viral response (SVR) reduces mortality, relatively few patients have undergone successful treatment.⁵ Historically, suboptimal efficacy and toxicity of IFN-based therapy has limited therapeutic options for many; however, opportunity is on the horizon. Multiple

Abbreviations: AIDS, acquired immune deficiency syndrome; CARE, Comprehensive AIDS Resources Emergency; DAAs, direct-acting antiviral agents; FDA, U.S. Food and Drug Administration; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; LT, liver transplantation; SVR, sustained viral response.

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agents are in the late stages of development. These drugs will target various aspects of the HCV life cycle, making combinations of these agents a natural strategy to more effectively treat HCV and eliminate intolerable side effects or adverse events. Data involving various combinations of DAAs, often from different manufacturers, is rapidly becoming available; however, many of these studies are performed as proof of concept and are unlikely to progress to FDA-approved combinations. Combining DAAs based on these data in an off-label manner may be an attractive option for patients unwilling to undergo IFN-based therapy in addition to patients with comorbidities that have previously disqualified candidacy for standard-of-care therapy. This strategy is not without risk. Insurers may be unwilling to pay for off-label therapy,⁶ and these combinations may have inadequate supporting safety and efficacy data.

Recent Centers for Disease Control and Prevention and U.S. Preventive Services Task Force guidelines to screen all patients born between 1945 and 1965 will help identify many patients who have been infected for decades and are at risk for developing complications of chronic liver disease. Although most of these patients are candidates for standard-of-care therapy, with anticipated rates of SVR reaching 75%,^{7,8} many patients and providers have chosen to defer therapy in anticipation for IFN-free regimens. Deferring therapy comes with risk, which includes progression of disease, change in health status, which may make future treatment impossible, possibility of infecting others, and change in patient insurance status, making therapy unaffordable. Although FDA-approved IFN combinations will likely be available in upcoming years, patients and providers may begin to feel restless, deferring therapy, and opt for a readily available off-label IFN-free combination. This patient population will likely represent a “short-term” utilization of off-label DAA combinations, which will diminish as IFN-free regimens come to market.

Alternatively, there are many subsets of individuals with HCV that are in need of DAA-based treatment, but will be excluded from upcoming FDA labels because of limitations in supporting data. These patients include those with decompensated cirrhosis, first-generation protease inhibitor failures, chronic kidney disease, pediatric populations, HIV coinfection, and post-LT. Because many of these populations represent relatively small numbers of patients with HCV, it may be difficult to accumulate requisite data and possibly cost prohibitive for manufacturers to apply for FDA approval. These patients may represent “longer-term” utilization of off-label treatment.

Is There Precedent for Off-Label Use of Therapy?

The Human Immunodeficiency Virus Paradigm.

Acquired immune deficiency syndrome (AIDS) was identified in 1981; however, zidovudine was not available until 1987. Between 1987 and 2008, 25 anti-HIV (human immunodeficiency virus) compounds were licensed for use. Similar to HCV, these agents directly target various aspects of the HIV life cycle. As single agents were approved, there was pressure by clinicians and advocates to find off-label combinations that would prevent emergence of viral resistance. By 1996, combination regimens were widely accepted, although the first regimen, Combivir (zidovudine and lamivudine), was not FDA approved until September 26, 1997.⁹ The turning point in therapeutics began in 1996, when data presented at the 11th International Conference on AIDS in Vancouver, British Columbia, Canada, represented HIV as a highly efficient virus, producing 10 billion virions per day. Several key publications followed, illustrating the substantial benefit of three agent-based highly active antiretroviral therapies.¹⁰ Although multiagent therapy was quickly incorporated into clinical practice and eventually established as the standard of care, this principle was first supported by expert opinion and guidelines—not necessarily the package insert. In most instances, payers reimbursed these off-label combinations and the Ryan White Comprehensive AIDS Resources Emergency (CARE) Act provided support. A loud and vocal advocacy campaign provided the necessary impetus for this outcome.

Experience With Hepatitis B. Before the approval of entecavir and tenofovir for hepatitis B virus (HBV), the combination of adefovir and lamivudine was used to control HBV resistant to monotherapy, as well as to prevent the development of resistance in those considered at high risk. Tenofovir, commercially available as an approved drug for HIV, was used off label in the management of hepatitis B well before the FDA approved the drug for this indication. Truvada (tenofovir in combination with emtricitabine) continues to be used off label in the management of HBV. Clinical guidelines advocate for off-label combinations of these medications to manage resistant HBV.¹¹

HCV Therapy May Be Different. Although there is precedent for off-label therapy in many diseases, HCV has unique considerations. First, unlike HIV, in patients without advanced fibrosis there is often no urgency to initiate therapy. Progression to clinically significant disease in HCV often takes decades, and patients and providers may be less willing to take on the

risk of off-label treatment when an approved regimen is only months to years away. Second, for many patients, the current standard-of-care HCV treatment is safe and offers high rates of SVR. Alternatively, drug-resistant HBV, HIV, and many cancers may have limited, if any, FDA-approved treatments, making an off-label therapy the only option. Finally, there is not the same intensity of HCV advocacy as there had been for HIV, a pivotal factor in swaying third-party reimbursement.

Practical Considerations in Off-Label Use of DAAs

How Much Supporting Data Will Be Required? Off-label use of upcoming DAAs will certainly occur; however, the degree of utilization will rely on availability of safety and efficacy data. One emerging source of data may come from prospective observational studies, such as HCV TARGET and CUPIC. These multicenter studies enroll large numbers of patients undergoing HCV therapy and have the potential to capture vast amounts of off-label therapeutic data. If a high level of evidence from observational studies or well-controlled clinical trials is available, it is possible that off-label combinations may be advocated by authoritative guidelines from well-respected academic associations. More likely, especially in understudied populations, robust data will not be available. In these cases, providers and patients will have to determine their minimal threshold of safety and efficacy data to initiate off-label therapy without the assistance of guidelines or a package insert. Treatment based on limited data will require extensive communication and understanding of therapeutic options between the patient and provider.

What Will Be the Role of Industry and How Will It Be Regulated? Although prescribing practices are unregulated, industry promotion of off-label use is highly restricted. Pharmaceutical companies are required to submit final promotional materials to the FDA for review at the time of public dissemination. Off-label promotion in these materials is strictly prohibited and is subject to FDA regulatory action. In contrast, the FDA has taken a more lenient position on activities that fall under the safe harbor of “scientific exchange” of information. Recent guidelines allow for industry dissemination of scientific literature of non-FDA-approved drug use, provided it is in an unabridged form, published in a peer-reviewed journal, and accompanied by a clear statement that indicates the study involves off-label use of a given therapy.¹² Another potential outlet for marketing will be

industry-sponsored continuing medical education activities, which may include nonpromotional discussion of off-label use of a therapy. Both of these practices are already highly utilized in the HCV therapy market and will likely increase in volume as new agents prepare to come to market and are approved. Providers who treat HCV will encounter vast amounts of data presented in these formats that are unregulated by the FDA and will be required to critically evaluate the quality and utility of these data before integrating it into clinical practice.

Reimbursement of Off-Label Therapy. Opportunities for off-label HCV treatment with newer DAAs will only be realized if payers reimburse drug costs. Because most health plans rarely publicize policy regarding off-label reimbursement, there tends to be heterogeneity among plans with regard to reimbursement procedures. In general, the likelihood of reimbursement can be thought of as a continuum in which FDA-approved use has the highest probability of reimbursement; mention of an off-label use in society guidelines, compendia, or peer-reviewed literature are less likely to be reimbursed, and expert opinions of off-label use, including data presented in non-peer-reviewed abstract form being least likely to be reimbursed. This continuum is affected by both cost of drug and availability of therapeutic alternatives. In 2009, 34 third-party payers representing approximately one quarter of Medicare and Medicaid beneficiaries nationwide were surveyed regarding practices in off-label reimbursement.¹³ Approximately 25% of these payers refused payment for off-label therapy of any kind. Of those who did reimburse off-label therapy, data sources that were felt to be “very important” in determining eligibility for reimbursement included peer-reviewed literature (74%), clinical practice guidelines (53%), and cost-effectiveness data (21%). In instances where off-label reimbursement was allowed, restrictions of use were reported to be imposed 85% of the time. Examples of restrictions included requirement for previous authorization, step therapy (i.e., failing less costly treatment first), and quantity limits.

Off-label uses of therapies supported by high-quality evidence and seen as standard of care are more likely to be reimbursed by payers. The competitive development of HCV therapy is unique and may uncover exceptions to this rule. First, the rapid progress of the HCV therapeutic pipeline combined with the chronic nature of HCV and a highly effective standard-of-care therapy may de incentivize payers to reimburse off-label treatment when similar FDA-approved therapeutic regimens are projected to be only months away. For

example, payers may be reluctant to allow for payment for both simeprevir and sofosbuvir based on the COSMOS trial when IFN-free regimens, offering similar safety and efficacy data, are under consideration for FDA approval in the near future.¹⁴ In addition, as newer agents continue to minimize toxicity and optimize efficacy, payers will be less likely to reimburse potentially costly off-label regimens that offer only incremental benefits of efficacy, safety, or duration of therapy. Finally, because price will be independently negotiated on a per-drug basis, mixing different agents may skew cost/efficacy ratios and threaten to increase financial burden to payers.

Off-label HCV therapy will offer a unique opportunity for providers to use innovative combinations of drugs to treat patients in need; however, this treatment will come at a cost. To mitigate this cost, we can expect increasing payer requirements to justify off-label use. Ironically, third-party payers may become a *de facto* regulatory body by making decisions on which off-label regimens will be allowed.

Summary

The availability of new DAAs will provide unprecedented opportunities for off-label HCV therapies in many patients. These patients will include those who are unwilling to take, or intolerant of, IFN and those in need of HCV therapy with no other treatment options. For many, this will ultimately be tempered by FDA-approved all-oral options, but until that time, patients, prescribers, and payers will struggle in an environment where more questions exist than answers. There are no rules, and thus there will be little consistency. Historical precedent only serves as proof of concept. Hepatitis C therapy is not offered under the Ryan White CARE Act rules, and as a consequence, HCV treatment will certainly become polarized. No standard for the minimal amount of safety and efficacy data exists, and in many cases, providers will make treatment decisions without the support of the FDA or treatment guidelines. Patient communication, critical evaluation of available evidence, and meticulous management of off-label treatment recipients will be of

paramount importance as we enter into the next era of on- and off-label DAA therapy.

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