Case Studies: Direct-Acting Antiviral Agents in the Practice Setting—Video 1

Introduction

Hello, I’m Dr. Steven L. Flamm, professor of medicine at the Northwestern Feinberg School of Medicine in Chicago. I’m also the medical director of liver transplantation. Thank you for joining us for this CME/CE video case vignette titled “Case Studies: Direct-Acting Antiviral Agents in the Practice Setting.” Today, we’re going to highlight two cases that reflect some of the challenges surrounding current hepatitis C treatment with direct-acting antivirals. Let’s begin with the first case.

Case One: Patient Presentation

The first case is a 46-year-old white female who was diagnosed with chronic hepatitis C virus infection approximately 10 years ago after elevated liver enzymes were noted upon routine blood testing. Additional workup was undertaken at the time, and she was found to have hepatitis C virus, genotype 1. She subsequently underwent a liver biopsy, and this revealed a mild lymphatic histologic inflammation, grade 1, and stage 2 fibrosis.

The patient heard about the availability of new medications for chronic hepatitis C and she’s referred for evaluation. She has not been previously treated. She opted to defer antiviral therapy in the past because of the poor response rates that were present with the previous standard of care. She does not complain of fatigue, abdominal pain, pruritus, or arthralgias. She has no peripheral edema, increased abdominal girth, encephalopathy, or GI bleeding. She consumes alcohol only on a rare basis.

Hepatitis C virus risk factors include a short-lived period of intravenous drug use when she was 19. She has no history of intranasal drug use or blood transfusion. Her past medical history is only remarkable for a tonsillectomy at age 8. The only medication she takes is a multivitamin. She’s married, has two healthy children, and works in human resources for an accounting firm. She does not smoke cigarettes.
On physical examination, she’s well appearing. Her height is five feet five inches, her weight is 166 pounds. She has anicteric sclerae. Her neck has no lymphadenopathy. Her lungs are clear.

Her cardiac examination reveals a regular rate and rhythm without rubs or gallops. Her abdomen is soft, nontender, and she does not have hepatosplenomegaly to palpation. Her extremities are without edema, and she has no spider angiomata or asterixis.

On labs, her white blood cell count is 5400, her hemoglobin is 13.8 g/dL, and her platelet count is 260,000. Her BUN is 10, her creatinine is 0.9, and her total bilirubin is 1.3. INR is 1.1. Her liver enzymes are mildly elevated with an ALT of 88 and an AST of 76. Her alkaline phosphatase is normal at 118. Her TSH is 3.3.

Hepatitis C virus testing was then performed and revealed a hepatitis C virus RNA level of 900,000 IU. And she was found to have genotype 1b.

Ultrasound was performed to visualize the liver and revealed a normal appearing liver and spleen. No other abnormalities were described.

Now, this leads us to our first decision point.

**Case One: Decision Point One**

*Should the patient be treated now, or should she be counseled to wait for interferon-free medical regimens?*

Her options include, or our options, include the following: First, should we wait to treat until an interferon free regimen is available; two, should we treat now with pegylated interferon alfa and ribavirin; or three, should we treat now, but with triple therapy—pegylated interferon alfa, ribavirin, and either one of the protease inhibitors, telaprevir or boceprevir?

The first option—wait to treat until an interferon-free regimen is available—is not the best option for this woman. First of all, she has advancing fibrotic liver disease with stage 2 fibrosis. While there’s a lot of excitement about the prospects of interferon-free medical regimens in the future, we have no idea, for sure, if such regimens will become available. And if they do, we don’t know when they will become available. It could be many many years from now. And in a person with stage 2 fibrosis, it may not be in her best interests to wait for therapy.

The second option—treat now with pegylated interferon alfa and ribavirin—is also not the best choice. Pegylated interferon alfa and ribavirin is approved for treatment of patients with
HCV genotype 1 who are treatment-naive, but the sustained response rates are not that high, and it’s not the current standard of care.

The third option—treat now with triple therapy, including pegylated interferon alfa, ribavirin, and either one of the protease inhibitors, telaprevir or boceprevir—is the correct option. Why? This is a young patient who has fibrotic liver disease, as I mentioned before, stage 2 fibrosis. There are no contraindications to antiviral therapy. And with this new triple regimen, very high sustained response rates are to be expected, with results ranging from 66% to 79% in published studies for patients with hepatitis C virus genotype 1.

Case One: Decision Point Two

The case continues. The patient is treated with antiviral therapy. She’s started on pegylated interferon alfa-2a at a dose of 180 µg/week, ribavirin weight-based dosing 1000 mg/day and divided dosages for this person, and it was opted to use telaprevir in this case, 750 mg, three times daily. One could also have used boceprevir, 800 mg, three times daily, for this case as well.

On therapy, the patient develops fatigue and arthralgias, but she generally tolerates the regimen well. She’s advised to take anti-inflammatory agents and to drink plenty of water, both of which are helpful for these systemic symptoms of fatigue and arthralgias on antiviral therapy.

Blood testing is performed at weeks 1, 2, and 4. At week 4, the hemoglobin declines to 10.0 from 13.8 that it started at. Fortunately, liver enzymes have normalized: ALT is now 28 and AST is 22. And better news yet, hepatitis C virus RNA is now undetectable and unquantifiable.

At week 4, the patient complained about having difficulty meeting the requirements to eat food containing 20 grams of fat with each dose, because telaprevir, one of the recommendations is that you are to take 20 grams of fat with each dose of the medication. Now, examples of food had been provided to her that would be appropriate, such as bagels with cream cheese, potato chips, peanuts, these kinds of foods. But she was having some trouble adjusting to this change in her diet. My nurse spoke to her on several occasions and told her that while it may at first not appear to be palatable, that she really has to do the best she can, because taking 20 grams of fat with each dose of telaprevir optimizes absorption.
Blood testing was performed at week 6, 8, 10, and 12. The hemoglobin fortunately remains stable and was noted to be 10.1 at week 12. Hepatitis C virus remained unquantifiable and undetectable at week 12. And this leads us to our second decision point.

What is the complete duration of therapy for this patient?

Twelve weeks is choice number one; 24 weeks is choice number two; and 48 weeks is choice number three.

The first option—12 weeks of triple therapy—is incorrect. There was a study group in a European trial with treatment-naive hepatitis C virus patients genotype 1, called the PROVE 2 trial, in which they looked at triple therapy for 12 weeks only, and sustained response rates in this group were not the highest, so this is not a good choice.

The second option—24 weeks—is correct. This patient achieved what is now known as an extended rapid virologic response, an eRVR. Now, that means the patient had undetectable and unquantifiable virus at week 4 and at week 12. This is a new term, one that we haven’t used before in treatment of hepatitis C. Studies have shown that if a treatment-naive hepatitis C virus genotype-1 patient achieves an eRVR, that they only require 24 weeks of antiviral therapy. Now, the antiviral therapy is 12 weeks of the triple therapy with telaprevir and then 12 additional weeks of double therapy with pegylated interferon alfa and ribavirin only. This, by the way, is called response-guided therapy, which is another new term for patients that are treated with the protease inhibitors. When patients have a brisk response like this one, they can receive a shorter course of therapy than we previously used in patients with genotype 1; 24 weeks in this case.

And consequently, the third option—48 weeks—is incorrect. There is no benefit from extension of antiviral therapy beyond 24 weeks to 48 weeks if a treatment-naive patient has an extended rapid virologic response. And this was actually proved beyond a shadow of a doubt in the ILLUMINATE trial, which was done to actually assess this particular issue.

Case One: Decision Point Three

Now, for this lady, telaprevir was discontinued at the end of week 12, as per the approved therapeutic regimen that I just mentioned. Pegylated interferon alfa and ribavirin were continued. The patient complains, not surprisingly, of ongoing fatigue and arthralgias, but she remains
active. Her hemoglobin remains stable, ranging from 10.0 to 10.4, and the CBC, by the way, was followed on a monthly basis.

The RNA level was again obtained at week 24 and was found to be unquantifiable and undetectable still. As I mentioned before, because of the response-guided therapy paradigm, antiviral therapy was discontinued at week 24. Flu-like symptoms resolved rather quickly, within a month or so. Hepatitis C virus RNA was checked again at week 48, 24 weeks after therapy was discontinued, and it was found again to be unquantifiable and undetectable. This leads us to decision point three.

The patient asks *if there was information available about the durability of a sustained virologic response*, which she now is. She’s now a sustained responder since she has undetectable virus 6 months after stopping antiviral therapy.

So what do we tell her? How do we answer her question? One, do we say information is not available; two, information is available, and the durability of an SVR after 1 year is approximately 80%; or 3, information is available, and the durability of an SVR over a period of approximately 2 years is greater than 99% with telaprevir.

The first option—that information is not available—is incorrect. There are data available regarding durability of response with telaprevir.

The second option—that the durability of SVR with telaprevir is 80% after 1 year—is also incorrect.

The third option—the durability of SVR with telaprevir is greater than 99% after approximately 2 years—is correct. Preliminary presentations of data from the EXTEND trial, during which patients who have been on telaprevir within the context of phase II and phase III trials and who achieved SVR and have been followed over the long term, have been reported. And patients have been followed on average nearly 2 years, and there have been over 200 patients with SVR followed. Only one patient suffered from late relapse, meaning that they were designated as an SVR, or sustained responder, and then later the virus came back. Interestingly, that patient received only 10 weeks of antiviral therapy total, so they didn’t get a full course; yet, they were designated as an SVR and followed as per the EXTEND protocol. That’s the only patient in over 200 patients that had what we call a late relapse. So durability of SVR with telaprevir is excellent.
Case One: Conclusion

What are our take-home messages?

One, antiviral therapy with the protease inhibitors offers high sustained virologic response rates in patients who are treatment-naive with genotype 1. Antiviral therapy should be recommended. We should not warehouse patients, particularly in patients with fibrotic liver disease.

Two, patients with extended rapid virologic response, undetectable virus at weeks 4 and 12 who were treatment-naive, should be offered a truncated therapeutic regimen of 24 weeks.

And three, sustained virologic response with a telaprevir-based therapeutic regimen is durable.
Case Two: Patient Presentation

For our second case, we have a 52-year-old white male with chronic hepatitis C virus infection that’s referred for evaluation. The patient was first noted to have abnormal liver enzymes in 2006 after life insurance testing. Additional workup was undertaken at the time, and he was diagnosed with chronic hepatitis C virus infection. Then, more workup was performed, and he was noted to have hepatitis C virus genotype 1a. A diagnostic liver biopsy was performed and revealed moderate inflammation, grade 2, in stage 1 fibrosis.

Antiviral therapy with pegylated interferon alfa-2b and ribavirin commenced in 2007. He tolerated the medications reasonably well, complaining only of mild flu-like symptoms. At the time, hepatitis C virus RNA levels declined three logs at week 12, but did not become undetectable by week 24. Antiviral therapy was discontinued in late 2007 after 24 weeks, and the patient was classified as a partial responder.

The patient has been followed since then with annual blood testing and office follow-up. He complains of mild fatigue, but denies abdominal discomfort, pruritus, arthralgias, peripheral edema, increase in abdominal girth, encephalopathy, or GI bleeding. He consumes alcohol only on an occasional basis.

Hepatitis C virus risk factors included blood transfusions at the age of 18 after a motor vehicle accident. There is no history of intravenous or intranasal drug use, nor does he have any tattoos.

The patient is highly motivated to eradicate hepatitis C, and he presents for his routine annual follow-up. Past medical history is remarkable for mild hyperlipidemia and the motor vehicle accident at age 18, during which he suffered a femur fracture. His only medication is atorvastatin. There is no family history of liver disease. The patient is divorced, has three healthy children, works as an electrical engineer, and he does not smoke.

On examination, he’s well appearing. His height is six feet. His weight is 190 pounds. He has anicteric sclerae. His neck is without lymphadenopathy, lungs are clear. Cardiac examination reveals regular rate and rhythm without rubs or gallops. His abdomen is soft, nontender, without palpable hepatosplenomegaly. Extremities are without edema. He has no palmar erythema. There are no spider angiomata, and there’s no asterixis.

On laboratory measurements, his white blood cell count is 7400. His hemoglobin is 14.1 g/dL, and his platelet count is 182,000. INR is 1.0. Liver enzymes are mildly elevated with an
ALT of 112, and AST of 90. Alkaline phosphatase was normal at 100, and the total bilirubin was normal at 1.0.

Hepatitis C virus RNA levels were drawn and were 1.1 million IU, and his genotype was double checked and it was in fact 1a. Abdominal ultrasound was performed to visualize the liver and revealed a normal appearing liver and spleen. There was a small cyst on the right kidney thought to be benign, and there were no other abnormalities identified. And this leads us to decision point one.

**Case Two: Decision Point One**

*Should antiviral therapy with pegylated interferon alfa, ribavirin, and either telaprevir or boceprevir be recommended?*

Options include, one, no, because very poor sustained virologic response rates are to be expected in patients with genotype 1 who are partial responders; two, no, because the protease inhibitors are not approved in historic partial responders; three, no, because the patient has only mild liver disease and does not really need therapy; or four, yes, we should recommend antiviral therapy.

The first option—no, because poor SVR rates are to be expected in genotype-1 patients who are partial responders—is incorrect. Reasonable sustained virologic response rates that I’ll discuss in a moment are to be expected in historic partial responders.

The second option—no, because the protease inhibitors are not approved in historic partial responders—is also incorrect. Both boceprevir and telaprevir are indicated for historic partial responders with hepatitis C virus genotype 1.

The third option—no, because the patient has mild liver disease and does not need therapy—is also incorrect. This patient is highly motivated for antiviral therapy. The expected SVR rates are reasonable, approaching 60% with telaprevir. And only because the patient has mild liver disease, this is not a reason that one should counsel a patient to defer therapy. We don’t know the rate of progression of liver disease in patients. Patients can present with more rapid progression at times. We don’t know when new medications will be available or what their effect will be in patients who are partial responders to pegylated interferon alfa and ribavirin. And therefore, it is
certainly not a bad idea to treat this patient with antiviral therapy, particularly since he is so highly motivated to undergo therapy.

The fourth option—yes—as I just alluded to, is the correct answer. Triple therapy is recommended, and that’s because expected SVR rates in historic partial responders approach 60% with telaprevir.

**Case Two: Decision Point Two**

Since telaprevir is only used for 12 weeks and boceprevir is used for 32 weeks in historic partial responders, a decision was made in this case to use telaprevir. But, I must point out that boceprevir is also approved for treatment with partial responders, and it is absolutely an acceptable choice as well.

Prior to starting therapy, the current medication list is reviewed for potential contraindications in drug-drug interactions. And if you wonder why, that’s because with the protease inhibitors, both boceprevir and telaprevir, there are multiple drug-drug interactions that must be dealt with prior to starting therapy. And this leads us to decision point two.

The patient is maintained on atorvastatin. *Is there an issue with usage of a statin with the protease inhibitors?*

Options include: no, there are no issues; yes, statin levels decline with usage of protease inhibitors because of interactions with the cytochrome P450 system, in particular, 3A4, with drug metabolism at that site; or yes, statin levels can rise with usage of the protease inhibitors because of interactions with that cytochrome P450 3A4 system.

The first option—no, there are no issues with statins—is incorrect.

The second option—yes, statin levels decline with usage of protease inhibitors because of interactions with these CYP 3A4 drug metabolism—is also incorrect. The reason for this issue is that statin levels do not decline when you use the protease inhibitors.

The third option—statin levels can rise with usage of protease inhibitors because of this CYP 3A4 drug metabolism interaction—is correct. Why? Because in this case, the protease inhibitors are also metabolized by the same cytochrome P450 system that statins are. When the protease inhibitor, and that’s either boceprevir or telaprevir, occupy this cytochrome system, the statins,
which are usually metabolized by the same system, are not metabolized as quickly. Therefore, even when you take the same dosage you’ve taken for many, many years, the levels can rise and toxicity is possible. Therefore, there are drug-drug interactions with the protease inhibitors and statins. In particular, with atorvastatin, boceprevir is listed as a drug with significant drug interactions, and with telaprevir, it’s listed as a contraindicated drug completely.

**Case Two: Decision Point Three**

Hence, in this gentleman, it’s decided to hold atorvastatin during the protease inhibitor therapy, which with telaprevir is 12 weeks. Antiviral therapy with pegylated interferon alfa-2a at a dose of 180 µg/week, and ribavirin weight-based dosing, 1200 mg/day in divided dosages, and telaprevir, 750 mg, every 8 hours, commences.

Blood testing is performed weekly for the initial 4 weeks. At week 4, the hemoglobin level declines to 10.8 g/dL. The HCV RNA is unquantifiable and undetectable. The patient notes mild fatigue, but is otherwise tolerating medications well.

At week 9, the patient develops an eczematous rash on the trunk and extremities. It is patchy and somewhat pruritic. By week 10, the rash slightly worsens and he presents for evaluation. You observe that the rash involves about 30% to 40% of the patient’s body. It is not erythematous and it is not confluent. The patient does not have fevers. A CBC is obtained and reveals a white blood cell count of 5200 without neutropenia or eosinophilia.

This leads us to decision point three. The patient has now completed ten weeks of antiviral therapy and has a moderate diffuse rash attributed to telaprevir.

*Should all antiviral therapy be discontinued? Should telaprevir alone be discontinued with pegylated interferon alfa and ribavirin maintained? Should the patient be hospitalized because of this rash?*

Options include: one, continue antiviral therapy and treat the rash with aggressive local measures; two, discontinue all antiviral therapy and hospitalize the patient; three, discontinue telaprevir, but continue pegylated interferon alfa and ribavirin and apply aggressive local measures to the rash.

The first option—continue antiviral therapy and treat the rash with aggressive local measures—is correct. The patient has only a moderate skin rash, and that’s defined by the fact
that approximately 30% to 40% of the skin is involved. Now, the telaprevir-associated skin rash is usually described as an eczematous one. It’s a little bit different than the ribavirin rash that we have seen previously, which is generally more erythematous and less eczematous. Interferon can also be associated with skin rash primarily through exacerbation of autoimmune skin rashes that a patient might have, like eczema or psoriasis. The differences between a mild rash would be that the mild rash is involving less of the body, and a severe rash it would be involving more of the body, more than 50% of the body surface area.

When one is very worried about a skin rash in patients on antiviral therapy for hepatitis C is when the rash involves more than 50% of the body and there are systemic symptoms, such as fevers or lymphadenopathy, and patients may have eosinophilia. This is called DRESS syndrome: “DR” is drug rash, the “E” is eosinophilia, and systemic symptoms are the “SS.” But this patient doesn’t have any signs of that, because they don’t have systemic symptoms and less of the body surface area is afflicted.

So what is recommended is aggressive topical therapy. You can use corticosteroids for instance, which would hopefully help mitigate the rash while antiviral therapies continue. You follow the patient closely, you discuss progression of the rash with the patient and the potential need to discontinue the telaprevir if the rash worsens.

Now, if you did have to discontinue telaprevir, is all hope lost? And the answer is no. in the ADVANCE trial, there was a treatment arm in which patients received 8 weeks of triple therapy followed by a complete course of pegylated interferon alfa and ribavirin alone. So the telaprevir was used 4 weeks less than it is in the currently approved regimen where we use it for 12 weeks. In that study, the sustained response rate was still 72% compared with 79% for the people that got the full 12 weeks of therapy, so 12 weeks is optimal. However, 8 weeks again certainly doesn’t mean all hope is lost, and therefore all attempts should be made if somebody is undetectable already and has a rash to keep the patients on pegylated interferon alfa and ribavirin to optimize chances that they attain a sustained response.

The second option—discontinuing all antiviral therapy and hospitalizing the patient—is also incorrect. This would be needed only if the rash was severe, and if there is evidence of this DRESS syndrome or Stevens-Johnson, where you actually have sloughing of the skin.
The third option—discontinue telaprevir, but continue pegylated interferon alfa and ribavirin and apply local measures aggressively to the rash—is also incorrect at this point, and that’s because the rash is not yet severe.

**Case Two: Decision Point Four**

The recommendation would be to treat aggressively with local therapy and stay the course, keep the patient on antiviral medications. However, the patient should be followed very closely and if the rash worsens, then telaprevir should be discontinued. All attempts should be made, again, to keep pegylated interferon alfa and ribavirin on board. The rash is treated aggressively with topical corticosteroid ointment and cream, antiviral therapy is continued with pegylated interferon alfa, ribavirin, and telaprevir through week 12. At week 12, hemoglobin is 10.2. Hepatitis C virus RNA remains unquantifiable and undetectable. The rash is stable with continued topical therapy.

The patient asks, can therapy be truncated at week 24, since he has an extended rapid virologic response, again meaning that the RNA was undetectable at both weeks 4 and 12. This leads us to decision point four.

*Is response-guided therapy with the option of truncated antiviral therapy to 24 weeks applicable to this patient who is an historic partial responder, even though he has achieved an extended rapid virologic response?*

Options include: one, yes, therapy should be truncated at week 12 because the patient has undetectable RNA and has a moderate skin rash, so this is a choice where we truncate therapy at week 12 even because of the rash; or two, yes, therapy can be truncated at week 24, as it would be in a treatment-naive patient; or choice three, no, antiviral therapy with peginterferon alfa and ribavirin should be continued to complete a 48-week course if possible to optimize chances of attaining a sustained virologic response even in the setting of an extended rapid virologic response.

The first option—yes, truncate therapy at week 12—is not recommended because of the skin rash, because the skin rash, again, is moderate; it would be expected to improve after discontinuation of telaprevir. And just because the RNA is undetectable, it’s still not a good idea to stop therapy that early.
The second option—yes, truncate therapy at week 24—is also incorrect. Patients who are partial or null responders with telaprevir are not candidates to truncate therapy at 24 weeks, even with an extended rapid virologic response.

And that leads us to choice number three, which is the correct choice—no, continue peginterferon alfa and ribavirin through week 48. The approved regimen with telaprevir for partial and null responders is a 12-week course of triple therapy followed by a 36-week course of pegylated interferon alfa and ribavirin, assuming no futility rules are violated.

**Case Two: Conclusion**

In this patient, telaprevir is discontinued at the end of week 12, as it always is. Antiviral therapy with peginterferon alfa and ribavirin is continued for 36 additional weeks. The skin rash slowly improves and resolves by week 20. I will say that the telaprevir-associated skin rash may take a number of weeks to resolve. Hepatitis C virus RNA fortunately is unquantifiable and undetectable at week 48, and then again at week 72, 24 weeks after the antiviral therapy is discontinued, and therefore the patient is classified as a sustained virologic responder.

The takeaway messages are, number one, antiviral therapy is indicated in patients with prior treatment failure.

Two, drug-drug interactions must be considered with usage of the protease inhibitors. In this case, we mentioned atorvastatin, but there are many, many, many drug-drug interactions that must be reviewed prior to starting therapy with either of the protease inhibitors.

And number three, mild to moderate skin rash can be managed aggressively by topical therapy. Antiviral therapy should be continued if possible with or without telaprevir to optimize chances of attaining an SVR. However, if the rash is severe or if there are signs of systemic symptoms, urgent evaluation by a dermatology consultant or hospital admission should be arranged.

I’d like to thank you for joining us for this presentation today. I hope you will participate in other hepatitis C courses offered by Projects in Knowledge. Have a nice day.