6

THE FUTURE OF HCV TREATMENT

Beyond Triple Therapy

I am still on treatment and almost halfway through the trial. I do not have hepatitis C at the present time. I hope this treatment has cured it, and I hope I will not need future treatment. The results were immediate. Before I began the QUAD Therapy clinical trial, there were over four million copies of the virus per milliliter of my blood. After the first week, that was down to only 160 copies per milliliter, and, at week two, I tested negative for hepatitis C. The virus is still undetectable in my blood—hopefully, this is it, and I am cured.

— Mark

TWENTY YEARS ago, I treated patients with HCV genotype 1 infection with interferon monotherapy, and five percent achieved SVR. Results improved to an SVR of 45 percent with peginterferon/ribavirin. Now, the new standard of care of triple therapy is expected to raise SVR up to 75 percent. What's next?

In this chapter, I look to the future, focusing on the next generation of direct-acting antivirals: new protease inhibitors, polymerase inhibitors,

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NS5A inhibitors, and others. The future for treating HCV is, indeed, bright. Hopefully, the time will soon arrive when nearly every person infected with HCV will have safe, tolerable, and effective options for treatment.

The year 2011 marked the beginning of a new era in the treatment of the hepatitis C virus (HCV) with the introduction of telaprevir and boceprevir. These two drugs are inhibitors of the HCV NS3/4A protease, and are the first FDA-approved direct-acting antivirals for chronic hepatitis C. They will not be the last. Many pharmaceutical companies have targeted several HCV proteins (including the NS3/4A protease), and multiple new compounds and effective strategies are either under development or already entering later phases of testing in clinical trials.

In this chapter, I will discuss the following topics:

- Status of Clinical Investigation into Future HCV Therapies
- Next Generation Triple Therapy
    - Lambda interferon
    - Inhibitors of NS3/4A protease
    - Inhibitors of NS5B polymerase
    - Inhibitors of NS5A protein
- Interferon-Free Regimens
    - Mericitabine plus danoprevir
    - Daclatasvir plus BMS-650032
    - BI-201335 plus BI-207127 ± ribavirin
    - GS-7977 plus ribavirin
    - Genotype 1b versus 1a
- QUAD Therapy
    - Daclatasvir plus BMS-650032 plus peginterferon/ribavirin
    - Telaprevir plus VX-222 plus peginterferon/ribavirin
- Host-Acting Antivirals
    - Cyclophyllin inhibitors
    - Entry blockers
    - Micro-RNA inhibitors
- Viral Resistance
- Concluding Remarks

The ongoing developments in the treatment of chronic hepatitis C will be discussed in this chapter. Although the material in the following pages may give you a glimpse into future treatments, this is not an exhaustive review of all the possibilities. Instead, I have focused on those therapies that progressed furthest in Phase II or Phase III clinical trials. Promising drugs that are at earlier stages of development or with less clinical data may not be included in the following discussion.

WARNING: You should understand that the treatments discussed in this chapter are experimental, currently under investigation, and at various stages of testing in clinical trials. None of the treatments described in this chapter have received approval from the FDA, and, therefore, you cannot be prescribed these treatments. The only access to these treatments is through participation in clinical trials. You can check www.clinicaltrials.gov to see which trials are registered and available within your region. Also, because the treatments described in this chapter are experimental, they may be proven to be ineffective or toxic, and it is possible that only a minority of these drugs may successfully emerge for treatment of HCV in clinics.

STATUS OF CLINICAL INVESTIGATION INTO FUTURE HCV THERAPIES

> *I have no symptoms, my laboratory tests are normal, and my doctor says I have minimal liver disease. I want to wait and be treated with more effective drugs that have fewer side effects. I've heard there are new drugs in the pipeline. Which ones are in clinical trials and show potential promise for emerging or future treatments?*
>
> — *Robert*

Currently, the field of hepatology is hyper-focused on the treatment of hepatitis C. Hepatitis C was listed as the main topic of 541 abstracts at the 2011 meeting of the American Association for the Study of Liver Diseases, representing 24 percent of the entire meeting. Three hundred and nine abstracts were focused on clinical trials or treatment of chronic hepatitis C, representing 13 percent of the meeting. In addition, scanning

websites revealed a plethora of activity, including 285 registrations on clinicaltrials.gov. At hcvdrugs.com, there were listings for eight trials of combination treatments, 96 trials of single direct-acting antivirals, and 37 trials of immune modulators. At hcvadvocate.com, there were listings for 10 Phase I trials, 19 Phase II trials, and four Phase III trials. Another outstanding website with current information on treatments for HCV is www.natap.org. There are many additional websites devoted to hepatitis C and evolving treatments. I recommend that you take efforts to stay informed by visiting these sites periodically. New, more tolerable, and more potent drug therapies for chronic hepatitis C and HCV will undoubtedly be a future reality[88] (Figure 6A).

FIGURE 6A: EMERGING TREATMENTS (ABSTRACTS AT AASLD 2011)

	↑eRVR	↑SVR	↓SEs	↓Pills	↓Freq	NoIFN
TT Regimens with PR						
TMC-435	√	±	√	√	qd	-
BI -201335	√	±	√	√	qd	-
BMS-790052	√	+	√	√	qd	-
PSI-7977 G1	√	++	√	√	qd	-
PSI-7977 G2/3	√	++	√	√	qd	√
Danoprevir	√	++	?	√	bid	-
Vaniprevir	?	+	?	√	bid	-
Narlaprevir/rtv	√	++	√	√	qd	-
QUAD Regimens						
BMS (PR+NS5A-I+PI)	√	+++	±	√	DAAs qd	-
VX (PR+PI+NNI)	√	+++	±	-	-	-
IFN-Free Regimens						
BMS (NS5A-I+PI) G1 a/b	±	±	√	√	qd	√
BMS (NS5A-I+PI) G1b	√	+++	?	√	qd	√
BI (PI+NNI+RBV)	√	?	√	√	qd	√
PSI (NI+RBV) G2/3	√	+++	√	√	qd	√
Alisporivir ± RBV G2/3	-	?	√	±	qd	√

FIGURE 6A: This table lists some, but not all, of the emerging treatment options for chronic hepatitis C. A checkmark in a given column indicates enhancement of eRVR and SVR, or reduction in side effects, number of pills, frequency of dosing of the direct acting antiviral, and the possibility of IFN-free treatment. The regimens listed were presented in part at the last meeting of the American Association for the Study of Liver Diseases (AASLD 2011).

My advice to anyone who is considering a trial is simple: just keep going. The more attention you give to how badly you feel, the worse it becomes. Just maintain your daily routine throughout the trial, and try to keep on track with your life and commitments. Strictly follow the protocol and live your life.

— Barb

The first week, the virus was cleared. I won't know whether I am still infected until I complete this round of therapy, though. If I test clear six months after I complete the therapy (and I hope I do), I will be considered cured. But, for now, I'm still in the thick of it. I'll know for sure in about a year. If I still have hepatitis C, I would try another trial. There are so many clinical trials going on; there are about 75 throughout the country. It's a very dynamic time for hepatitis C research. Sooner or later, someone will hit the Holy Grail of hepatitis C treatment. I may very well be in the trial that is the cure.

— Frank

Stick it out. I put needles in my arm for many years, and I was strung out. I'm drug-free for over 27 years, and that was a big accomplishment. But doing this clinical trial is the greatest accomplishment in my life. You don't hear the word "cure" used for anything. Now, it's being used as "hepatitis C cure." So, the chance that I will be cured of this is worth any of the side effects. Plus, I have come to appreciate the staff who are treating me—they are phenomenal. I have to keep going.

— Butch

NEXT GENERATION TRIPLE THERAPY

Some of the emerging regimens contain the backbone of peginterferon and ribavirin, typically when the regimen includes a single direct-acting antiviral. The single direct-acting antiviral could be a NS3/4A protease inhibitor, NS5B polymerase inhibitor, or NS5A inhibitor. These regimens are the next generation of triple therapy.

Lambda Interferon

If triple therapy remains the standard of care for the foreseeable future, then new options for the peginterferon/ribavirin backbone may be developed. The current interferons that are FDA-approved for treatment of chronic hepatitis C are alfa interferons, including peginterferon alfa-2a, peginterferon alfa-2b, consensus interferon, interferon alfa-2a, and interferon alfa-2b. Lambda interferon is a relatively new type of interferon that has also shown promise in the treatment of chronic hepatitis C[89, 90]. A pegylated form of lambda interferon (PEGIFN-lambda) is completing Phase II clinical trials, and likely will soon move to Phase III testing.

PEGIFN-lambda may have greater antiviral potency than the alfa peginterferons and, perhaps more importantly, fewer side effects. PEGIFN-lambda inhibits the bone marrow less than the alfa interferons. Why is that good? Your bone marrow produces all of your blood cells: red blood cells, white blood cells, and platelets. Compared to alfa-interferons, patients taking lambda interferon have less anemia (lowering of red blood cells), and maintain higher levels of white blood cells (the cells that fight infection) and platelets (the cells that aid clotting). The main clinical benefits of these effects could include a reduced need for ribavirin dose reduction, less transfusion of red blood cells, and decreased use of treatments to raise red blood cells (erythropoietin analogues) or white blood cells (granulocyte-colony stimulating factors). PEGIFN-lambda might be a better tolerated interferon for use with emerging triple therapy regimens.

Inhibitors of NS3/4A Protease

As you learned from reading chapters 4 and 5 of this book, the first two direct-acting antivirals to be FDA-approved for treating hepatitis C, telaprevir and boceprevir, are NS3/4A protease inhibitors. Clearly, telaprevir and boceprevir enhance the treatment of chronic hepatitis C. Yet both require interferon/ribavirin, are active mainly against HCV genotype 1, and side effects are an issue. For these reasons, there remains great interest in the development of additional protease inhibitors with greater potency, fewer side effects, and activity against all HCV genotypes.

TMC-435. TMC-435 is a new protease inhibitor that has just begun Phase III clinical trials[91, 92, 93]. In Phase II trials, up to 86 percent of

patients treated with TMC-435-based triple therapy achieved eRVR, and were thus eligible for early discontinuation of treatment at 24 weeks. Also, the maximum reported SVR was 86 percent, and TMC-435 was not associated with rash or the lowering of white blood cells, red blood cells, or platelets. During treatment, some patients did experience an increase in bilirubin without evidence of liver damage. The increase in bilirubin was stable during treatment, and resolved itself after the discontinuation of TMC-435. The Phase II studies suggest that triple therapy with TMC-435 appears to be highly effective and well-tolerated. Phase III trials with TMC-435 are ongoing.

BI-201335. BI-201335 is another new protease inhibitor that has just begun Phase III clinical trials[94, 95]. In the Phase II trials, up to 87 percent of patients treated with BI-201335-based triple therapy achieved eRVR, and were thus eligible for early discontinuation of treatment at 24 weeks. The maximum reported SVR was 83 percent, and BI-201335 was not associated with any additional or new adverse effects. As with TMC-435, transient elevations in bilirubin were reported, and, in the Phase II trials, triple therapy with BI-201335 also appeared to be highly effective and well-tolerated. Phase III trials with BI-201335 are ongoing.

Danoprevir (RG-7227). Danoprevir is also highly effective[96, 97]. In the Phase II trial, ATLAS, eRVR was 79 percent, and SVR was 85 percent for danoprevir-based (600 milligrams twice daily) triple therapy. In the ATLAS trial, a high dose arm of 900 milligrams twice daily was associated with alanine aminotransferase (ALT) elevations, and this arm was closed prematurely. To address the ALT elevation and also enhance potency, danoprevir is now being studied with ritonavir (RTV) in clinical trials. The Phase II results of triple therapy using danoprevir/RTV are encouraging (DAUPHINE trial, SVR 12 up to 93 percent [EASL 2012]).

Narlaprevir/Ritonavir (RTV)[98]. In a recent Phase II trial, triple therapy with narlaprevir/RTV yielded a maximum SVR of 85 percent. Ritonavir boosted the potency of narlaprevir by altering its metabolism in the body, allowing once daily dosing, and it also reduced side effects. The status of development of narlaprevir is unclear.

Many other protease inhibitors are proceeding down the path of clinical development. These include vaniprevir, BMS-650032, GS-9256,

ACH-1625, IDX-320, VX-985, and ABT-450. Many of these compounds appear very promising as potent and well-tolerated inhibitors of the HCV NS3/4A protease.

Inhibitors of NS5B Polymerase

Polymerase inhibitors target the NS5B RNA-dependent RNA polymerase of HCV, an enzyme critical for viral replication. There are two types of polymerase inhibitors: nucleoside or non-nucleoside. Nucleoside inhibitors target the active site of NS5B in a competitive manner, have broad spectrum activity, and lead to RNA chain termination. Non-nucleoside inhibitors bind at a site distant to the catalytic center of the polymerase. An increased genetic barrier to resistance is reported for the nucleoside inhibitors, while the non-nucleoside inhibitors have had significant issues with resistance and suboptimal viral suppression.

Mericitabine (RG-7128). Mericitabine is a cytidine nucleoside analog[99, 100]. In Phase I trials of HCV genotype 1 non-responders, 14 days of treatment with mericitabine produced a 2.7$\log_{10}$ IU/mL decline in viral load at a dose of 1,500 milligrams twice daily. No serious adverse effects were reported in the treatment group. Subsequent trials of mericitabine in combination with peginterferon/ribavirin demonstrated a 5$\log_{10}$ IU/mL decline in HCV RNA by week four of treatment.

Results from the JUMP-C trial indicated an SVR at week 12 of 76 percent for response-guided therapy with mericitibine-based triple therapy. Importantly, there was no evidence of the emergence of breakthrough related to viral resistance. Mericitibine is undergoing further investigation in combination with danoprevir.

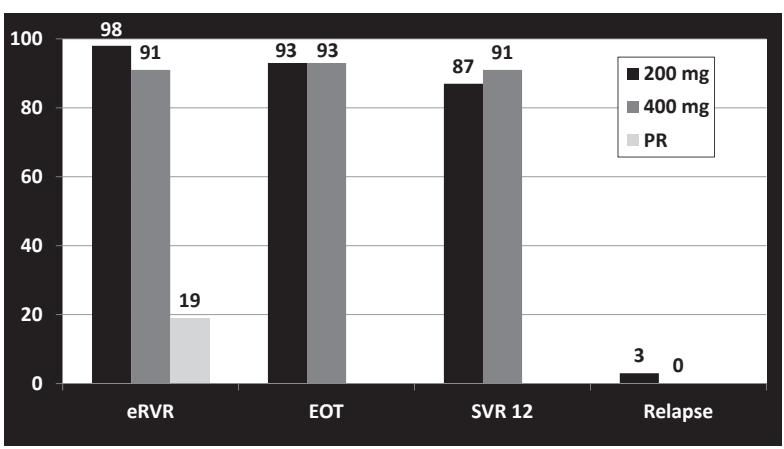
> *The treatment of my hepatitis C with peginterferon, ribavirin, and the new drug (mericitabine) is best described as the worst case of flu I've ever had—but now I'm over it, and, lucky for me, no hepatitis C.*
>
> *— Terry*

GS-7977. GS-7977 is a potent nucleoside (pyrimidine) NS5B polymerase inhibitor that has generated intense interest as a potential break-

through in HCV treatment[93, 100, 101, 102]. In a Phase II study, PROTON, GS-7977-based triple therapy was evaluated in 121 treatment-naïve patients with HCV genotype 1 infection (Figure 6B). Stages of fibrosis ranged from F0 to F2 (mild fibrosis), and there were only a few black patients. This regimen was quite potent: 98 percent of patients at week four of treatment had undetectable HCV RNA. The SVR at week 12 reported at AASLD 2011 was 91 percent. These encouraging results have catapulted GS-7977 into the forefront of emerging HCV therapies—the pharmaceutical company, Gilead Sciences, purchased the maker of GS-7977, Pharmasset, for $11 billion. GS-7977-based triple therapy is beginning Phase III trials.

NOTE: When Gilead purchased Pharmasset, PSI-7977 was changed to GS-7977.

FIGURE 6B: RESULTS FROM THE PROTON STUDY OF GS-7977 TREATMENT-NAIVE PATIENTS WITH HCV GENOTYPE 1



No new safety events. There were 3 viral breakthroughs and 1 relapse in the 200mg arm. All 4 were CT by IL28b polymorphism.

FIGURE 6B: The results of the PROTON study are shown (as presented at AASLD 2011). SVR 12 was highly favorable (91 percent) with a regimen of GS-7977/peginterferon/ribavirin. GS-7977 is a nucleoside NS5B polymerase inhibitor.

An advantage of HCV polymerase inhibitors is they may be active against non-1 HCV genotypes. Mericitabine, GS-7977, PSI-938, and other NS5B polymerase inhibitors have activity against non-1 HCV genotypes.

Several additional polymerase inhibitors are at various stages of clinical investigation. These include VX-222, GS-9190, PSI-7792, BI-207127, IDX-375, IDX-184, ALS-2200, ALS-2158, MK-0608, TMC-649128, PF-868554, ANA-598, VCH-759, ABT-837093, ABT-072, ABT-333, INX-189, and GSK-625433. Many of these compounds appear very promising as potent and well-tolerated inhibitors of the HCV NS5B polymerase.

Inhibitors of NS5A Protein

Daclatasvir (BMS-790052). NS5A is an HCV protein with no known enzymatic function, but is a co-factor in HCV replication[103, 104, 105]. The drug daclatasvir (BMS-790052) has demonstrated potent inhibition of NS5A and HCV replication. In a placebo-controlled trial of 48 treatment-naïve patients with HCV genotype 1, SVR at week 12 was 92 percent (11 out of 12 patients) with 10 milligrams per day for 48 weeks, and 83 percent (10 out of 12 patients) with 60 milligrams per day for 48 weeks of daclatasvir. Side effects and adverse events were similar between treatment and control arms. Daclatasvir is being studied in a triple therapy regimen in ongoing Phase III trials.

Other NS5A inhibitors are in early phases of clinical trials. These include ACH-2928, PPI-461, AZD-7295, and others. Once again, many appear promising as components of triple therapy or other combination treatments.

INTERFERON-FREE REGIMENS

With the explosion of new direct-acting antivirals for HCV, the dream of interferon-free treatment is edging closer to clinical reality. As you know, the side effects of interferon and the burden of injections dominate management issues for patients and providers. Elimination of interferon could greatly simplify the treatment regimen, and improve

patient adherence and compliance. Several interferon-free protocols are currently under clinical investigation.

> *I'm glad I was able to get into a trial that was interferon-free. Interferon is brutal; I had numerous side effects during my last treatment with peginterferon and ribavirin. Now I understand what women experience when they have bad PMS. The mood swings come so suddenly, and your reactions are so quick and uncontrollable.*
>
> *I've had very dry skin, anxiety, extreme fatigue, and depression. I coped with the help of my family and the staff at the clinic. I had trouble sleeping, too, so I was given 50 milligrams of Trazadone to help with sleep.*
>
> — *Michael*

Mericitabine Plus Danoprevir

INFORM was the first clinical trial to investigate the efficacy of the combination of a protease inhibitor with a polymerase inhibitor.[99] This Phase I double-blinded ascending dose trial investigated the combination of 14 days of the polymerase inhibitor, mericitabine, with the protease inhibitor, danoprevir. Some patients were treatment-naïve, and others had previous therapy with interferon-based regimens. Significant viral load decline was noted over 14 days, with a median reduction in viral levels of 4.8 to 5.2 $\log_{10}$ IU/mL. Sixty-three percent of treatment-naïve and 25 percent of prior null responders receiving dual therapy were HCV RNA negative at 14 days. Further studies are underway to modify and better define this treatment regimen. This combination, with and without peginterferon or ribavirin, is currently under investigation in the MATTERHORN trial.

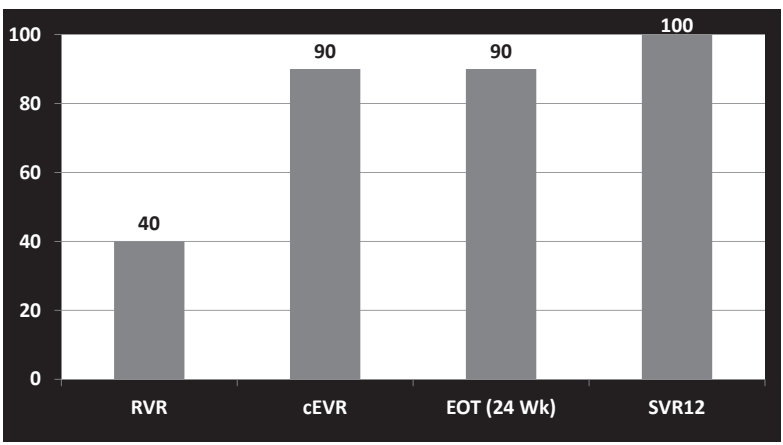
Daclatasvir Plus BMS-650032

This combination of inhibitors of NS5A protein and NS3/4A protease was studied in 11 null responders to prior treatment with peginterferon/ribavirin who were infected with HCV genotype 1[106]. All 11 patients demonstrated a brisk decline in HCV RNA, and four achieved

SVR despite only 24 weeks of treatment. The only breakthroughs were patients with HCV subtype 1a. Neither of the two patients with HCV subtype 1b experienced breakthrough.

This combination, given for twenty-four weeks, was also used in a study of ten Japanese null responders, all of whom were infected with HCV subtype 1b. The SVR was 100 percent[104]. Interferon-free, ribavirin-free dual DAA therapy may become a reality for patients infected with HCV genotype 1b (Figure 6C).

FIGURE 6C: DUAL INHIBITION OF NS5A PROTEIN AND NS3/4A PROTEASE
IO JAPANESE NULL RESPONDERS WITH HCV GENOTYPE 1B



Baseline RAVs to BMS-790052 and BMS-650032 did not affect response to treatment. 1 patient who stopped at week 2, and the 9 who took 24 weeks achieved SVR12.

FIGURE 6C: A pilot study of interferon-free, ribavirin-free treatment using DUAL inhibition of NS5A protein and NS3/4A protease was highly effective in 10 Japanese patients infected with HCV genotype 1b who had a prior null response to peginterferon/ribavirin.

Although daclatasvir/BMS-650032 may be very effective against the subtype 1b of HCV genotype 1, it is less effective against subtype 1a. For subtype 1a, daclatasvir/BMS-650032 will likely need to be combined

with other drugs (such as peginterferon, ribavirin, or other direct-acting antivirals) to provide additional potency and broader activity.

BI-201335 Plus BI-207127 ± Ribavirin

Potential efficacy of this regimen was first suggested from the results of the SOUND-C1 trial[94]. SOUND-C2 is an ongoing Phase II study of three interferon-free regimens: two with ribavirin and one without. The patients were infected with HCV genotype 1 and were treatment-naïve. All arms received a single daily dose of BI-201335. In the ribavirin-free arm, BI-207127 was given three times daily. In one ribavirin-containing arm, BI-207127 was also given three times daily, and, in the remaining ribavirin-containing arm, it was given twice daily. Virologic responses have been higher in the two arms containing ribavirin, suggesting that ribavirin may be required in interferon-free treatment regimens. On-treatment virologic responses have been brisk: up to 88 percent had cleared HCV RNA by week four of treatment and up to 82 percent achieved SVR 12 (EASL 2012).

GS-7977 Plus Ribavirin

This 12-week interferon-free dual regimen was used in 10 treatment-naïve patients with HCV genotype 2/3 infection[102]. The regimen was well-tolerated with few side effects, and 100 percent of the patients achieved SVR, despite the very short course of only 12 weeks of treatment.

After these results were known, a small exploratory study of GS-7977 monotherapy (no ribavirin or interferon) for genotype 2/3 patients was undertaken. On-treatment responses were brisk, but some patients broke through or relapsed. Thus, it appears that ribavirin may be required for optimal virologic responses with GS-7977 when used in interferon-free protocols.

ABT-450/r Plus ABT-333 Plus Ribavirin

This 12-week interferon-free triple regimen was used in a pilot study of 33 treatment-naïve patients and 17 prior nonresponders to peginterferon/ribavirin—all with HCV genotype 1 infection. The regimen was

well-tolerated with few side effects. Up to 95 percent of the treatment-naïve patients and 47 percent of the treatment-experienced patients achieved SVR12—with only 12 weeks of treatment and no interferon (EASL 2012)! Additional studies with this combination and other drugs are ongoing.

A number of interferon-free regimens, with and without ribavirin, are currently under study. Some of the combinations of direct-acting antivirals include telaprevir with VX-222, GS-9190 with GS-9256, IDX-184 with IDX-320, BMS-790052 with BMS-650032, BI-201335 with BI-207127, mericitibine with danoprevir, and GS-7977 with PSI-938. Many of these combinations appear promising as interferon-free treatments.

Genotype 1b Versus 1a

HCV genotype 1b, compared to 1a, may be particularly responsive or susceptible to interferon-free treatment. There is something very different about HCV genotypes 1a and 1b: the barrier for emergence of viral variants resistant to the protease inhibitors is higher for HCV genotype 1b. This means, during treatment of a patient infected with HCV genotype 1a, resistant viral variants may emerge that compromise virologic response. This translates to a lower chance for cure with interferon-free treatment regimens in patients infected with HCV genotype 1a. Do not be alarmed if you have HCV genotype 1a infection, as the rates of SVR are excellent with many of the new treatments. Nonetheless, maximizing your chances to achieve SVR if you are infected with HCV genotype 1a may require multi-drug regimens and peginterferon.

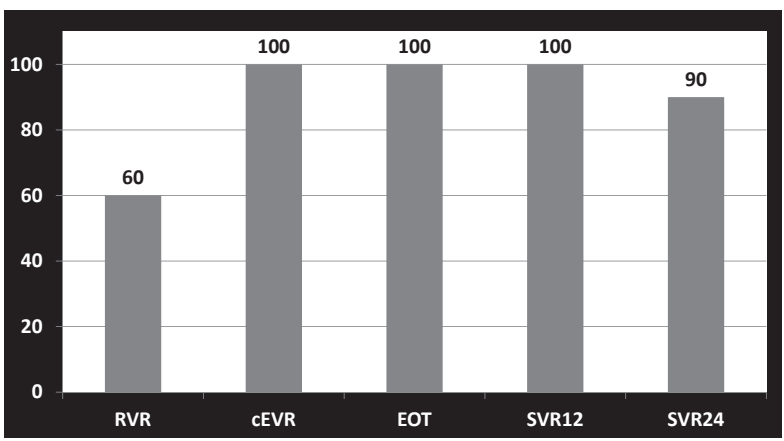
QUAD THERAPY

QUAD therapy implies the use of two direct-acting antivirals with peginterferon/ribavirin. The early experience with QUAD therapy in a very small number of patients has been promising. QUAD therapy dramatically enhances SVR and also blocks the emergence of resistant viral variants.

Daclatasvir Plus BMS-650032 Plus Peginterferon/Ribavirin

This combination of inhibitors of NS5A and NS3/4A protease plus peginterferon/ribavirin was studied in 10 null responders to prior treatment with peginterferon/ribavirin who were infected with HCV genotype 1, mostly subtype 1a (Figure 6D). Nine of the 10 patients achieved SVR despite only 24 weeks of treatment. Additional studies of this QUAD regimen are underway.

FIGURE 6D: QUAD THERAPY OF NULL RESPONDERS (N=10) WITH HCV GENOTYPE 1 NS5A AND NS3/4A INHIBITORS + PR FOR 24 WEEKS



Lok A, et al. N Engl J Med 2012;366:216-224.

FIGURE 6D: These preliminary results in 10 patients suggest that QUAD treatment may be effective in re-treatment of HCVgenotype 1a and 1b null responders. QUAD included inhibitors of NS5A protein and NS3/4A protease with peginterferon/ribavirin.

Telaprevir Plus VX-222 Plus Peginterferon/Ribavirin

This combination of NS3/4A protease inhibitor, NS5B non-nucleoside polymerase inhibitor, and peginterferon/ribavirin was tested in 59 treatment-naïve patients infected with HCV genotype 1. There was a

very interesting twist to this study: the patients who had a very rapid virologic response (vRVR), defined as undetectable HCV RNA at weeks two through eight stopped treatment at week 12. Fifty percent of the patients achieved vRVR and stopped all treatment at week 12. Ninety-three percent of those patients then went on to achieve SVR. Those not achieving vRVR were given an additional 12 weeks of peginterferon/ribavirin. The overall rate of SVR for all patients on this QUAD regimen was 90 percent.

> *The virus is gone, and has not been detected. I will get blood work every two weeks. As of today, I am not infected. As of today, I am cured. I never had a treatment clear the virus before . . . not even close. So, I feel as though it's cured. We'll know for sure after six months, but, as of today, I am not infected. If, in six months, I still have the virus, I would treat, again. I have complete faith that, ultimately, I will be cured of this infection—if not now, in the future.*
>
> — *Gary*

Additional QUAD regimens are currently under study. QUAD therapy may push the limits of SVR to near 100 percent, and will likely cover the broad range of genotypes and subtypes. The high potency of QUAD therapy reduces the need for baseline predictors of response (such as IL28B polymorphism), prevents the emergence of resistant viral variants, and allows further shortening of the duration of the antiviral therapy.

HOST-ACTING ANTIVIRALS

Interferon was actually the first host-acting antiviral to be used clinically in the treatment of HCV. Interferons exert their antiviral effects via interaction with specific receptors on your cells, which then triggers a number of reactions aimed at clearing HCV. Interferons are not directly antiviral, since they do not bind to HCV or directly attack the replication of HCV. Instead, interferons activate a number of antiviral genes within your cells, which then inhibit various pathways necessary for viral

replication. A number of additional host targets beyond interferon have now been identified that can inhibit HCV or aid in its clearance.

Cyclophyllin Inhibitors

Cyclophyllin is a common cellular protein that plays an important role in facilitating the replication of HCV. Cyclophyllin interacts with both NS5B polymerase and NS5A protein to enhance viral replication. Inhibitors of cyclophyllin, such as alisporivir, SCY-635, and EP-Cyp546, block the cyclophyllin-mediated HCV replication. The most extensive clinical experience is with the cyclophyllin inhibitor, alisporivir[107, 108, 109].

Entry Blockers

A number of compounds have been developed that inhibit the uptake of HCV by liver cells (hepatocytes). Although clinical development is at an early stage, this strategy could be particularly useful at or near the time of transplantation to prevent the infection of the allograft (donor liver from an unrelated person).

Micro-RNA Inhibitors

Micro-RNA inhibitors, particularly miR-122, stabilize HCV replication. An anti-sense oligonucleotide inhibitor (an RNA that binds to other RNA) of miR-122, miravirsen, was given intravenously weekly for four weeks to patients with HCV genotype 1 infection. HCV RNA declined by nearly $2\log_{10}$ IU/mL. Additional studies are planned.

A number of other host factors have been targeted for their potential antiviral effects. These include the innate immune system and vaccination strategies to enhance immune mechanisms for the recognition and clearance of HCV.

VIRAL RESISTANCE

HCV replicates at a rate of approximately one trillion copies of virus each day. During this replication process, mistakes in the transcription of the genetic code of HCV are made, and some of these mistakes result in virus that is still capable of replication, but varies from the native or

"wild-type" HCV. Generally, these variants exist in all patients, and are only uncovered by the use of drugs that primarily inhibit replication of the wild-type virus. Inhibition of the wild-type virus allows the variants to emerge as a dominant species of HCV. In the laboratory, these variants are identified by sophisticated genetic sequencing. In the clinic, the emergence of resistant viral variants is detected by a rebound in HCV RNA during the course of antiviral treatment. A typical example of this would be a patient taking telaprevir/peginterferon/ribavirin, whose HCV RNA was negative at week four of treatment, and who experiences a positive HCV RNA at week eight of treatment. In another example, a patient experiences rapid decline in HCV RNA to 500 IU/mL by week four, but then has a rebound in HCV RNA to 2500 IU/ml at week eight. Both of these cases are examples of breakthrough due to the emergence of resistant viral variants.

> *I was feeling fine, with no serious side effects. During week four of treatment, I felt great, my blood tests were normal, and HCV RNA was no longer detectable—but at week eight, I received a call from my nurse to stop the medications because the virus had broken through: the HCV RNA, which was undetectable, was now 1500 IU/mL. By immediately stopping the drugs, the doctors were trying to reduce the chances that I would remain resistant to the telaprevir. In fact, over the last nine months, the viral variants of HCV that were resistant to telaprevir are no longer detectable. I have the same HCV in my blood now that I had prior to treatment.*
>
> — *Carol*

If resistance is recognized, and the protease inhibitor is discontinued, the HCV RNA reverts back to wild-type HCV RNA over the course of several months or even years (slower for HCV genotype 1a compared to 1b). The concern regarding viral resistance is resistance may dictate response to future courses of direct-acting antiviral treatment. Selection of viral variants resistant to the first-generation protease inhibitors may create new strains of HCV with broad resistance profiles. Sequential use

of monotherapy protocols would favor this phenomenon, while use of combination, multi-drug regimens would tend to prevent this.

Variants of HCV resistant to the administered protease inhibitor may emerge during triple therapy. Risk factors favoring the emergence of viral resistance include low plasma concentrations of the protease inhibitor, peginterferon (and possibly ribavirin), a lack of adherence to treatment regimen, and other factors that may compromise virologic response (such as advanced liver disease, HIV, or immunosuppression). If side effects, such as those mentioned above, cause a decreased adherence to a treatment regimen, the development of resistance could be substantial. Considerations in the development of drug resistant HCV variants include an inability to obtain complete viral suppression, drug metabolism and clearance, and poor adherence to a specified triple therapy regimen resulting in lower serum levels. Prolonged monotherapy with a direct-acting agent may also result in a progressive accumulation of mutations, given the virus's high replication rate and the poor fidelity of its change to replication.

As a patient undergoing treatment, you have a role to play in preventing viral resistance. Take the direct-acting antiviral drugs and any other administered antivirals, such as interferon or ribavirin, only as prescribed. Never alter dose or dosing frequency of direct-acting antivirals: if you are not tolerating these drugs, they must be discontinued, not dose-reduced. In addition, adhere to the recommendations of your care providers regarding the dosing of interferon and ribavirin.

CONCLUDING REMARKS

Many options for the treatment of HCV are emerging. These include new NS3/4A protease inhibitors, NS5B polymerase inhibitors, NS5A inhibitors, and host-acting antivirals. These drugs and emerging combinations may further improve treatment options and enhance the outcome for patients with chronic hepatitis C. New triple therapy regimens, interferon-free treatment, QUAD therapy, and other combinations are extremely potent and seemingly well tolerated. Within the next five

years, there may be treatment options that can eradicate HCV in nearly every patient.

In addition to the cited references, much of the data quoted in this chapter was extracted from abstracts and talks presented at the meeting of the European Association for the Study of the Liver in April, 2011, and the meeting of the American Association for the Study of Liver Diseases in November, 2011. These abstracts and most of the data can be found in:

1. Abstract Book from The International Liver Congress 2011. 46th annual meeting of the European Association for the Study of the Liver. *Journal of Hepatology* 2011; 54: Supplement 1.
2. Abstract Book from The Liver Meeting. 62nd Annual Meeting of the American Association for the Study of Liver Diseases. *Hepatology* 2011; October Issue.