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VOLUME 2 — ISSUE 12: TRANSCRIPT

Featured Cases: Hepatitis C and Host Genetics

Our guest author is Raymond T. Chung, MD, Associate Professor of Medicine and Director of Hepatology at Harvard Medical School and Vice Chief of Gastroenterology at Massachusetts General Hospital in Boston.

AAfter participating in this activity, the participant will demonstrate the ability to:

- Explain the potential for host genetic factors to cause inter-individual effects on the course of hepatitis C,
- Discuss potential uses of the *IL28B* genotype in clinical decision-making, and
- Describe the impact of *IL28B*-associated genetic variation on response to both interferon-based and interferon-free therapies.

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to hepatitis C and genetics in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 2, Issue 11 *eViralHepatitis Review* newsletter—Hepatitis C and Host Genetics.

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Faculty Disclosure
Dr. Chung has disclosed that he has received grants and/or research support from Merck, Roche/Genentech, Gilead, and Mass Biologic and he is also a consultant for Enanta Pharmaceuticals, Inc.

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- Clinicians do not effectively identify their patients at risk for, or infected with, HBV
- Clinicians lack the ability to interpret positive HBV screening
- Clinicians do not adequately counsel their patients regarding their HBV status (for treatment or vaccination)
- Clinicians do not properly treat, monitor, or refer their HBV patients, and moreover, they lack awareness of current treatments and emerging research

INTENDED AUDIENCE

This activity has been developed for hepatologists, primary care physicians, infectious disease specialists, nurses, nurse practitioners, and others involved in the care of patients with viral hepatitis.

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HARDWARE & SOFTWARE REQUIREMENTS

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MR. BOB BUSKER: Welcome to this *eViralHepatitis Review* Podcast.

eViralHepatitis Review is presented by The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing. This program is supported by educational grants from Gilead Sciences and Vertex Pharmaceuticals.

Today's program is a companion piece to our eViralHepatitis Review newsletter issue: Hepatitis C and Host Genetics.

Our guest is one of that issue's authors and an eViralHepatitis Review program director, Dr. Raymond Chung from Harvard Medical School.

This activity has been developed for hepatologists, infectious disease specialists, primary care physicians, nurses, and nurse practitioners. There are no fees or prerequisites for this activity.

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Learning objectives are, that after participating in this activity, participants will demonstrate the ability to:

- Explain the potential for host genetic factors to cause inter-individual effects on the course of hepatitis C;
- Discuss the potential uses of the IL28B genotype in clinical decision-making; and
- Describe the impact of IL28B-associated genetic variation on response to both interferon-based and interferon-free therapies.

I'm Bob Busker, managing editor of eViralHepatitis Review. On the line we have with us Dr. Raymond Chung, associate professor of medicine and director of hepatology at Harvard Medical School and Vice-Chief of Gastroenterology at Massachusetts General Hospital.

Dr. Chung has disclosed that he has received grants and/or research support from Merck, Roche/Genentech, Gilead, and Mass Biologic and that he is also a consultant for Enanta Pharmaceuticals, Inc.

He has indicated that his presentation today will not reference the unlabeled or unapproved uses of any drugs or products.

Dr. Chung, welcome to this eViralHepatitis Review Podcast.

DR. RAYMOND CHUNG: Happy to be here.

MR. BUSKER: IIn your newsletter issue, you reviewed recent investigations into how host genetics can influence therapeutic response and treatment decisions in patients with hepatitis C. What I'd like to do today is discuss how that new data might be applied in clinical practice. So if you would, Dr. Chung, start us out with a patient description.

DR. CHUNG: Surely. A 35-year-old Caucasian man was recently discovered to be antibody to HCV positive. His HCV RNA was 1.5 million/IU/ml, and he had genotype 1A infection. His ALT was 98. The HBV and HIV markers were negative. He had stopped using intravenous drugs with frequent needle-sharing at the age of 29. He now leads a healthy lifestyle, except that he used to drink alcohol, one to two cans of beer per day, until the diagnosis. He was shocked by the diagnosis and wants to discuss treatment options. He is keenly interested in eliminating the virus and is particularly interested in his chances to clear the virus with current therapy. He obtained an *IL28B* genotype, which demonstrated a CT genotype using the RS12979860 SNP.

MR. BUSKER: The pertinent characteristics in the history of this patient — talk to us about those if you would.

DR. CHUNG: This is a rather common scenario in clinical practice: a person who had harbored a significant period of risk factors, in this case injection drug use with needle-sharing, for some time and has now terminated that practice. Some years later, he is now faced with the discovery of having hepatitis C, and in all likelihood having transmitted during that risk period, but confesses great surprise in that diagnosis.

He has features characteristic for chronic hepatitis C. He has genotype 1A, easily the most common genotype in this country, and subtype for that matter in this country. He also has a high viral load, which is a tendency that one sees with genotype 1 infection. He also has elevated liver enzymes in the form of an elevated ALT, which is consistent with a largely active hepatitis, likely with necroinflammatory activity if one were to perform a liver biopsy.

The presence of high-risk factors, risk behavior in the past with cessation of behavior now, elevated viral load with genotype 1 hepatitis C, and importantly, the presence of a great deal of motivation to eliminate the infection, appear to be the most germane features of this case.

MR. BUSKER: Let's assume that a decision to treat has been made for this patient. What would the current standard of treatment be?

DR. CHUNG: Since May 2011 we have had two FDA-approved regimens for treating genotype 1 HCV in previously untreated patients: and that would include peginterferon and ribavirin given in a weekly injection regimen for the peginterferon, and ribavirin dosed by weight. The protease inhibitor in this case, either telaprevir or boceprevir, are both given as three-times-daily regimens for differing durations. In the case of telaprevir, this would be a 12-week regimen given simultaneously with peginterferon and ribavirin from the outset and the subsequent duration of therapy, either another 12 weeks of peginterferon and ribavirin, or another 36 weeks of peginterferon and ribavirin would be dictated by the response of the patient in the first 12 weeks. Persons with rapid responses or what we call extended rapid virologic responses who are virus-negative at weeks 4 and week 12 would be eligible to truncate the total duration of therapy to 24 weeks.

In the case of boceprevir, this would be a similar regimen with response-guided characteristics. In this case, though, the peginterferon and ribavirin four-week lead-in would be followed by treatment with boceprevir for the ensuing 24 weeks. Patients in the event of a rapid response, that is to say negativity at early time points in the course of that treatment would allow and make that patient eligible for premature truncation of therapy at 28 weeks of treatment. Alternatively, patients who did not have an extended rapid virologic response would then be asked to go to a total duration of 48 weeks with triple therapy, peg, ribavirin, and boceprevir. So slightly different schedules of treatment, but both indicated for genotype 1, treatment-naïve hepatitis C infection.

MR. BUSKER: Now you say that both regimens are indicated for genotype 1. Does that mean that those therapies would not be recommended for all patients with HCV?

DR. CHUNG: That is correct. The current label for peginterferon and ribavirin and either of the two protease inhibitors is for genotype 1 infection. The substantial trials in other genotypes have not been conducted to justify the practice of using these treatments in those patients.

MR. BUSKER: What factors in this patient might predict therapeutic outcome?

DR. CHUNG: Several factors could be associated with therapeutic outcome. When we think about pretreatment factors, it's worth considering several demographic features. For instance, the ethnic group of this patient is Caucasian. The data, collectively speaking, have supported the idea that Caucasian race is associated with better overall response rates compared to black race.

A classic study that directly compared peg and ribavirin head to head between Caucasians and African Americans was the VIRAHEP-C trial, and this trial, published in *Gastroenterology* a number of years ago, demonstrated that Caucasians experienced roughly double the sustained virologic response rate compared to African-Americans with genotype 1 infection.

Another important determinant of outcome within genotype 1 is viral load. Persons who have higher viral loads, which in some measures, depending on the study cited, usually hover around in excess of 600,000 IU/ml, have shown that these patients have lower likelihood of response compared to their counterparts with low viral loads under 600,000 IU/ml.

The presence of advanced fibrosis, specifically cirrhosis, on a liver biopsy in these patients has also been associated with diminished overall response rates. We do not know that status in this patient, but the finding of cirrhosis would be associated

with diminished response rates, not only for peginterferon and ribavirin, but has also been demonstrated for therapy with peginterferon and ribavirin and either telaprevir or boceprevir.

Genotype subtype, 1A versus 1B, has also been associated with subtle distinctions in outcomes. For instance, for patients enrolled in the registrational trials of peginterferon, ribavirin, and boceprevir, SPRINT-2, subtype 1B was more likely to clear than was subtype 1A. SPRINT-2 had an odds ratio of 2; that is, there was double the likelihood of these patients clearing with subtype 1B compared to subtype 1A.

And of course, host genetics are relevant. Certainly the *IL28B* genotype was relevant in the era of peginterferon and ribavirin, and it remains relevant despite the improved overall outcome conferred by adding a protease inhibitor. Comparing the favorable IL28B genotypes, namely CC, to the less favorable, TT and CT, we found that there was still, even in the era of triple therapy, an improved overall outcome of responsiveness in patients with CC compared to those without CC, with odds ratios ranging between 2.1 and 2.6 for the comparison with CT and TT.

So in this case, our patient being CT, he would be on track for a more diminished response rate compared to a patient with CC. The patient also has 1A infection, so he has less favorable character-istics, at least from the vantage point of viral characteristics, having a high viral load, genotype 1A, and a less favorable *IL28B*.

Things moving in his favor would be his Caucasian race. We do not know about his cirrhosis status at this point in time.

MR. BUSKER: This is a patient who is motivated to begin therapy — what would you tell him?

DR. CHUNG: I think that is a terrific question. It really gets at the whole issue of weighing not only positive predictors versus negative predictors, but I think we can do our best to try to prognosticate by weighing these pretreatment factors. I think the tie-breaker in the particular instance of this patient would be, assuming we don't have histologic information, that patient's motivation to be treated; and I think what we have learned from this case based on his sentiment is that he is very aggressive about trying to eliminate this infection.

If we had our druthers, I think a liver biopsy would be of additional help in decision-making, helping us drive us toward either a movement to treat in the case of more advanced fibrosis, and potentially a movement away from treating, should he have a more limited fibrosis. However, that has to be kept in context with his willingness to be treated. In other words, if he maintains that he wants to be treated irrespective of what that biopsy shows, then a biopsy really will be of little utility in this setting. This is a decision that has to be made in concert with the patient and the patient's own sentiment.

Other factors that should be brought into focus include the time horizon for investigational agents, which appears to be getting more and more compressed. We are anticipating the arrival and ultimately approval of several investigational agents that might be able to spare the use of interferon in the future. Most patients, if they had their choice, would prefer to be on an interferon-sparing regimen given the unfavorable side-effect profile that we find associated with interferon.

So in that context, it may be worth our knowing whether there is an urgency to be treated from a histologic vantage point; that is, is this patient's natural history sufficiently advanced that it's best that we move on and get on with things now, as opposed to deferring therapy to such time that we might find an approval of an interferon-sparing, all oral, direct-acting antiviral regimen that might be here as early as late 2013 or early 2014? That decision could be predicated on the histologic information that might be obtained in this setting.

The other point is that trials of these investigational agents are ongoing, so that third option might be available to him if he had access to a center testing those combinations. If he decided to pursue that track, we might decide not to pursue peginterferon and ribavirin and telaprevir and boceprevir treatment.

One final comment I would make to him would be no matter what decision is made among the choices I've just outlined, that he should pursue, of course, strategies to reduce harm to his liver. And, of course, the one to two drinks of alcohol per day that he has in fact been practicing to this point is something that we will want to absolutely eliminate from the background, no matter what decision is made about treatment.

MR. BUSKER: Thank you for that presentation and discussion, Dr. Chung. Let me ask you to bring us another patient now, if you would, please.

DR. CHUNG: The next patient is a 55-year-old Caucasian male patient with chronic hepatitis genotype 1B infection visits you in the office. Two years ago he had a null response to peginterferon and ribavirin. He is worried about the risk of developing liver cancer and a pretreatment liver biopsy at that time demonstrated moderate fibrosis, METAVIR F2.

His ALT and AST are double the upper limit of normal. His *IL28B* genotype has now been tested and was returned as a CC. He has heard about the novel drugs that are being studied for hepatitis C and wonders whether he might be a potential candidate to be treated with a regimen other than repeating the previous one or taking peginterferon and ribavirin and telaprevir and boceprevir.

MR. BUSKER: You say the patient mentions "novel" drugs. Translate that for us. What's he referring to?

DR. CHUNG: Several novel drugs of several classes are in clinical testing as we speak. Indeed, this is a renaissance period for the testing of so-called direct-acting antivirals for hepatitis C.

When we think about classes of therapy, telaprevir and boceprevir are the first versions of what we consider HCV protease inhibitors, which block an important step in the viral life cycle that is responsible for faithful proteolytic cleavage of the viral protein that enables the viral life cycle to be completed in an orderly manner.

There are two other major classes, polymerase inhibitors that work against the RNA-dependent RNA polymerase, which catalyzes the copying of the RNA genomic strand of the virus into replicative intermediate RNA, which in turn is copied back into new genomic RNA that then gets packaged into new virus particles. This is a key enzyme responsible for replicating the viral genetic material and has no counterpart in the host cell. Therefore, and an attractive target, two classes of therapy directed against the polymerase inhibitors, which include both nucleoside analogs or nucleotide analogs, along with the non-nucleoside polymerase inhibitors, both of which work at different sites within the polymerase to induce inhibition of viral replication.

The fourth class of therapy is the so-called NS5A class of inhibitors. The NS5A protein is an important protein responsible for multiple steps in the viral lifecycle, including formation of the replication complex, as well as assembly of the virus. It is not an enzymatic target, but nonetheless small molecules have been developed to this protein that are very effective and potent at bringing down viral load.

So if you might imagine combining these agents, each of which produces, works at a different target, and each of which when given alone can select for resistance of the virus to the agent because of the selection pressure being applied at that particular target to mutate around that site and leads to the emergence of a resistance variant.

The advantage of combining multiple classes of so-called direct- acting antivirals then allows us to maximize potency for suppressing viral load, but at the same time minimize the emergence of resistant variants because these agents work through complementary, non-overlapping mechanisms of action.

This is the key to providing sustained suppression of virus to the point where a true extinction of viral infection can be entertained. This concept has been and is being tested in a variety of trials looking at combinations of agents potentially from each of these different classes of treatment, and potentially in conjunction with ribavirin and/or interferon.

We're seeing an enormous number of these trials being conducted and very promising data which have been presented at national or international meetings, demonstrating very high rates of sustained virologic response are possible with these regimens in genotype 1 in either treatment-naïve or treatment-experienced contexts.

There is a great deal of excitement about these trials, and this is to which the patient is referring to you in the office.

MR. BUSKER: The *IL28B* test — was that necessary for this patient?

DR. CHUNG: That is a terrific question, because he has always demonstrated to you phenotypically that he is a null responder. He had a less than 2 log response presumptively and a less than 2 log response

by week 12 of therapy with a prior course of peginterferon and ribavirin. In many ways the phenotype ultimately trumps genotype. Occasionally there will be a discordance between the *IL28B* genotype and the actual observed treatment response. Ultimately it's the actual observed treatment response that dictates a subsequent outcome with the strongest predictive value, so his being a null responder is really the more important historical feature than his being *IL28B* CC.

He has shown through the integration of perhaps not just host genetic factors, but also through other factors that may be influencing his ultimate response, that those other mitigating factors appear to be important here and have ultimately led to an unsuccessful treatment response history.

MR. BUSKER: This patient tested as CC. Did you find that surprising?

DR. CHUNG: It is somewhat surprising for the reasons I outlined earlier, that CC is associated with excellent outcomes and excellent response to virus. But again, given that sometimes other extenuating and mitigating factors go into the phenotypic response of a null response in many ways, trumps the predication that the genotype provides.

MR. BUSKER: Key question, doctor: what do you tell this patient? Do you treat now or do you wait?

DR. CHUNG: When we look at the overall response rates of patients with a prior null response history, it is worth knowing that those patients do not fare as well with subsequent treatment with peginterferon and ribavirin and a protease inhibitor. They generally respond with about a 30% to 40% response rate when subsequently retreated with a triple-therapy regimen.

Moreover, if a biopsy showed cirrhosis, the response rate for a null response cirrhotic drops down to about 15%. So we're now talking about diminishing returns in a patient with a prior null response and advanced histology. So it is worth broaching the discussion of what the histology demonstrates, and of course, in his case, demonstrated moderate fibrosis of approximately two years back.

I would say that his response will be somewhere in the neighborhood of 30% to 40% percent, and we need to weigh that likelihood of response against the impending arrival and approval of other agents that are likely to produce even higher response rates.

Given his motivation and his aversion to developing liver cancer, I suspect this is a motivated patient who will want to give triple therapy a real chance up front.

MR. BUSKER: And we'll return with Dr. Raymond Chung from Harvard Medical School in just a moment.

MS. JULIE MCARTHUR: Hello. I'm Julie McArthur, Adult Nurse Practitioner in the Division of Infectious Diseases at Johns Hopkins University. I'm one of the Program Directors of *eViralHepatitis Review*.

eViralHepatitis Review is a combination newsletter and podcast program delivered via e-mail to subscribers. Newsletters are published every other month. Each issue reviews the current literature in areas of importance to hepatologists, infectious disease specialists, primary care physicians, nurse, nurse practitioners and other clinicians caring for patients with viral hepatitis

Bi-monthly podcasts are also available as downloadable transcripts, providing case-based scenarios to help bring that new clinical information into practice in the exam room and at the bedside.

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MR. BUSKER: Welcome back to this eViralHepatitis Review podcast. I'm Bob Busker, managing editor of the program. Our guest is Dr. Raymond Chung, associate professor of medicine and director of hepatology at Harvard Medical School. And our topic is Hepatitis C and Host Genetics.

We've been looking at how some of the new information Dr. Chung reviewed in his newsletter issue can be applied in clinical practice. So if you would, Doctor, please bring us another patient.

DR. CHUNG: This is a 49-year-old African-American female with chronic hepatitis C who comes in with a new diagnosis of genotype 1B. She is currently not depressed and has no history of mood disorders or suicidal ideations. A liver biopsy demonstrates a bridging fibrosis.

She would like to avoid interferon if at all possible but is willing to discuss the options.

MR. BUSKER: *ILB28B* testing — does that have a role here?

DR. CHUNG: It could very well have a role here, but it's worth saying a few things about this scenario. African-Americans in general have a much lower frequency than do Caucasians of the favorable *IL28B* allele, namely the C allele. The gene frequency of the C allele in general in African-Americans is somewhere in the neighborhood of about 40% or so. To have the CC allele, we would imagine that that frequency would be somewhere in the neighborhood of about 15% to 20%, which is about half the frequency of the CC allele in Caucasians.

Indeed, it has been demonstrated that the *IL28B* genotype and the frequency of the favorable allele in African-Americans explain probably half of the observed difference in outcome between African-Americans and Caucasians generally when it comes to response to peginterferon and ribavirin.

In all likelihood, her *IL28B*, based on her ethnicity, is likely to be unfavorable. But that being said, given the fact that she is treatment-naïve and we don't know that she does not have unfavorable characteristics, it's worth thinking about an *IL28B* in helping nudge her decision-making in one direction or the other.

However, I would finally comment here that so much of this is predicated on the patient's true aversion to interferon. If this is a nonstarter, she is completely unwilling to pursue interferon at all costs, then an *IL28B* will not influence at least this initial treatment decision, because with a categorical rejection, the decision has been really essentially made for us.

But bridging fibrosis would be an important factor that would drive me to at least give her triple therapy serious consideration. In my view, the *IL28B* would be helpful in making a decision about treating with a general sense that I would like to recommend a treatment given the more advanced nature of her liver disease.

MR. BUSKER: Explain a bit more, if you would, about the relationship between the *IL28B* genotype and the ethnic and racial differences that have been found to impact treatment effectiveness.

DR. CHUNG: As I alluded to in the previous question, the *IL28B* genotype, the allele frequency of the favorable allele, is different between ethnic groups. Asians tend to have the highest frequency of the favorable allele at about 90%, Caucasians have a frequency of the favorable allele in the neighborhood of 60% to 70%, and African Americans or Africans tend to have a frequency of the favorable allele more in the neighborhood of about 30% to 40%.

When you look at the homozygocity for the CC allele, squaring each of those gives you an estimate of the frequency of the actual CC genotype in those populations. We find a predicted frequency of somewhere in the neighborhood of about 40% for Caucasians and somewhere in the neighborhood of about 15% to 20% for African Americans.

We would look at that spread as being responsible for perhaps half of the observed differences in overall SVR rates between African Americans and Caucasians in the original peginterferon and ribavirin trials.

Of course, as I suggested, as we move into the triple therapy era or have moved into the triple therapy era for genotype 1 patients, the importance of *IL28B* genotype has diminished somewhat because, if you will, the addition of the telaprevir and boceprevir has raised all boats somewhat including those persons with the unfavorable *IL28B* genotype.

So the stark difference we observe in the old peg/ribavirin data is blunted because of the improved outcomes for all patients with the addition of a protease inhibitor. We still see a contribution of *IL28B* genotype in the triple therapy population, but it's somewhat watered down.

MR. BUSKER: So with this patient — would you treat now or would you wait?

DR. CHUNG: The patient is keen on holding off on therapy with interferon. The *IL28B* testing and her ethnic group suggest she is unlikely to have a

favorable *IL28B* genotype. If those end up being true, the only factor I think pushing you to treatment is the bridging fibrosis.

Given the rapid pace of development and the expected timeline of introducing all oral, direct-acting antiviral therapies, it is worth saying that deferring therapy is likely to be justifiable in a person who has not yet approached full-blown cirrhosis.

I would recommend, at least in this case, that we are probably not doing her a service by waiting the year to year and a half for the ultimate approval of the all oral direct-acting antiviral regimens that would be potentially suitable for her. That is a time horizon in which deferral is potentially justifiable.

MR. BUSKER: Thank you, Dr. Chung, for those interesting cases you've shared with us today. I'd like to do now is review today's discussion in light of our learning objectives. So to begin, the potential for host genetic factors to cause inter-individual effects on the course of hepatitis C.

DR. CHUNG: One of the important features of host genetics is the influence of host genetics on treatment response, but there also appears to be evidence that host genetics influence the ultimate course of infection itself.

That's true at the inception of infection in which studies of patients contracting acute hepatitis C with either spontaneous clearance or movement into a chronic phase were, in fact, influenced by the *IL28B* status of those patients.1 Parallel studies demonstrated that possession of the favorable *IL28B* genotype was associated with a higher frequency of spontaneous clearance with an odds ratio > 2.

I should also note that there are potential implications for *IL28B* status with the overall natural history of untreated hepatitis C generally. Some studies have suggested that there may be an altered course in these patients, although this is far from definitive, and further study will be required to determine whether the natural history of untreated infection is influenced by *IL28B* status.

MR. BUSKER: And the potential uses of the *IL28B* genotype in clinical decision-making?

DR. CHUNG: As we improve therapy — and we have now advanced into the triple therapy era — and are now looking at even more improved treatments soon to follow, you will find that *IL28B* testing will assume diminishing importance in the overall decision to treat. Because as we improve our overall ground-floor sustained response rate, the decision to treat becomes a lower and lower threshold decision. Coupled with improvements in tolerability of these agents and the movement away from interferon, the threshold for treating anyone with chronic hepatitis C lowers.

We are effectively seeing hepatitis C being converted from a liver disease, in which we stage patients and we stratify our approach based on those stages, to one where we are treating hepatitis C more or less as an infection, where anyone with infection can potentially be a candidate for treatment with a well-tolerated, high-potency regimen.

Today *IL28B* can be useful in treating our patients with genotype 1 with peginterferon, ribavirin and telaprevir, perhaps as something of a tie-breaker as we make decisions. In patients with favorable genotypes, we might be more inclined to pursue treatment for somebody who might have been sitting on the fence, as it can justify and will be associated with a higher likelihood of truncating a course of peginterferon, ribavirin and telaprevir or boceprevir-based therapy. In some instances — and this has been studied in some smaller, strategy-based studies — potentially in those *IL28B*-favorable patients it might even justify the exclusion of a protease inhibitor from regimen, as these patients would be viewed as rapid interferon responders who will do well no matter what regimen is offered to them.

That strategy has to be supported by additional evidence, but it is intriguing to consider that *IL28B* status might be used to potentially strip down the course of therapy in somebody with a favorable determination.

In persons with unfavorable *IL28B*, that might be perhaps the tie-breaker in helping make a decision to defer therapy for a given patient. We came across that in one of our cases, and we believe that the rapid evolution of treatment options in the near future will allow us the luxury in many ways of deciding that deferral of therapy may be completely defensible under circumstances where an unfavorable *IL28B* status is present.

MR. BUSKER: And finally: *IL28B*-associated variation on the response to both interferon based and interferon free therapies.

DR. CHUNG: The original finding in interferon and ribavirin was that the utility of *IL28B* is highest in that context. As we've moved into triple therapy where the bar has been raised for all comers, the distinction made by *IL28B* testing for outcome has diminished. There has been a catch-up of the less favorable *IL28Bs* in overall response rate because of the added benefit of the direct-acting overall agent, in this case the protease inhibitor.

As we move into interferon-free therapies where ground-floor response rates may exceed 90%, it is likely that the utility of *IL28B* testing will be diminished even further. I think it would be a reasonable presumption that the day of *IL28B* being of no utility is rapidly moving towards us, insofar as a treatment regimen that is capable of producing across-the-board excellent response rates may, in fact, obviate the use of these tools that previously were able to differentiate subsequent responsiveness.

A more total response rate, nearing 90% to 100%, clearly puts everybody in a good response category and no longer allows us to determine less responsive groups of patients. The finding of 90% to 100% response rates applies principally to naïve patients of non-cirrhotic nature. Obviously, we will find some pockets of patients for whom those response rates will not necessarily apply.

So whether the *IL28B* applies to those patients who are somewhat less responsive remains to be seen, but I think with the continued ascent of performance of our direct-acting antiretroviral regimens in general, the utility of tests such as *IL28B* can only be viewed as diminishing.

MR. BUSKER: Dr. Raymond Chung from Harvard Medical School, thank you for participating in this eViralHepatitis Review Podcast.

DR. CHUNG: My pleasure, Bob.

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Thank you for listening.

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