Post: Thank you, Tony. Thanks for the introduction. So, I’m going to talk about some of the AASLD abstracts on Hepatitis B; there are quite a few abstracts.
And, I’ve kind of narrowed it down to four that I think are particularly important and two of them refer to a single topic that I think is crucially important, both to primary care doctors, oncologists and hepatologists. And, that involves the diagnosis and management of Hepatitis B reactivation in patients receiving chemotherapy. We have two abstracts I would like to talk about today involving that subject. Quantitative Hepatitis B surface antigen titers are now available, what role they play in management of Hepatitis B patients is not clear, and I’m going to present some data about how these can be used to manage our patients and why they’re worthwhile to get this fairly inexpensive test. And then, of course we’re all concerned about patients with Hepatitis B who have severe fibrosis and are likely to go on to need a liver transplant or develop liver cancer and does any of our new treatments available, does it affect outcome? Can we really do anything about our patients with severe liver disease and Hepatitis B.
So, the first paper I’d like to discuss is Reactivation of Hepatitis B infection among Patients with Liver Cancer. It comes from the MD Anderson Cancer Center in Houston, Texas. The goal was to describe the prevalence and predictors of Hepatitis B screening and reactivation in a comprehensive cancer center; this is probably the largest comprehensive cancer center in the country.
This was a retrospective cohort of patients from January 2004 to September of 2007. They screened patients with simple tests; they looked both at surface antigens and anti Hepatitis B core antibody in total, and reactivation in the study was defined as an ALT greater than 100 and/or a bilirubin greater than 2.5 developed while on therapy, or a positive DNA in patients previously undetectable for Hepatitis B, or a DNA that was low prior to therapy then went over 100,000 copies while on therapy.
They treated a huge number of patients at the MD Anderson with chemotherapy, over 10,000 patients during this period of time, yet only 17% of them were screened for Hepatitis B. And, of that number, 151 or 8% of the ones screened were Hepatitis Bsurface antigen positive and/or hepatitis core antibody positive. Thirty four of those patients, or a quarter of them went on to develop decompensation of their liver disease. So, patients who got chemotherapy or were surface antigen or core antibody positive, fully a quarter of them, or almost a quarter of them went onto develop decompensation. Those who received prophylactic antivirals, only 9 of these patients, and those who received antivirals only after chemotherapy only represented 11. So, only 20 of the 34 patients received any therapy once they developed decompensation.
What happened to those patients. Well, those patients who got the prophylaxis, only 22% of them died, but they were all cancer patients and we can expect a fairly high mortality. However, in the patients only that got treatment after they developed decompensation, 72% of these patients died, and we can presume that a significant percentage of this is because of recurring Hepatitis B that went on to kill these patients.
So, the authors concluded that reactivation occurred in about 25% of patients with Hepatitis B, and it really had severe consequences in terms of mortality, and that very few patients were screened unfortunately. Only 17% of the patients at the MD Anderson Center were screened.
Well, I want to turn to a cancer center on the other side of the country in New York City in Sloan Kettering, who presented this data of Entecavir is helpful in preventing Hepatitis B reactivation in cancer patients receiving chemotherapy. So, the aim of their study was to report on the efficacy of using Entecavir, one of the new antiviral agents that’s effective against Hepatitis B in preventing reactivation in patients undergoing chemotherapy. So, they’re going to try and prevent these patients from developing severe consequences from their Hepatitis B.
So, this was a prospective study of all patients who were begun on chemotherapy at the Sloan Kettering Memorial Hospital in New York between January 2009 and April 2011 and were screened for Hepatitis B. So, they didn’t really look at the percentage who were screened they just looked at the patients who were screened. So, we could presume that they probably had a similar amount of screening as they had at MD Anderson, which would be less than 20%. But, having said that, this is where the patients who were screened for Hepatitis B. They included patients who were Hepatitis B surface antigen with normal transaminases. If they had abnormal transaminases, I believe they were always treated with Entecavir. So, these patients were in the study or they were looked into other types of therapy if they had normal transaminases. But, these were patients who were just discovered to have surface antigen who wouldn’t have been discovered if we were just screening for transaminases. All patients who were surface antigen positive were treated with Entecavir, the standard dose of 0.5 milligrams PO a day at the start of chemotherapy and was stopped six months after chemotherapy. Important that the prophylaxis has to be continued for six months after the chemotherapy because it’s the reactivation of the Hepatitis B and then the immune response, the immune reconstitution that leads to the severe illness. So, this has to be continued for six months after the patient has already discontinued their chemotherapy. Patients were followed with three month ALT levels and Hepatitis B viral DNA’s.
Results

- 33 patients were HBsAg (+)
- DNA was >1000 IU/ml in 12/33 (36%)
- Only one case of reactivation occurred.
- Reactivation was in a patient who stopped entecavir and became negative again when started on tenofovir.

So, of this group, 33 patients were found to be Hepatitis B surface antigen positive, the DNA was over 1000 in 12 of 33, so most of them had inactive disease, which is important because even patients with inactive disease can get severe recurrence afterwards. Only one case of reactivation occurred, so this is in patients that were given prophylaxis, only one of the patients developed reactivation. And in fact, that patient who developed reactivation stopped his Entecavir on his own and then became negative again when he was started on tenofovir after the virus turned positive.
So, these authors conclusion from this paper was that Entecavir was highly effective in preventing reactivation of Hepatitis B in patients undergoing chemotherapy.
My Comments

- All patients undergoing chemotherapy should be screened for Hepatitis B.
- Entecavir is an effective way of preventing potentially lethal reactivation in those found to be surface antigen positive.
- We need to make our oncology colleagues aware of this important information.

So, what conclusions can we make from these two important papers that were presented at the ASLD meeting? Well, first of all, all patients undergoing chemotherapy I think should be screened for Hepatitis B. It’s very simple to do, it’s an inexpensive test and has you know absolutely incredible consequences to these patients if they develop reactivation. I think from the Sloan Kettering paper Entecavir is shown to be effective in preventing this potentially lethal reactivation in those found to be surface antigen positive. So, certainly all patients undergoing chemotherapy shown to be surface antigen positive should be treated with a nucleoside nucleotide analog to suppress from coming back. I’m not sure Entecavir is the only drug that can be used, but certainly it was effective in the Sloan Kettering study. I think we really need to make our oncology colleagues aware of this important information. Even at the MD Anderson Center, only 17% of patients were screened for Hepatitis B. Again, simple to do, inexpensive, and potentially lethal consequences to these patients who are not screened.
Okay, so let’s turn to a different subject now, and that’s the use of Quantitative Hepatitis B Surface Antigen levels are significant independent predictors of Hepatitis B viral DNA and surface antigen clearance in Hepatitis B carriers, quantitative carriers. So, quantitative Hepatitis B surface antigen levels are now available and readily available for testing. You can send them off. And what role they play in defining the natural history of Hepatitis B is really unclear and how we can kind of use this new test is in need of some validating studies.
So, the aim of this study from Taiwan was to look at the association of quantitative Hepatitis B surface antigen levels and spontaneous loss of HBeAg, HBV DNA and HBsAg in untreated patients. So, these patients were not given any therapy, they were just followed prospectively over time and they looked at E antigen DNA and surface antigen.
So, in this Chinese cohort, 3466 patients with Hepatitis B surface antigen without cirrhosis were followed. I think that they felt that the patients who had cirrhosis would need to be treated and so they were excluded from this follow up study. All patients had quantitative Hepatitis B surface antigen levels measured at their baseline.
Hepatitis B surface antigen levels did predict clearance of HBsAg and DNA but not HBeAg clearance.

- With HBsAg > 10,000 IU Clearance 3.2%
- With HBsAg < 10 IU Clearance 85%
So, the authors concluded that Hepatitis B surface antigen levels can play a role in predicting clearance of Hepatitis B viral DNA and surface antigen.
I think that’s a realistic conclusion. Hepatitis B surface antigen levels may be a good way to predict who will eventually clear the virus and probably do not need to be treated with nucleoside or nucleotide analogues. So, if we see a patient who comes to see us who has low surface antigen levels we probably can just follow those patients and just watch and see what happens over the next year or two. If they have very high levels we probably need to consider putting them on nucleoside or nucleotide analogues depending on the severity of their liver disease of course.
The last paper I’d like to talk about comes from the European Hepatitis Network and was abstract number 240 and was titled, “Virologic response to entecavir is associated with a lower probability of disease progression.” So, its background was patients with severe fibrosis and active Hepatitis B can have their Hepatitis B suppressed with multiple drugs nowadays. Whether this suppression is associated with improved outcomes is still somewhat unclear, so you know we can suppress the Hepatitis B, but is that going to make a difference for our patients in the long run?
Aim

- Investigate the effects of entecavir on Event Free Survival in Chronic Hepatitis B infected patients

So, the aim of this European Center study was to investigate the effects of Entecavir on event free survival in patients who were infected with Hepatitis B.
So, they looked at a very broad population of ten European centers who provided data, they were looking at one drug in particular, that’s Entecavir. And, they looked at a complete viral response which was making the Hepatitis B viral DNA essentially undetectable, less than 80 international units per mil, and their clinical end points were development of decompensation, or development of hepatocellular carcinoma, or death.
The results: they had 377 patients at these trans European centers, 133 of them had advanced liver disease, so the majority of them did not have advanced liver disease, and fully ten of them, or 8% had decompensated liver disease at their baseline when they were started on their medication.
Results (cont.)

- 6 developed decompensation
- 4 Hepatocellular Carcinoma
- 8 patients died
- Mean follow up of 19 months
- Patients with complete virologic response had a hazard ratio of 0.2 (0.06-0.67) of developing an event.

What happened to these 377 patients? Well, the ones who weren’t decompensated obviously, six of them went onto develop decompensation, four developed hepatocellular carcinoma, and eight patients went on to die of liver failure. The mean follow up was 19 months in this fairly short study that will be ongoing. So, what they concluded was that patients with complete virologic response had a hazard ratio of only 0.2 of developing one of the events that they were looking at, decompensation, hepatocellular carcinoma, or dying. So, markedly increased rate of progression to one of the end stage events in those patients who responded to the entecavir.
So, the authors concluded that patients with, who show progression to Hepatitis B, I’m sorry, in patients who showed suppression of Hepatitis B on entecavir improved the probability of event free survival.
So, I think it makes a lot of sense to suppress Hepatitis B in these patients. It’s fairly easy to do, it’s fairly cost effective, although these new medications, the ones with low resistance profiles are fairly expensive, but I think it does make sense to suppress it in these patients to prevent progression of disease. Though, on the other hand in this study, it’s not clear that those who did not fully suppress were sicker to begin with and that’s why they had poorer survivals. So, I’m not sure we can completely conclude based on this paper that survivals are improved by suppression, but I think it’s reasonable to think that that’s true. I’m not sure that these weren’t two different patient populations.
So, to summarize the papers I presented this morning, despite the fact that Hepatitis B reactivation is a serious problem in patients undergoing therapy, few patients are screened for Hepatitis B. Reactivation of Hepatitis B can be easily prevented if discovered prior to the institution of chemotherapy and starting one of these patients on a neucloside/neuclotide inhibitor.
Hepatitis B surface antigen is useful in predicting spontaneous clearance of chronic HBV and I think should be used in these patients. Especially if a patient we want to follow with treating them would want to know what their surface antigen quantitative level is to know what their chances are of spontaneously sero converting. And, response to Entecavir can predict favorable outcome in patients with HBV and severe fibrosis. And, I think certainly all of our patients with severe fibrosis and cirrhosis should have suppression of their Hepatitis B done with one of the nucleoside or nucleotide analogues. That’s all I have to say, thank you. (applause)
Gholam: Thanks, Don. Good morning and I would like to join Bill in thanking everyone for coming this morning. It’s great to see a larger audience and a broader spectrum of specialties and interests. I’ve deliberately chosen to talk about abstracts and advances in liver disease that reflect themselves on our practices, on our everyday practices as opposed to going into the more super specialized areas of Hepatitis C treatment. I will say that based on the AASLD statistics, about a third of the meeting was pretty much related to Hepatitis C. That would translate into about 2,000 abstracts and presentations.
So, there’s no way I can realistically give you the full picture, but basically just a little bit in terms of background about 4 million Americans are believed to be infected with Hepatitis C. It is estimated that by 2030 about 85 million, uh 85 billion dollars will be spent in health care expenses on Hepatitis C by then it will be probably one of the top five most spent on conditions in the United States. We know that the percentage of patients with chronic Hepatitis C progress to cirrhosis. And, once you get cirrhosis, the annual risk of developing cancer is about three to five percent. This is by far the most common cause for transplantation in the United States, and as far as I know the only viral infection that can be cured with medication.
In order to understand this better, I think you have to look at the natural history of hepatitis C, and for those who are not very familiar, I think it's important to remember that even though Hepatitis C is typically, typically progresses to a chronic state, about 25% of patients actually spontaneously clear the infection. Those are typically patients who tend to be younger, more typically female. Certainly, not infrequently in your practices will you see patients who will get acutely infected and then clear on their own. Nonetheless, in the 75% or so patients that do not clear, there are spectrums of disease that are affected to some extent by co infection with HIV and alcohol intake. But, overall about 20% of patients progress to cirrhosis during their lifetime. And, of those, some develop decompensated liver disease or the need for liver transplantation, or unfortunately death. And some, as I said about three to five percent per year progress to hepatocellular carcinoma with the consequences being, again either a need for liver transplantation, other therapies, or ultimately death. So, clearly this is a disease worth our attention, this is a condition that we need to focus on in our practices because it is fairly common, fairly treatable in a large majority of patients and important to recognize.
This is sort of a recurrent theme now for the past five years people have been looking at the future impact of Hepatitis C in terms of the burden of cirrhosis, decompensated liver disease, hepatocellular carcinoma and liver related death. If you look at this table where around 2010 or in 2011 you can see that HCV infection shown in the first slide will gradually decline over time from three million in 2000 to about two million in 2040. However, the number of patients who develop cirrhosis and decompensated liver disease will exponentially increase. And, the number of cases of hepatocellular carcinoma will increase also. The burden of patients who will die from liver related causes will increase three fold over the next two decades. So, if you think you’ve seen the brunt of the Hepatitis C epidemic, you have not. Over the next twenty to thirty years we’re going to have to deal with much more complications of Hepatitis C then we ever thought we would need to.
Hepatitis C of course is a curable illness. You can actually give patients medications and in a certain percentage of them, and we’ll go over that in a minute, they achieve what we call a Sustained Virological Response (SVR) defined as undetectable HCV viral load 6 months after stopping therapy are cured over 97% of the time. 

• SVR is the gold standard for cure in all clinical trials.
So, I think the first and perhaps most important issue we are hopefully making advances in over the next few years is screening. If you do not know someone has Hepatitis C, you can’t treat them. So, screening needs to be a focus, and this is a collective responsibility of both primary care physicians, gastroenterologists, hepatologists, and other people who potentially see patients who are infected. These are, this is a synopsis of the CDC guidelines as they stand today as to whom should be, which patients should be screened for Hepatitis C, and there are two categories. If you’ve been exposed, obviously, a health care emergency personnel person or a child born to an HCV positive woman, that would be based on exposure. Or, if you have an increased risk and this includes intravenous drug use, certain high risk groups from the days from when we did not test for Hepatitis C because we didn’t know it existed. If someone was ever on a chronic hemodialysis, if they have evidence of chronic liver disease, if they’re HIV positive. This is what we use today to determine whether we order a Hepatitis C antibody on someone or not.

**CDC Testing Recommendations**

- Person who ever injected illegal drugs
- Persons with selected medical conditions (clotting factor concentrates produced before 1987, long-term hemodialysis, persistently abnormal ALT)
- Prior recipients of transfusions or solid organs before July 1992
- Health care, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV positive blood
- Children born to HCV positive women
Well, we know now very well that this does not work. The number of patients who have Hepatitis C but are not aware of their diagnosis is estimated at about 75% of all patients. So, even though we're making efforts to screen patients, these efforts have been acknowledged to be unsuccessful. So, perhaps there is a new way of looking at this. And, that’s what many of the recent studies including abstracts at AASLD have focused on. If you look at the prevalence of Hepatitis C based on age categories, or what we call Birth Cohorts, it becomes evidently clear, based on insurance claims, from patients that were tallied over the year in 2008, that over 75% of patients, about 80% of patients, were born between 1945 and 1965. So, if you actually look at all patients who have Hepatitis C today, if you just narrow it down by age and test patients in that age category, you will likely pick up the overwhelming majority of patients.
So, that led to people to actually think about how this would objectively be tested to see whether it would have downstream benefits on patients. I will say that both studies I’m going to cite on this are models, they are statistical models. It is practically impossible to do a study where you actually screen by age over time. It would cost billions, not millions, billions of dollars. But, these models are statistically accurate and based on very good information. The first was initially reported on this year’s Digestive Disease Week and published in last month's Hepatology for those who wish to read it. This basically breaks down the impact of birth screening for Hepatitis C compared to risk based screening, and if you actually look at this model that compares the impact of screening by birth vs. by risk factor in patients born in people born between 1946 and 1970, and if you look at the impact of treatment on these patients, you will find without getting into too much statistical detail that if you use the Birth Cohort screening method you would actually have 54,500 fewer cases of compensated (slide says decompensated) cirrhosis, 31,000 fewer cases of cancer. About 6,000 fewer cases of liver transplant, and about 50,000 fewer deaths. That all looks great. But, you would end up having more health care expenditures because you’re now identifying more patients and treating them. Your expenditures would go up to about 80 billion dollars just for screening vs. about 54 billion. You would pay less costs in terms of treating advanced liver disease because you’d be treating it at an early stage, and you would have something called an ICER, which is an incremental cost effectiveness ratio, just a way of saying that you’re actually advancing care in a cost effective manner of about 38 thousand dollars if you use the Birth Cohort approach vs. the risk based screening.
This is another abstract that chimes on the same thing. This was presented at AASLD, published just a few days ago in the Annals of Internal Medicine, which basically looks at an even broader cohort of the National Health and Nutrition Examination Survey, looking at patients who were born between 1945 and 1965. Again, this is a statistical model that included about 67 million people. And, if you basically look at that approach, the lifetime cost of treating the estimated 2.4 million patients that you would test and test positive, the illness related lost productivity and the increased loss of quality of life and other factors would lead to the following.

Birth Cohort Screening for HCV

- National Health and Nutrition Examination Survey, census data, Medicare reimbursement information, and published sources
- Analytic model included the estimated cost of HCV testing in the 67 million Americans born from 1945 through 1965
- Authors calculated the lifetime cost of treating the estimated 2.4 million patients with HCV-positive test results, illness-related lost productivity, increased loss of QALYs, and other relevant factors.
Birth Cohort Screening is Cost Effective

- Birth-cohort screening would identify 808,580 additional cases of HCV infection at a cost of $2,874 per case.
- Treatment of the additional cases would result in an additional 348,800 QALYs gained at a total cost of $5.5 billion, resulting in incremental cost-effectiveness ratio (ICER) of $15,700 per QALY.
- Expanding the definition of treatment to consist of a direct-acting antiviral, pegylated interferon, and ribavirin results in an additional 532,200 QALYs gained at a cost of $19 billion and an ICER of $35,700 per QALY saved.

You would end up spending more money to treat additional cases. This would be an increment of about 5.5 billion dollars and an increment in quality of life, this ICER measure, of about 16 thousand dollars. You would end up gaining an additional 530,000 something quality of adjusted life years, which is a validated way of showing addition of survival with factoring quality in. But, this would cost you about 19 billion dollars and your increment in cost effectiveness would be about 35 thousand dollars per quality of adjusted life years saved. All of this is statistical lingo, it tells you that it is cost effective to do this even though it costs a lot of money.
So, my conclusions based on these two papers now, no longer abstracts is that screening based on risk factors will miss many cases, screening based on birth cohort, and the consensus seems to be 1945-1970, so any patient you see, if they’re born between 1945 and 1970, you do not need to ask them about risk factors. You just order a Hepatitis C antibody on them, you will pick up a lot more patients that will likely benefit from advances in treatment. This is more intuitive, makes more practical sense and is cost effective.

Major criticism is that there are no randomized studies of risk factor versus birth cohort based screening (will never happen).
So, we’re going to talk a little bit about treatments, but I think for the broader audience one of the issues that come up very frequently, certainly in my practice, is the issue of milk thistle, silymarin, and does milk thistle work? And, if it works, should patients take it, and for how long? And, for a long time, we really did not have any clear objective answers to give to patients, so historically we would tell patients it’s okay to take milk thistle because we don’t think it’s harmful. Well, a few years ago the government, the NIH and NCAAM funded a study looking at the impact of milk thistle on enzymes and Hepatitis C. It did so based on the knowledge that the milk thistle is safe, it has anti oxidant, anti inflammatory properties, up to 30% of patients with Hepatitis C take it. Four centers basically gave their patients who had an ALT greater than 65 a medication Legalon which is silymarin at the dose of, at the doses of a hundred, at the doses of 420 or 700 milligrams administered three times daily, and they were basically three groups, those two doses plus a placebo group. The primary endpoint here was only a reduction in ALT. ALT less than 45 so understand that this does not include histology, and does not include any objective measures of liver tissue improvement. They also monitored Hepatitis C RNA PCR because there is some thought that perhaps silymarin has some antiviral properties.
The adherence to silymarin was excellent, even in patients who had to take up to 15 pills per day, pretty much everybody took their full dose. So, people have no problem taking silymarin, they did not appear to have any adverse events, compared to placebo, but this does not appear to lower your liver enzymes. So, if you look at all the patients that were in the study, there were only six participants, and only two in each treatment group that met the primary endpoint of reducing their ALT. The mean decline in serum ALT activity overall was no different between the placebo group and the two treatment groups.
So, what does that tell us and what are my conclusions? Oral milk thistle, even when given at high doses in a fairly purified manner, not what you buy at GNC or your local nutrition store, does not seem to be beneficial for Hepatitis C infection. It is very well tolerated, but the cost is not trivial, if you go online and look at so many preparations they range between 50 to 75 bucks. My own personal take is to tell patients not to take milk thistle. If they absolutely insist they want to take it, they can. But, I would not encourage any patient to take milk thistle at this point. Of course, the major criticism is that this is not a study based on histology, which is the gold standard for measuring liver histological improvement. I would, there are some additional results that are going to be available, but I don’t think they change our recommendations dramatically.
Moving onto more conventional therapy, last year we talked about two anticipated treatments that were going to become approved for the treatment of Hepatitis C. They have since then become commercially approved, they're Boceprevir which is given the dose of 800 milligrams three times daily, and Telaprevir, given at the dose of 750 milligrams three times daily in combination with pegolated interferon and ribavirin. As you know, these treatments are approved for both treatment naïve patients, patients who have never experienced treatment before, as well as previous treatment failures. They can be given to patients of compensated cirrhosis, and up to 50% or so of patients with both drugs you can actually qualify for shortened duration of therapy. With one drug you have to take food, with the other you have to take with food that is not low in fat, but that's sort of a small difference. And, last but not least they're only approved for genotype I patients. So, patients who have Hepatitis C genotype II or III, IV, V, VI cannot take these medications, they're not FDA approved for them.
And, in the year that has, well not actually year, but in the seven months that have gone since these drugs were approved, the AASLD has come up with new treatment guidelines that endorse the use of these drugs in combination with peglated interferon and ribavirin. They also endorse most importantly that in the case of anemia, which is a frequent occurrence in both drugs, a key, a keystone, a key issue in management is with reduction of ribavirin, and I will show you some data in a few minutes that indicates that this can be done without compromising the outcome very significantly. The AASLD guidelines also indicate that if somebody fails the one protease inhibitor, they should not be retreated with the other because we do not have data at this point that show us what will happen in that scenario.
Both these drugs are called protease inhibitors and they affect the NS3/NS4 protease in the viral genome,
and they clearly have an increment in the sustained virological response, AKA cure compared to the various treatments. So, whereas almost fifteen years ago the cure for Hepatitis C did not exceed 10, 15%, now we’re looking at close to 70, 75% with these agents. As I said, with short, potentially shorter duration of therapy and markedly improved outcomes even in previous treatment failures. So, that is terrific. That’s why you want to have your patient go through the time and effort and pain and suffering to actually take these medications because they improve their likelihood of cure.
Now, unfortunately, additional better outcomes are not associated with simpler regimens or less complications. This is a non exhaustive list of drug-drug interactions that occur with both Boceprevir and Telaprevir. There’s really no easy way to do this other than to consult either the package insert or some web database that looks at drug-drug interactions, which is what I do. But, very important for people out in practice to know that when they start medications it’s important to know if your patient is on a protease inhibitor and how the drugs may be adjusted and contract their treaters accordingly.
Of course, the previous generation of drugs, pegolated interferon and ribavirin have their own slew of side effects of their own. So, flu like symptoms and anemia, rashes, dyspnea, etc. etc.
And now you're adding, on top of that, specific side effects or increments in side effects associated with protease inhibitors. So, for Boceprevir, the main association when given this drug plus pegolated interferon and ribavirin are anemia, neutropenia, and an altered taste sensation or dysgeusia. Notice that anemia occurs in up to 50% of patients in the Boceprevir containing arms compared to 30% just by taking peg and riba alone. Neutropenia more common and dysgeusia altered taste sensation and more common. So, not all side effects from the previous sort of backbone of therapy but sensational side effect with a protease inhibitor.
The good news is that even though you get anemia with Boceprevir, the cure rates, the SVR rates appear to be even higher in patients who become anemic than non anemic patients. And, as seen in this table which breaks down patients who had dose reductions the RBVDR, can’t really point at to it, patients who got EPO GEN, who got neither, and patients who got both, there is really not much difference in the sustained virological response. So, if you have a patient on treatment and they become anemic, ribavirin dose reduction is the way to go. There is no doubt in anybody’s mind about that at this point.
The other drug, Telaprevir that was approved at the same time also has its own share of potential incremental side effects. Rash occurs in about half of patients compared again to about a third of patients who just take peg interferon and ribavirin, and anemia occurs in about 36% of patients, and anorectal symptoms, primarily parotitis and a discomfort at the time of defecation occurred in about 29% of patients.
And if one again looks at the management of anemia in patients who take Telaprevir, it appears that based on these two tables that look at ribavirin dose reductions in patients who took the drug plus peglated interferon and ribavirin vs. no ribavirin dose reduction, it appears that neither anemia nor ribavirin dose reductions were associated with a lower SVR. So, again, with Telaprevir, if you experience anemia, ribavirin dose reduction is a reasonable way to go that preserves a decent outcome for your patient.
Though overall, the reason why I’m harping on anemia is because in the era of first
generation protease inhibitor, anemia is clearly the Achilles Heel of therapy. This is
what will potentially cause patients serious adverse events and may threaten their
ability to stay on therapy. And, with both drugs, both Bocerprevir and Telaprevir, and
granted in the studies with Boceprevir, patients were allowed to use growth factors
with Telaprevir as they were not, so these are by no means head to head
comparisons. A high percentage of patients had anemia with a hemoglobin less than
10, a significant percentage in the Boceprevir arm had to undergo ESA therapy.
And, up to 3% of anemic patients in the Boceprevir trials required both transfusions
vs. about 12% of patients of anemic patients who dropped their hemoglobin to less
than 10 in the Telaprevir studies. So, these are data that show you very clearly that
you have to manage anemia effectively, you have to manage it aggressively, and
you have to be prepared for it if you are going to use the first line protease
inhibitors.
And, in fact here I've summarized some of the guidelines that I think all of us could go by so that we could navigate patients successfully through treatment. Again, ribavirin dose reduction plus or minus growth factors even though we want to prevent blood transfusion at any cost, that's never a good thing that may be necessary at times. Anemia management is critical so that patients do not discontinue therapy. The general background is that once you discontinue a protease inhibitor you should not restart it if it's been discontinued for a significant period of time. You cannot dose reduce a protease inhibitor because that does not lead to a good outcome. And I think you should spend the good time and effort, you or your nurse practitioners, PA’s or other support staff, spend time and effort to discuss with patients the side effects of therapy, educate them about what could potentially happen so that you can identify them and prevent them. And, I think for the primary care physician or internist, calling the treater or whoever that is, hepatologist, gastroenterologist before making any changes in Hepatitis C medications should be the way to go.
A few words about goals of future treatments, so that was the bulk of the meeting. The goals of treatment are obviously to find more effective treatments, shorter treatments, simpler treatments, less pills, less frequent, and less toxic treatments, which basically means drop the interferon and see if you can get away with it.
And, clearly and I think this is a summary of about 30 abstracts, the drugs that are coming along, we don’t know when, will at minimum preserve the efficacy of the first generation protease inhibitors. So, I do not anticipate that any drugs will become FDA approved if they have an SVR less than what we get right now with boceprevir and telaprevir and this is a list of these drugs, you don’t have to remember any of them, none of them may make it to market for all we know, but basically they all have comparable or superior efficacy in terms of patients who have genotype I and their SVR. And, most of the studies that have been done, which again have not for these drugs reached phase III trials yet.
The other issue that I think is quite critical is trying to give patients a drug less frequency. And, as you can see, the bulk of agents that are being developed are either once a day or twice a day regimen. And so, clearly over time we will need to have drugs that are administered less frequently and there's plenty of them in development.

### Several Drugs in Development Are Dosed Once or Twice Daily

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*With RTV boosting.*
And, ultimately the Holy Grail of hepatitis C therapy is to drop the interferon and basically do an all oral regimen. And sort of the, I’m not a big fan of sensationalism, but the sensation of this meeting was a small presentation, an oral presentation, where a drug called ESI 7977, which is a nucleotide analog when given with ribavirin alone, not for genotype I, genotype I is what we talked about all along, the more difficult to treat genotype. But, rather for genotypes II and III, this drug when given for 12 weeks with ribavirin and for different periods of time with pegolated interferon for 12 weeks, 8 weeks, 4 weeks, or no interferon, in about ten patients in each group led to a 100% SVR in all groups including the ten patients that got no interferon. So that, basically, is at least proof of concept that patients can be cured for hepatitis C without the need for interferon obviously a lot more work needs to be done. So, I’m not a big fan of speculation, but if you read the Wall Street Journal or New York Times you’ll know that somebody thinks this actually is of value because the company that makes this drug was purchased by Gilead Sciences for 11 billion dollars at a 90% premium. So, there’s a lot of money going into this, there’s a lot of uncertainty but certainly there is a lot of hope, there’s a lot of hope for patients with hepatitis C in the future.
I’m going to conclude by going over the following: I think you cannot treat patients if you don’t diagnose them. I think birth cohort screening is going to be the way of the future. Certainly, I would start implementing that in my practice, patient autonomy is important but milk thistle probably isn’t…

Treatment is currently more effective and complicated but will eventually get easier. HCV treater and PCP communication critical!

HCV treatment is a dizzyingly fast moving target. Approval of new agents may not be…

Conclusions

• You cannot treat patients if you don’t diagnose them → Birth Cohort (1945-1970) screening
• Patient autonomy is important but milk thistle probably isn’t…
• Treatment is currently more effective and complicated but will eventually get easier → HCV treater and PCP communication critical!
• HCV treatment is a dizzyingly fast moving target. Approval of new agents may not be…

I don’t know when these new agents will be approved, so we have to make due with what we have right now. Thank you for your attention. (applause)