Thank you, Tony. Pleasure to be here once again, and we’re going to talk a little bit about some of the hepatitis B papers. I must say there were hundreds of abstracts; I didn’t see very much that was truly in a breakthrough mode, but at least there were some interesting, interesting papers.
So, just by way of brief background, I think most of you know that although in North America hepatitis B is not a huge problem. Certainly around the world it is, there is an awful lot of infected patients, an awful lot of cirrhosis due to hepatitis B, an awful lot of hepatocellular carcinoma as a consequence. And, it is a huge worldwide problem. It remains a significant problem in immigrant populations to many parts of the United States, and so it is a matter of some interest to us.

Hepatitis B affects millions around the world and is a major cause of morbidity and death.

- 2 billion have been infected
- 400 million chronically infected
- 50 million new cases per year
- 15%-25% will die from complications
You know, of course, that if you acquire hepatitis B as an infant, a neonate, you’re never going to get rid of it. And, if you are acquire it as an adult you almost certainly will get rid of it on your own, and they’ll be no chronicity or subsequent problems. But, of course, some people will have a chronic B hepatitis even acquired as an adult. And, the consequences of this are significant as outlined here.
One way to look at the life cycle of hepatitis B is represented on this slide, and what we really pay most attention to is the individual who has active liver disease with hepatitis B. So, the hepatitis e-antigen positive immune active phase or the hepatitis e-negative active phase are both target populations for treatment. And, inactive phase not so much, although that may change in time.
At last year’s meetings we talked a lot about reactivation of hepatitis B represented here by the broad arrows. An individual with inactive hepatitis B can have reactivation under a number of influences, perhaps most importantly under the influence of immune suppression medication. But, even those individuals who have cleared their hepatitis B may also reactivate under some intense immune suppression, and these are of great interest going forward.
I’m going to talk about six abstracts, and there are many more in your handout that, because of time we’ve eliminated from discussion, but those are related to hepatitis B treatment.
Here is one using entecavir in those who are surface antigen positive and e-antigen positive. And, the goal of the treatment was to determine, the goal of the study was to determine whether adding a peglated interferon to entecavir might speed the conversion of e-antigen positive to e-antigen negative status in individuals. So, this is a 48 week study; it's a multi center study from around Europe and Asia, and this is an interim analysis from the so called “ARES “study. So, this is the basic outline, and the goal, the primary endpoint of this study is to e-antigen loss and an HBV DNA less than 200 international units per ml

<table>
<thead>
<tr>
<th>Study: RCT 184 HBeAg+ patients with compensated liver disease enrolled in 15 sites in Europe and China</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETV 0.5/day x 48 weeks</td>
</tr>
<tr>
<td>ETV x 24 weeks Add PIFN x 24 weeks</td>
</tr>
</tbody>
</table>

Primary Endpoints: Response = HBeAg loss AND HBV DNA < 200 IU/ml

Sonneveld et al Rotterdam
Abstract # 19
And, here in summary are the results. They found that if we look at quantitative HPSAG, if we look at HBV DNA, if we look at clearance rates of e-antigen from positive to negative, there did seem to be a benefit to adding pegolated interferon after 24 weeks of entecavir.
And, here is the same data represented in a graphic format.

Now, I will point out that none of these results are truly statistically significant. The conclusion's that e-antigen loss was greater in those who received combination therapy for the second 24 weeks of therapy; it's close to statistical significance, but it's not really there yet
And, these were the factors associated with the response. And so, the authors’ conclusions are that there is a place for pegolated interferon along with nucleoside analog therapy, and this may speed the conversion of e-antigen positive to e-antigen negative. And, it then implies the possibility that more finite therapy with nucleoside analogs may be, may be possible from this kind of a strategy. My own conclusion is this remains to be determined; I’m not at all convinced that we ever know when to stop nucleoside analog therapy. And, maybe this will be a subject for the questions and answer period.

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA week 0</td>
<td>0.69 (.51-.93)</td>
<td>0.016</td>
</tr>
<tr>
<td>qHBsAG (log) week 0</td>
<td>0.46 (.28-.76)</td>
<td>0.003</td>
</tr>
<tr>
<td>qHBeAg (log) week 0</td>
<td>0.57 (.37-.86)</td>
<td>0.008</td>
</tr>
<tr>
<td>Therapy PIFN</td>
<td>2.41 (.92-6.34)</td>
<td>0.068</td>
</tr>
</tbody>
</table>

**Conclusions**

Addition of PIFN to NUC
1. increases decline in HBV DNA, qHBeAg and qHBsAg
2. Increases response at week 48
3. Is well-tolerated
4. May increase chances of finite therapy

Sonneveld et al Rotterdam
Abstract # 19
I’m going to pivot to looking at those who have been treated with hepatitis B successfully with nucleoside analog therapy. Does this have any bearing on the risk of the development of hepatocellular carcinoma?
And, I will remind you of the AASLD Guideline that says we don’t know. The guideline says if you have hepatitis B cirrhosis, and if you cleared surface antigens spontaneously or with treatment, they likely have a reduced risk, but if not quantified therefore they need to undergo continued surveillance. And, this study I think adds at least some data to this recommendation which I don’t think needs to be modified.
Based on this “CLEO” study of 246 patients from ten liver units, mainly from Southern Europe they had been given nucleoside treatments for at least 18 months. They excluded everyone who had HCC at the outset of the trial and those who developed it within the first 18 months of RX because they thought that this might have been a pre-existing HCC and therefore will get better results if we have those exclusion criteria. They had the typical follow up of labs and ultrasounds, and so we have pretty good data.
These are the results: the majority of the patients were given entecavir treatment, and the next largest number of patients were given tenofovir treatment, and you can see the risk of HCC in all of these treated patients from mean follow up of 6.8 years over all HCC developed in almost 14%. And, I suppose this is a statistical quirk, but the lamivudine group did particularly badly. So, again these were all individuals who had advanced liver disease who developed the HCC

<table>
<thead>
<tr>
<th>NUC used</th>
<th># Patients</th>
<th>HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>7</td>
<td>86%</td>
</tr>
<tr>
<td>Entecavir</td>
<td>120</td>
<td>13%</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>27</td>
<td>13%</td>
</tr>
<tr>
<td>Lam plus adefovir</td>
<td>18</td>
<td>22%</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>2</td>
<td>0%</td>
</tr>
</tbody>
</table>

• Mean follow up 6.8 years
• HCC developed in 32 patients (13.6%)
and this is the multi variant analysis, which tells you what the risk factors were for the development of HCC during this follow up period. And what it really shows is that age and cirrhosis, whether compensated or decompensated, these were the three major things that were associated with subsequent development of liver cell cancer.
And so, the conclusions, I think, are quite reasonable. That is cirrhosis, compensated or not and particularly in those age 60 or greater, no matter what the response has been to nucleoside analog therapy, they are at high risk for HCC and continued surveillance as per the AASLD guideline is certainly something that we ought to advocate.
is certainly something that we ought to advocate.
Okay, going to say a word about a couple of studies, H, hepatitis B and liver transplantation.
The liver transplant segment will actually discuss the most important hepatitis B patient in this study in this category, but we’ll talk about a couple of the others. We all know that hepatitis B used to be a very bad disease for transplantation. It would often recur, it would often recur with a vengeance, fibrosing cholestatic hepatitis and early death made this a particularly bad disease to transplant for, but now things have changed completely, and a low recurrence, excellent survival. And, this has been attributed to the use of big hepatitis B immune globulin and nucleoside analog therapy, and again more about that later.
So, here is a study from the “UNOS’s” database from 2002 to 2010 again showing the very excellent likelihood of a good outcome for hepatitis B for which liver transplantation is done. And, the good outcome exists whether or not HCC is present, so we see these are not exactly aligned. The one year survival of 89%, two year survival 86%, and five year survival of 80% in those who have HBV as the cirrhosis as the indication for transplantation. And, very comparable one and two year survival even if HCC is present with a little bit of a drop off after five years. And, most of the lack of survival, the mortality after transplantation was due to recurrent HCC rather than recurrent of hepatitis B

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### Outcomes of Liver Transplant for Hepatitis B Infection in the Post MELD era

**UNOS database 2002 – 2010**

1,979/50,071 (4%)

<table>
<thead>
<tr>
<th>Survival</th>
<th>Year</th>
<th>1</th>
<th>2</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV/no HCC</td>
<td></td>
<td>89%</td>
<td>86%</td>
<td>80%</td>
</tr>
<tr>
<td>HBV/HCC</td>
<td></td>
<td>92%</td>
<td>87%</td>
<td>77%</td>
</tr>
</tbody>
</table>

HBV has one of the most favorable outcomes

No increased risk of death at year 2 in those With HBV/HCC

Increased risk after 2 years appears related to HCC recurrence

Zheng et al UC San Francisco
Abstract # 718

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And, in a somewhat similar study from Europe showing the changing indications for transplantation and the background for transplantation. It has changed in the cohorts that were transplanted between 1988 and 1995 compared to 2006 to 2010. Decompensated cirrhosis used to be the major indication, 82%, it’s now still is a major indication, but it’s gone from 82 to 70%. And, the amount of transplantation for hepatitis B cirrhosis complicated by HCC has gone up from 16 to 30%. They did also find that HBV DNA levels undetectable at the time of liver transplantation were associated with increase graft and patient survival. HBV recurrence rate has gone from 40% to 8%, a tribute I think to strategies which have been developed over time.

<table>
<thead>
<tr>
<th>Indication</th>
<th>1988-1995 (%)</th>
<th>2006-2010 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decompensated cirrhosis</td>
<td>82</td>
<td>70</td>
</tr>
<tr>
<td>HBV – HCC</td>
<td>16</td>
<td>30</td>
</tr>
</tbody>
</table>

HBV DNA levels undetectable at OLT > increased graft and patient survival

HBV recurrence decreased from 40% > 8%

Germani et al
Abstract # 693
Hepatitis B and Liver Transplantation
Is HBIG Necessary?

I’m not going to get into this abstract, but this is the key abstract that you’ll hear about a little later this morning
I’m just going to address a little bit the notion of taking a donor organ that is positive for anti HB core. As you know, the presence of anti HB core is certain, makes it a certainly that that individual has been exposed to hepatitis B. They may have hepatitis B incorporated into their DNA even if they’re surface antigen is negative. And so, the question is, can we use hepatitis B anti HB core positive liver donors?
This is a really kind of a small experience from Saudi Arabia. It turns out that in this series, all recipients receive nucleoside analogs and HBIG. And, what they found is that recurrences of hepatitis B were limited to recipients who have been negative or anti HB core and anti HBS, and I think that makes sense. They also point out that even though recurrences happen, that they were successfully managed, and it wasn’t a major impediment to the success of the transplant, host transplant setting.
### Hepatitis B at AASLD 2012

#### Conclusions

1. In HBeAG+ patients interferon added to powerful NUC may provide benefit
2. In cirrhotics successfully treated with NUC HCC risk remains high
3. In LAM resistant patients monotherapy with top-tier NUC is effective in most
4. Quantitative HBsAg may be useful to predict freedom from reactivation
5. IL 28 B polymorphism not useful in predicting response to interferon in HBV
6. Outcome for OLT for HBV is excellent; undetectable viral load at OLT favorable
7. Use of HBIG after OLT in HBV - discussed later this morning
8. Use of anti HBC grafts for OLT appears safe

So, the conclusions are that we really can, we really can do this successfully.

So, my conclusions from the abstract that I presented, and again some that I have left out are in your handout, that in e-antigen positive hepatitis B patients, interferon added to powerful nucleoside analog, particularly entecavir but probably also tenofovir may provide benefit, but really I think we have a lot more to learn about that, and I don’t think this has changed my practice, and I’d be very interested in the question and answer period whether it’s changed anybody’s practice. About the use of nucleoside analogs, in cirrhotics I think we can take this as a given that in cirrhotics who have been successfully treated for hepatitis B they remain at very high risk for the development of liver cell cancer and they need to be screened. I didn’t present the data on lamivudine resistant patients, but another abstract showed that if you have lamivudine resistance, they can be managed successfully with powerful single agent nucleoside analogs rather than multiple drug therapy. I didn’t present the data on IL-28 B polymorphism, not particularly useful in hepatitis B whereas it is at least moderately useful in hepatitis C analysis. And, outcomes for liver transplantation in hepatitis B you’ll hear about that later. Use of HBIG will be discussed later. And, it looks like the use of anti HB core donor organs is at least a reasonable thing to consider in selected patients who are in need of liver transplantation. Tony, I did it! (laughter)