



Expert Physician Conference Call with Dr. Melissa Palmer

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HCV Therapeutics and the Current Developments: Why the Approach Matters

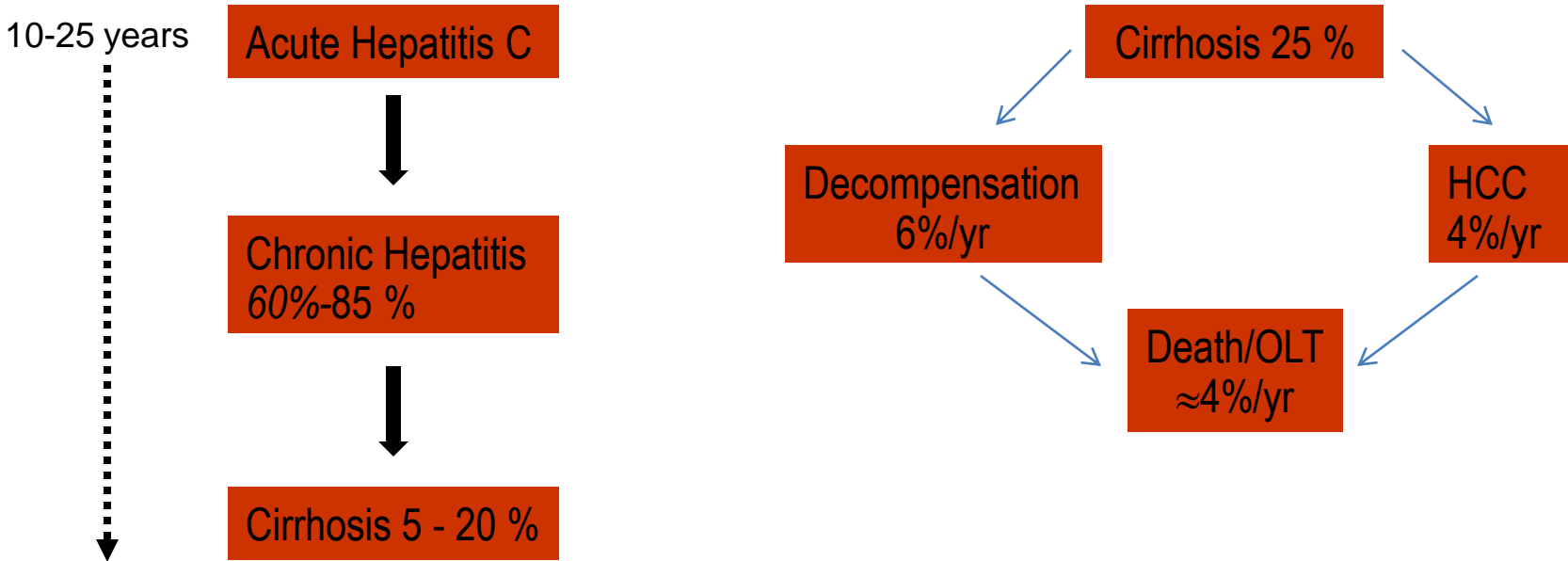
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Natural History of HCV

Of the 25% of cirrhotic patients, approximately 6% of patients can be expected to develop hepatic decompensation per year, 4% will develop HCC per year, and 3% to 4% per year can be expected to die or require liver transplantation. Detection of the virus in the blood was only made possible in 1990, causing a generational effect.



Hoofnagle JH Hepatology. 1997;26 (suppl 1): 15S-20S
Di Bisceglie, Hepatology, 2000

The HCV market is Growing: Estimated HCV Disease Burden by 2030

- The number of patients with cirrhosis will almost double (472,103-879,747)
- The number of patients with decompensated cirrhosis will more that double (65,294-146,408)
- The number of patients with liver cancer will almost double (7,271-13,390)
- Deaths due to liver disease will more than triple (13,000/yr – 39,875/yr)

Adapted from Davis,G et al Liver Transplantation 2003; 9:331-338

Protease Inhibitors (PIs): Telaprevir and Boceprevir for Genotype 1

- Potent inhibitors of HCV NS3/4A protease
- Require concomitant use of Peg/IFN
- Both approved by FDA in May 2011
 - Indicated in combination with pegIFN/RBV for treatment of genotype 1 HCV–infected patients
 - Previously untreated or previous treatment failures
- New Standard of Care for GT1 patients
- AEs are significant (anal itch and pain, notably)

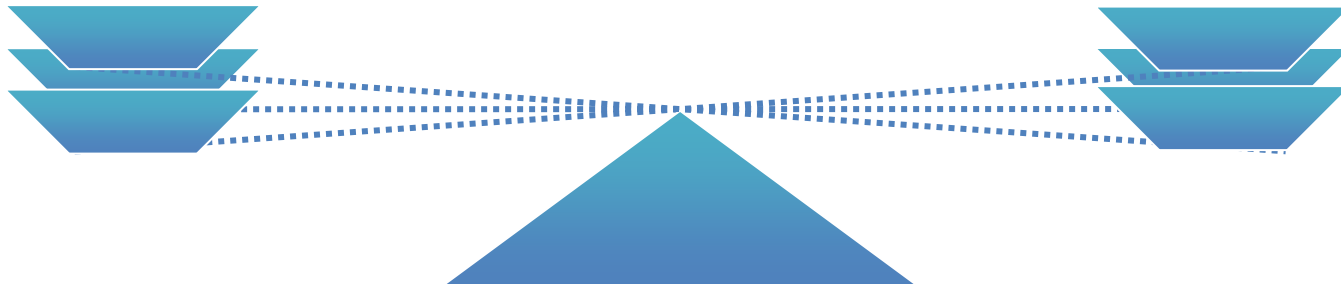
HCV treatment decisions for protease inhibitors

Pros

1. PIs substantially increase chance of SVR across a majority of patient groups
2. PIs shorten duration of therapy in many patients
3. Successful treatment improves morbidity and mortality

Cons

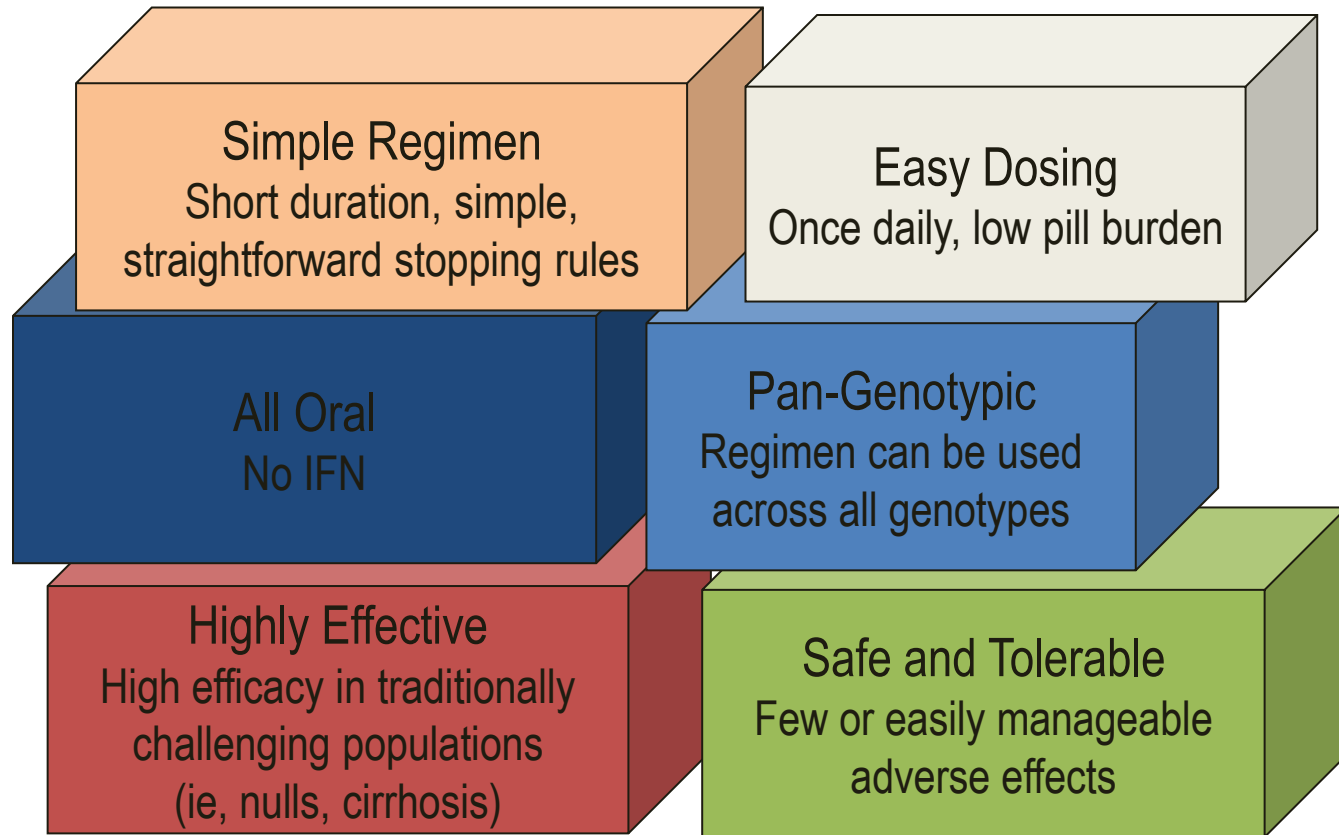
1. Suboptimal response rates or limited/no data in several populations
 - HCV-HIV co-infection, transplant, decompensated cirrhotics
2. Complicated regimens, challenging AEs, and DDIs
3. Risk of resistance if therapy fails: impact on future options?



Current and New Therapies: Each Drug Class Has Unique Features

NS3/4A Protease Inhibitors	NS5B Polymerase Inhibitors		NS5A Inhibitors	Cyclophilin A Inhibitors
	Nucleos(t)ide Analogue	Non-nucleos(t)ide		
<ul style="list-style-type: none"> ▪ High efficacy ▪ Low genetic barrier to resistance ▪ Macrocyclic or linear ▪ Phase III: BI 201335, TMC435 ▪ ACH-2684 ▪ Phase II: ACH-1625 	<ul style="list-style-type: none"> ▪ Mimic natural substrates of the polymerase ▪ Incorporated into RNA chain causing chain termination ▪ Broad genotypic coverage ▪ High genetic barrier to resistance ▪ Phase III: PSI-7977 ▪ INX-189 ▪ IDX184 	<ul style="list-style-type: none"> ▪ Bind to several different allosteric enzyme sites; results in conformational change ▪ Resistance more frequent than nucs ▪ Several agents in phase II ▪ ABT-333 and ABT-072 ▪ VX 222 	<ul style="list-style-type: none"> ▪ NS5A has role in assembly of replication complex ▪ Mechanism of inhibition under study ▪ Phase III: Daclatasvir (BMS-790052) ▪ ACH-2829 ▪ ACH-3102 	<ul style="list-style-type: none"> ▪ Supports HCV-specific RNA replication, protein expression ▪ Interacts with NS2, NS5A, NS5B ▪ May regulate polypeptide processing, viral assembly ▪ Phase III: Alisporivir

What are the Key Elements of an Ideal HCV Regimen?



Nucleotide Analogues have Key Advantages

- Nucleotide analogues targets the RNA-dependent HCV polymerase NS5B as a decoy substrate, inhibiting further RNA production
- Have potent antiviral activity against ALL HCV genotypes, with a high-barrier to resistance
- Excellent PK values allowing once a day oral dosing
- PSI-7977, IHX-189 and IDX-184 in this class

Phase 2 Studies of Nucs INX-189 and IDX-184 in combination with IFN and RBV

- Genotype 2/3: INHX-189 August 2011 safety, tolerability and antiviral activity w/ P-IFN/RBV/Designed to enroll approximately 90 pts
- Patients in the 3 treatment arms of INHX-189 25, 50, and 100mg that include:
 - INX-189 with P-IFN + RBV who achieve a eEVR will terminate all therapy after 12 weeks.
 - Patients in those treatment arms that do not achieve a eEVR will continue to receive P-IFN/RBV for an additional 12 weeks.
- INHX-189 also is Phase I trials as monotherapy at 200 and in combination with RBV at 100mg doses showing *HCV RNA reduction from baseline of -4.25 log₁₀ IU/mL and -3.79 log₁₀ IU/mL respectively*
- Genotype 1 : IDX-184 January 4, Interim results announced of the first 31 patients to complete the 28 day therapy, either 50 mg or 100 mg of IDX184 qd + PIFN/RBV with approximately 100 patients
 - 73% of patients in the 100 mg IDX184 arm (n=15) and 63% in the 50mg arm (n=16) - *undetectable virus* (limit of detection < 25 IU/ml) at 28 days

What can we look forward to with Nucs?

- Can all Nucs move into interferon free treatments? will this encourage more patients seek treatment for their disease?
- What is the clinical difference of RNA reduction between -2_{\log} , -4_{\log} , and -5_{\log} ?

Protease Inhibitors: Achillion

- ACH-1625 is a reversible inhibitor of NS3 serine protease, with an open chain that binds the HCV NS3 protease
- Phase I results demonstrated the safety and tolerability of 1000-1200mg/d x 5 d
 - AEs reported in completed Phase I were mild or moderate with no serious SAEs – the safety profile may represent a clinical improvement over Boceprevir and Telaprevir
- Interim data in the first 35 Genotype I patients, Phase IIa study of either 200, 400, or 800 mg ACH-1625 in combination with P-IFN/RBV for 12 weeks
 - Regardless of whether patients had mutation CT/IL-28b which makes interferon therapy less effective, 100% of these patients achieved cEVR with HCV RNA declines from baseline of -4.79 log, -5.12 log, and -4.59 log respective to dose arms 200, 400, and 800 mg.
- Fast-track designation from the FDA granted January 4th, 2012
- Achillion is rapidly adding more NS3/4 and NS5A protease inhibitors to their pipeline

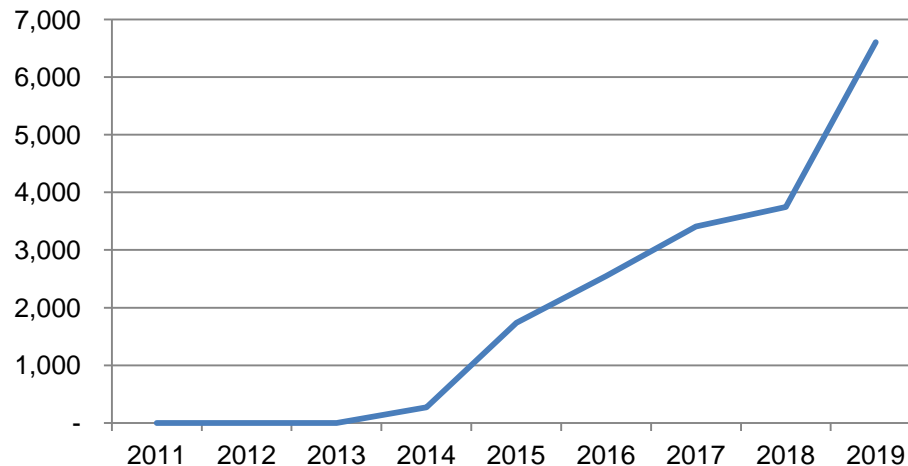
New HCV Drugs: Comparison to PSI-7977

PSI-7977 is Phase III making it the new drug that other developments will need to beat

Consensus Street Estimates for PSI-7977(\$M)

	<u>2011</u>	<u>2012</u>	<u>2013</u>	<u>2014</u>	<u>2015</u>	<u>2016</u>	<u>2017</u>	<u>2018</u>	<u>2019</u>
PSI-7977 annually	-	-	-	269	1734	2546	3409	3745	6604

PSI-7977 annually



U.S. HCV Market Outlook

Approved and in Development

- Protease Inhibitors and Pegasys
 - Incivek (telaprovir) and Victrelis (boceprevir) hit the market this year, with Incivek selling at roughly \$138 million per month, and Victrelis at roughly \$12 million per month
 - Pegasys continues to sell, as it is given with current therapies, approaching \$58 million per month
 - Achillion ACH1625 in Phase II, and ACH2684
- Nucleoside analogues in development
 - PSI-7977 in Phase III, now owned by Gilead
 - INX-189 Phase I/II
 - IDX-184 Phase II
- Non-Nuc inhibitors
 - Gilead drugs in developing Tegobuvir (GS-9190) a non-nuc NS5b inhibitor currently in Phase II and GS-9669, a non-nuc polymerase inhibitor in Phase I
 - ACH-2928 NS5A inhibitor in Phase I

M&A

- Anadys (ANDS) was acquired by Roche at a 265% premium for \$230 million in October
- Pharmasset (VRUS) was acquired by Gilead in November in \$11 billion (89% premium)
- This month Inhibitex entered a definitive agreement with Bristol-Meyers Squibb at a 165% premium in a \$2.5 billion deal that was highly competitive, indicating that more companies are seeking to expand into the HCV market



Thank you for your participation