Hepatitis C Virus: New Diagnostic and Therapeutic Options

Internal Medicine Grand Rounds

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At Dallas

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This is to acknowledge that Dwain Thiele, M.D. has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Thiele will be discussing off-label uses in his presentation.

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Interests: Dr. Thiele joined the faculty of the Department of Internal Medicine in 1983 and the Graduate Program in Immunology in the Graduate School of Biomedical Sciences in 1986. His prior research has focused on delineating mechanisms of cytotoxic lymphocyte function and exploring the role of immune effector mechanisms in clearance of viral infections from the liver and evolution of immune mediated liver diseases. He has broad interests in clinical hepatology and has cared for patients with non-A, non-B Hepatitis / Hepatitis C infection for more than 3 decades.

Learning Objectives:

1.) Be aware of the scope and magnitude of hepatitis C related liver disease in the U.S. and worldwide.
2.) Understand the role of viral and host genetic testing in predicting response to antiviral therapy of chronic hepatitis C.
3.) Be aware of the fact that hepatitis C is a curable infectious disease with rapidly evolving therapeutic options.
4.) Appreciate the clinical factors that are involved in decisions regarding the risks and benefits of currently available antiviral therapy for chronic hepatitis C.

Infection with the hepatitis C virus (HCV) is a major public health problem (1-3). In the U. S. it is the leading indication for liver transplantation, the leading cause of death from liver disease and now a more common cause of death than HIV infection(2, 3). Worldwide, an estimated 350,000 people die from hepatitis C-related liver diseases each year and, in Egypt, where prevalence of hepatitis C infection now exceeds 20%, liver disease is now the second leading cause of death ranking only behind cardiovascular diseases(1, 4). Other populations in which the prevalence of HCV infection now exceeds 3% include residents of China, Pakistan and Taiwan and persons born in the U.S. between 1945 and 1965(1, 5-7). The major role of hepatitis C in worldwide liver disease morbidity and mortality is a relatively recent phenomenon. Historically, rates of cirrhosis in Western countries correlated closely with national per capita alcohol consumption (8) and worldwide variation in incidence of hepatocellular carcinoma correlated closely with variations in prevalence of hepatitis B infection(9). The first clinical recognition of a parenterally transmitted non-A, non-B hepatitis virus now called HCV occurred in the mid-1970's following implementation of blood bank screening for hepatitis Band development of testing for hepatitis A (10). Less than a decade later there were multiple reports of an increasing incidence of non-B, non-B, hepatocellular carcinoma cases in Japan(11) and Southern Europe(12) and two decades later both an increased incidence of liver disease deaths and hepatocellular carcinoma attributable to HCV infection were appreciated in the U.S(13).

Evolution of the Hepatitis C Pandemic

Following cloning and sequencing of the hepatitis C virus in the late 1980's and the subsequent wide spread availability of serologic and molecular diagnostic testing for hepatitis C infection, a much better understanding of the evolution and extent of the worldwide HCV pandemic has evolved. HCV has been classified as a separate genus, hepacivirus in the family *Flaviviridae (14)*. Hepacivirus possesses an error-prone RNA replicase and the resulting genetic diversity among various strains or genotypes of HCV is much greater than for HIV or HBV. Indeed the pairwise differences in nucleotide sequences of the six major HCV genotypes are on the order of 31% to 33% and the differences among subtypes such as 1a and 1b are on the order of 20-25%. Incontrast, the pairwise differences in nucleotide sequences of human HBV genotypes and the chimpanzee HBV genotype are < 15%(14, 15). The rapid evolution of HCV genetic diversity appears to account for the ability to evade host adaptive immune responses and for the absence of protective immunity against HCV(16). In addition, the genetic diversity of HCV proteins involved in viral replication has complicated development of targeted drug therapies and resulted in the need, in many cases, to design genotype specific antiviral regimens(3, 17).

Based on evolutionary trees constructed by analysis of genetic diversity of HCV genotypes and current diversity within genotypes, it is estimated that HCV first existed in humans < 1000 years ago with genotype 1b representing the closest current similarity to the ancestral sequence of this virus(15, 18). Genotype 2 and then HCV genotypes 3-6 are estimated to have diverged from genotype 1b approximately 300-400 years before the present and then to have persisted as endemic infections (see figure 1) in relatively circumscribed areas of Central Africa (genotypes 1b and 4), Western Africa (genotype 2), Southern Africa (genotype 5), Southern Asia (Genotype 3) and Southeastern Asia (genotype 6)(14, 15, 18). Based on our current understanding of the relatively low rate of transmission between humans via common human interactions such as sharing of food, sharing of living quarters or even sexual intercourse, it is somewhat of a mystery as to how this relatively fragile, inefficiently transmitted virus managed to maintain a pattern of endemic infection prior to the development of modern medical devices and therapies(14). Even long term sexual partners of HCV infected adults or the children born to HCV infected mothers have a < 5% risk of HCV infection. It has been suggested that

Regions of Greatest Genetic Diversity / Longest Prevalence of the Major Hepatitis C Genotypes

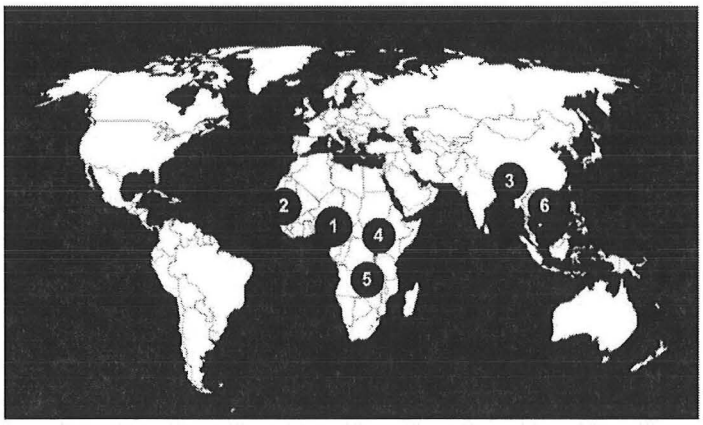
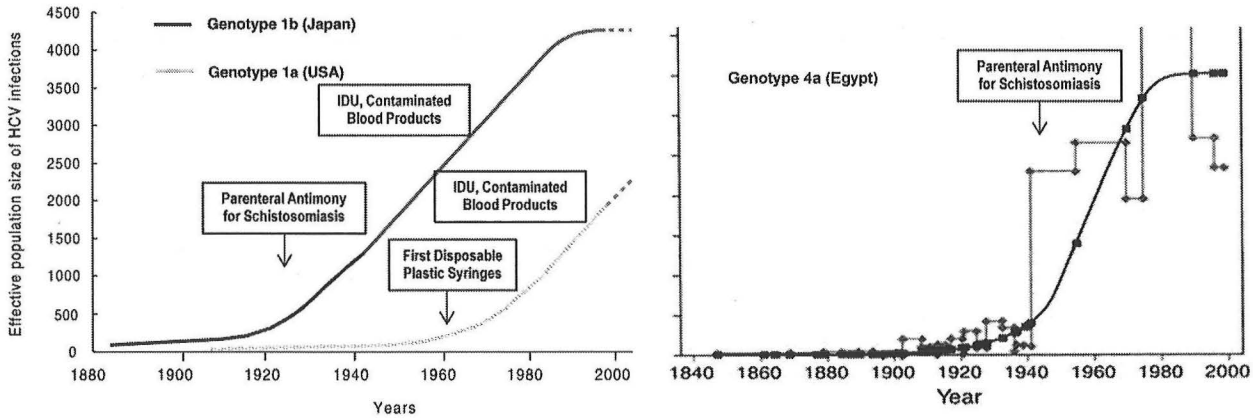


Figure 1

persistence of HCV infection in the pre-20th century era may have been most dependent upon ritual scarification or tattooing practices that directly transferred blood from rare HCV infected individuals to multiple potential new hosts(14).

Dissemination of hepatitis C genotype 1b and 2 infections to Europeans and Eastern Asians is estimated to have first occurred in the early 20th century(15, 18, 19). Somewhat later in the 1940's-1980's era(20), genotype 4 infection disseminated from central Africa into the Nile river valley and delta region of Egypt where genotype 4 remains the most common HCV genotype(6). Genotype 3 disseminated out of Southern Asia into Australia, the U.S. and Europe in the 1970's and 1980's. This genotype remains as the most common HCV genotype in modern Thailand, India and Pakistan(6). The evolution of the worldwide HCV pandemic (see figure 2) is closely tied epidemiologically to three phenomena(14, 15): 1.) Mass production of needles and syringes and increased use of injection therapies in medical practice in the post-1925 era; 2.) Expanded use, in the post-World War II era, of transfusion medicine and modern surgical procedures initially dependent upon frequent and often multi-unit transfusion of blood products; and 3.) Recreational use of injectable drugs in post-World War II Japan and peri- and post-Vietnam War U.S. and then other industrialized countries.

The effective population size of HCV in the U.S., Japan and Egypt estimated from Molecular Clock Analysis



Tanaka Y et al. PNAS 2002;99:15584-15589

Tanaka Y et al. J. Mol. Evol 2004;58:191-195

Figure 2

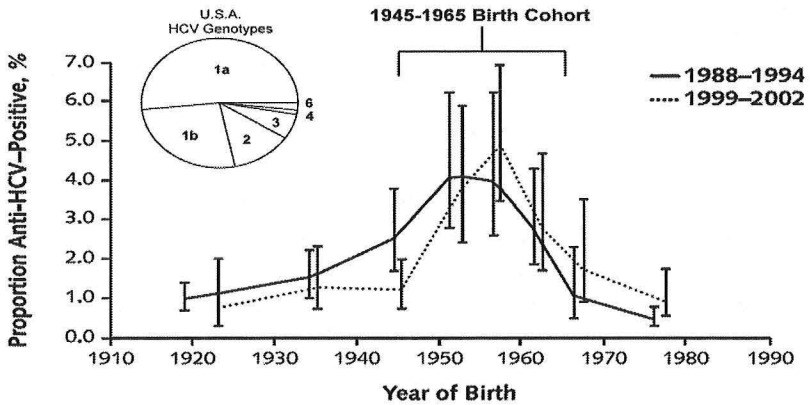
Japanese health officials have identified geographic areas of hyperendemic genotype 1b infection that correlate with use of injected antimony based therapy for schistosomiasis in selected rural provinces in the 1920's and 1930's(19, 20). A subsequent, nationwide Japanese pandemic of HCV infection is attributed to the use of injected amphetamines by World War II

veterans (21) and the enthusiastic adoption of transfusion therapies in Japanese medical practice in the late 1940's and 1950's (21, 22). Japanese patients in this era typically received 5-fold more units of blood product per recipient than U.S. patients due to differences in blood banking and medical practice (22). Furthermore, due to prior infection of a subset of the population during schistosomiasis therapy programs, there was likely a higher initial rate of HCV infection among blood donors in Japan than in the U.S. Japan subsequently passed laws banning parenteral amphetamine use and also modified transfusion practices. Incidence of new HCV infections in Japan has steadily fallen and the major HCV infected cohort is now elderly(21). For these reasons, incidence of HCV related liver disease and hepatocellular carcinoma in Japan is thought to have peaked.

A similar pattern of increased prevalence of genotype 1b HCV infection in the elderly and a similar time course for the appearance of HCV associated liver disease and hepatocellular carcinoma in Southern Europe suggests that the rate of HCV endemic infection in this region of Europe also increased at the greatest rate in the post-World War II era (14). Geographic pockets of hyperendemnicity of genotype 1b in Southern Europe implicate regional differences in unsafe therapeutic injection practices as a primary cause of HCV spread (14). Such practices likely related, as is observed today in under-developed countries, to inadequate or nonexistent supplies of sterile syringes, to administration by nonprofessionals of injections outside the medical setting, and to use of injections to deliver medications that are now delivered by the oral route in wealthier, developed countries.

The most dramatic example of the role of unsafe medical injections in the evolution of the HCV pandemic has been observed in Egypt. Genotype 4a evolved from the ancestral Central African HCV genotype 4 and became disseminated among Egyptians following use of re-useable glass syringes and metal needles for antimony based therapy for schistosomiasis in the 1960's and 1970's (4, 6, 19). In contrast to measures taken in Japan and other industrialized countries to limit new HCV infections, the Egyptian HCV pandemic continues to evolve due to persistence of unsafe therapeutic injection practices and suspected lack of attention to appropriate cleaning and disinfection of equipment used in hospital and dental settings (4, 23).

In the 1960's, genotype 1a diverged from genotype1b and rapidly became the most common genotype among both injections drug users (IDU) and transfusion recipients as the U.S. HCV pandemic evolved in the 1965 to 1990 era (15, 18, 19). Fortunately, following implementation of blood product screening for antibodies to HCV in 1990 and broad public recognition of the infectious risks of needle sharing in the same era, the incidence of new HCV infections in the U.S. decreased by > 90% between 1990 and 2002(5, 24). This has left the U.S. with a unique cohort of adults born between 1945 and 1965 which currently contains about 75% of all HCV infected U.S. residents and has a prevalence rate of HCV infection (3.3%) that is 6-fold higher than observed in Americans born prior to 1945 or after 1965 (0.55% HCV infected) (2, 5). Somewhat



Armstrong, GL, et al, Ann. Intern. Med. 2006, 144:705
Nainan, O.V., et al, Gastro. 2006, 131:478

Figure 3

later than the Genotype 1b Asian and European and Genotype 1a U.S. outbreaks, genotype 3 disseminated in the 1970's and 1980's from Southern Asia into Australia, Europe and North America where it is most common in HCV patients with a history of illicit IDU(14). Of interest however, this genotype, as well as Genotype 1a, are rarely detected in Japan or China (6).

Complications of HCV Infection

Despite the great diversity of HCV genotypes and subtypes, the natural history of liver disease is quite similar among humans infected with the various genotypes (3, 14, 25). Severe acute disease leading to liver failure is almost never seen. The acute infection is most often asymptomatic but leads to chronic infection in the majority of individuals (3). The likelihood of resolution of acute infection is greatest in humans capable of mounting a vigorous innate immune response(16). Those individuals who express HLA-C and NK cell Killer Inhibitory Receptor (KIR) phenotypes associated with decreased inhibition and therefore, more prolonged and more vigorous NK cell responses to virally infected hepatocytes (26) are more likely to resolve acute infections as are individuals with IL28B genotypes associated with more vigorous type III interferon (Interferon Lambda) responses(27-29). The best clinical correlate of a vigorous immune response capable of resolving acute infection is the presence of jaundice during the acute illness(16).

Even among healthy young adults with strong innate immune responses, more than 50% of acute infections lead to chronic infections and it is estimated that overall 60-85% of humans ever infected with HCV remain infected throughout life unless they receive effective anti-viral therapy(3). One of the most significant predictors of rapid progression of chronic hepatitis C to cirrhosis is patient age at time of initial infection, or the age of the donor liver re-infected at time of liver transplantation for end stage-liver disease(30). In some earlier studies of post-transfusion hepatitis in which the majority of HCV infected individuals were > 40 years of age at time of infection, a 20% incidence of cirrhosis developed between 1.5 and 16 years after infection(31). In contrast, among large cohorts of young German and Irish women infected by lots of HCV infected immunoglobulin anti-D, the incidence of cirrhosis after 20-30 years of follow-up has been less than 5%(32, 33). Higher rates of progression to cirrhosis are also seen with moderate or heavy alcohol consumption (25)and in immunocompromised patients with HIV co-infection or with chronic immunosuppression following organ transplantation(32). Neither viral load nor HCV genotype have been found to be predictors of rate of progression to cirrhosis (25, 32, 34, 35) but male gender increases risk of both cirrhosis and HCC. Overall, rates of cirrhosis among patients with chronic hepatitis C who are referred to referral centers is in the 20-25% range(17).Because of wide individual differences in rate of liver disease progression, the best predictor of future risk of liver disease complications in an individual patient is not the viral load, the HCV genotype or even the current ALT level, but rather is the stage of fibrosis present on a recent liver biopsy(17).

A variety of histological staging systems have been devised to assess degree of fibrosis and follow rate of fibrosis progression in patients with chronic hepatitis C. The staging systems most commonly used are the Metavir or the Batts-Ludwig systems that produce scores ranging from stage 0 (no fibrosis) to stage 4 (cirrhosis)(17). Many large series assessing stage of fibrosis in patients with known duration of infection or rates of progression of fibrosis in patients with multiple liver biopsies indicate that, in non-alcoholic patients, there tends to be steady progression of fibrosis at a rate of about 0.1 Metavir fibrosis units per year among patients infected as young adults (see figure 4)(25, 32, 35). However, fibrosis progresses at a much higher rate in patients infected later in life and is estimated to progress at rates as high as 0.3 fibrosis units per year in men infected after age 40(25, 35). Thus, by estimates derived from one

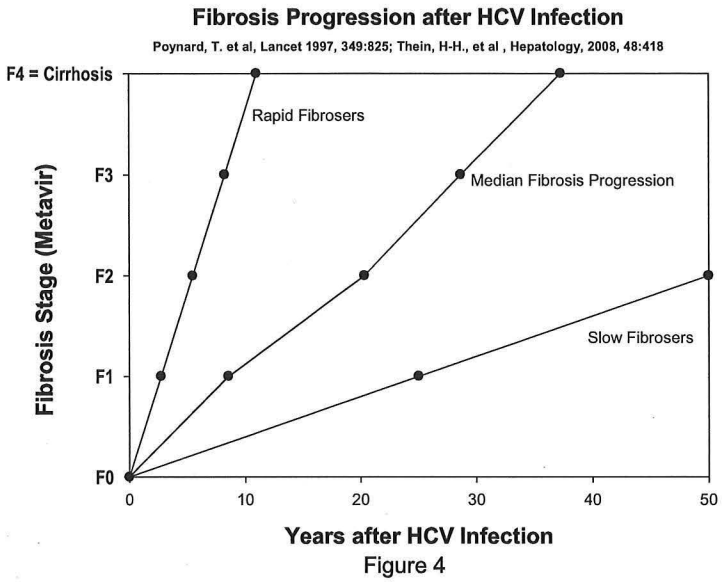


Figure 4

of these studies, men infected at age 20 and age 53 will each, on average, develop cirrhosis at age 70(25). As about half of patients develop either hepatic decompensation or hepatocellular carcinoma within 10 years of diagnosis of cirrhosis(36), these estimates imply that, in industrialized countries where median life expectancies of 78-83 years are now observed, approximately 50% of individuals currently infected with HCV will develop liver disease complications in the course of their life.

However, rates of progression observed among individual patients vary widely and the progression rates documented in large studies are not normally distributed (25, 34). It is estimated that approximately 1/3 of HCV infected patients have very slow rates of fibrosis progression and will never develop cirrhosis (25, 34). On the other end of the spectrum are the approximately 33% of patients with rapid progression rates(25). Among this latter group of rapid fibrosers, up to 50% are estimated to develop cirrhosis within 20 years of infection(25). This concept of a cohort of rapid fibrosers is also supported by the observed epidemiology of HCV associated liver diseases in the U.S. where HCV associated liver failure or hepatocellular carcinoma became common indications for liver transplantation within 20-30 years after onset of the U.S. HCV pandemic(3, 13).

Therapy of Chronic Hepatitis C, the First Two Decades

Some patients with HCV infection and minimal hepatic fibrosis will develop systemic non-hepatic complications such as mixed essential cryoglobulinemia that may lead to renal, rheumatologic or skin complications(37). However, the vast majority of life threatening complications in HCV infected patients are due to chronic liver failure or hepatocellular carcinoma; complications that typically develop 5-10 years after development of cirrhosis(3, 36). For these reasons, it is the anticipated time to development of cirrhosis that most commonly guides clinical decision making regarding need for and urgency of anti-viral therapy. Furthermore, in an era when all therapies have significant side effects, practice guidelines and consensus conference summaries reviewing indications for anti-viral therapy of chronic hepatitis C have consistently advised against treating patients with less than Metavir stage 2 fibrosis and have only strongly encouraged immediate therapy of patients already exhibiting bridging fibrosis (Metavir/Batts-Ludwig stage 3) or compensated cirrhosis (Metavir/Batts-Ludwig stage 4)(3, 17).

During the same time interval in which scientists at Chiron Corporation were cloning and sequencing the HCV genome and developing the first diagnostic tests for HCV infection, early studies of recombinant type 1 interferon therapy of chronic hepatitis C were initiated(38). Several years later the initial studies of ribavirin therapy of this disease were reported(39). Over the subsequent two decades, combination therapies employing ribavirin and recombinant interferon alfa 2a/2b/consensus have been steadily optimized and much has been learned about the benefits of therapy as well as the multiple side effects of these two antiviral agents. From 2001 to early 2011, the standard of care therapy has been a combination of pegylated

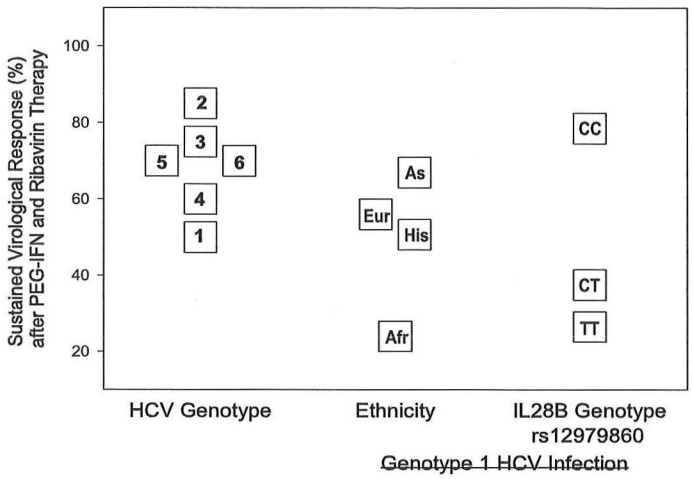


Figure 5

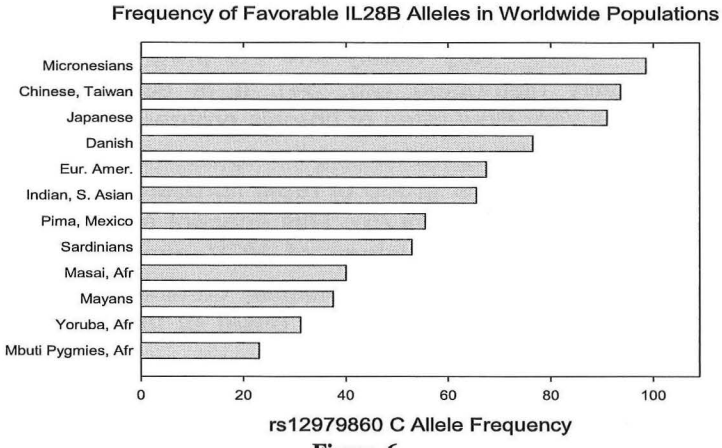


Figure 6

interferon alfa with ribavirin for 24 to 48 week courses (3, 40, 41). Early in the era of interferon based therapy of HCV infection, it was appreciated that responses differed greatly depending on the HCV genotype responsible for infection (see figure 5)(3, 42, 43). Later in this era it became increasing apparent that efficacy of therapy for interferon resistant genotype 1 subtypes varied widely among ethnic groups (40, 41, 44). More recently, ethnic differences in response rates have been found to relate largely to differences in allele frequency of polymorphisms of IL28B (interferon λ3, a type III interferon) among different human populations (see figure 6)(45). The favorable rs12979860 IL28B CC genotype associated with a 2-3 fold higher rate of SVR after interferon based antiviral therapy is also associated with a 2 fold greater rate of resolution of acute HCV infection(27, 28, 45). Thus, current populations of patients with chronic HCV are enriched in individuals with the unfavorable rs12979860 IL28B CT or TT genotypes.

As early as 1992 reports appeared indicating that at least a subset of patients completing courses of type I interferon based therapy were observed to lose all detectable HCV RNA during therapy and then remain persistently HCV RNA negative after therapy(46). Most such individuals were observed to have persistently normal serum ALT levels post-therapy, and when post-therapy liver biopsies were performed, liver histology was observed to be improved or without evidence of further progression(46, 47). Achieving a sustained virologic response (SVR), defined as a negative HCV RNA 24 weeks after completion of therapy has been shown to be the best predictor of long term benefits from therapy (see Table 1) and is now considered to represent a resolution of infection or "cure" as >99% of such individuals remain HCV RNA negative during long term follow-up(46). In addition, individuals who achieve an SVR before organ transplant do not relapse following institution of immunosuppressive therapy(48). Thus, unlike hepatitis B infection which leads to production of cccDNA copies of the virus that survive for decades in the liver; or HIV, a retrovirus capable of incorporating copies of viral sequence in host DNA; HCV, as an RNA non-retrovirus, has no ability to persist in a long-term latent phase following successful anti-viral therapy or successful host immune responses(14, 49). Despite the fact that many of the chronic hepatitis C patients undergoing anti-viral already have significant intra-hepatic fibrosis and some are already cirrhotic, those that achieve an SVR achieve multiple clinical benefits as detailed in Table 1(47).

Table 1
Benefits of Sustained Virologic Response to Antiviral Therapy for Chronic Hepatitis C
Aggregated Results of Studies Summarized by Ng, et al, Clin. Gastro. Hepatol. 2011, 9:923-930

	Mean Follow-up, Yrs	SVR group	Non-SVR Group
Undetectable HCV RNA	2.3-6.8	> 99%	< 1%
Disease Progression / Decompensation			
All Stages Fibrosis	3.7-8.5	3%	15%
Advanced Fibrosis, Pre-Therapy	2.5-8.5	5%	69%
Hepatocellular Carcinoma Occurrence			
All Stages Fibrosis	3.1-8.0	4%	12%
Advanced Fibrosis, Pre-Therapy	3.5-9.8	6%	21%
Liver Related Mortality			
All Stages Fibrosis	5.4-7.4	0.3%	3.7%
Advanced Fibrosis, Pre-Therapy	2.1-9.8	1.5%	10%

. Unfortunately, many patients never become HCV RNA negative during therapy, and are thus non-responders. Alternatively, patients may become HCV RNA negative during therapy but then during the first 12-24 weeks after discontinuation of therapy are observed to have increased ALT levels and once again detectable serum HCV RNA and therefore have "relapsed"(3). Early in the course of antiviral therapy it was recognized that patients who either have a less than 100-fold (2 log, base 10) decline in HCV levels during the first 12 weeks of therapy or fail to become HCV RNA negative within the first 20-24 weeks of therapy, have a < 5% chance of achieving an SVR and thus discontinuation of therapy is recommended(41, 50).

Over the past 10-15 years, attempts to decrease morbidity from side effects by identifying the shortest optimum course of therapy or to improve therapeutic outcome by extending duration of therapy have led to identification of different optimal durations of therapy for different HCV genotypes(3, 51). Thus, 48 week courses are recommended for interferon resistant genotypes 1 and 4 with shorter 24 week courses of therapy recognized as sufficient for genotypes 2, 3 and possibly 6(3, 42). Furthermore, when individual rates of response to therapy are closely monitored, response guided therapy (RGT) can be used to better predict therapeutic outcomes and to further optimize duration of individual courses of therapy(51). Thus, while overall SVR responses to pegylated interferon and ribavirin therapy for genotype 1 infections in European ancestry individuals is approximately 50%, if such patients achieve a rapid virologic response (RVR) by becoming HCV RNA within 4 weeks on therapy, their prospects for SVR are approximately 90% following 48 weeks of therapy with minimal loss of efficacy if therapy is abbreviated to a 24-28 week course (86-88% SVR rates)(51). Conversely, if genotype 1 HCV infected patients are slow virologic responders and do not become HCV RNA negative until after 12 but before 24 weeks of therapy, SVR rates are only about 25% but may be modestly increased if therapy is prolonged to 72 weeks(51). Of note, HCV genotype 1 infected patients who have the favorable IL28B rs1297978600 CC genotype are much more likely to achieve an RVR (25-30%) than those patients with the CT or TT genotype (5-10% RVR rates)(51). Thus, a CT or TT IL28B genotype identifies before therapy, those who will need more prolonged courses. In contrast, on therapy interferon response phenotype contributes further insight into therapeutic outcomes and guidance regarding optimal length of dual interferon and ribavirin therapy.

Similar effects of response "phenotype" are seen in HCV genotype 2 or 3 patients with RVR patients achieving 85-90% SVR rates after 12-24 week courses of therapy while patients who fail to achieve SVR rates only exhibit 25-30% SVR rates after 24 weeks of therapy(3, 52).

However, a much larger fraction (> 75%) of all genotype 2 or 3 patients achieve RVR on PEG-Interferon and ribavirin based therapies than is observed during treatment of genotype 1 patients (< 15% achieve RVR).

Development of Direct Acting Antiviral (DAA) Drugs for Therapy of Chronic Hepatitis C

Improved understanding of the HCV viral life cycle facilitated by the development of in vitro models of replication has led to the development of an ever increasing number of direct acting antiviral (DAA) drugs that target known steps in viral replication, enzymatic cleavage of the viral proteins or other necessary functions of HCV proteins(49, 53). The potential protein targets for DAA drugs are outlined in Table 2. The first of these new drugs to receive FDA approval and become widely available for therapy are two linear, NS3/4A serine protease inhibitors, boceprevir and telaprevir(54-60). Each of these agents, when used as monotherapy for genotype 1 HCV infection, induces potent inhibition of viral replication with rapid decline in viral load over the first 1-7 days followed by rapid selection of resistance variants(17, 49). The most common resistance mutation, R155K, occurs after a single (AGG→AAG) nucleotide change in the HCV genotype 1a sequence but requires a two nucleotide (CGG→AAG) change in genotype 1b sequences (54). Likely for this reason, at each stage of clinical trials, viral breakthrough due to resistance mutations has occurred more frequently in patients with genotype 1a infections. Combining either protease inhibitor with PEG-IFN and ribavirin limits selection of resistant variants and is associated with higher SVR rates than observed with prior standard of care dual PEG-IFN and Ribavirin therapy (see table 3)(54-60) or ribavirin free regimens of PEG-IFN plus protease inhibitor. As drugs specifically designed to target difficult to treat genotype 1 HCV infections, some NS3/4A protease inhibitors exhibit activity only against genotype 1 infections without effect on replication of either genotype 2 or 3(49). In limited clinical trials, telaprevir appears to also have potent antiviral activity against genotype 2 but not genotype 3 HCV infections(61). However, at this time both of the licensed NS3/4A serine protease inhibitors are only approved for use in genotype 1 HCV infected patients(3).

Table 2
Multiple New Drug Candidates for Treating Hepatitis C Infection in 2011
Abstracted from Nature 2011, 474:S5-S7 and 2011 Annual Meeting, AASLD

Class/Target	Approved, 2011	Examples in Phase II/III	Estimate #
Direct-Acting Antiviral (DAA)			
HCV NS3/4A Protease			18
Linear	Telaprevir, Boceprevir	BI-201335	
Macrocyclic		TMC 435	
NS5A Replicase		Daclatavir (BMS-790052)	14
NS5B Polymerase			
Nucleoside		PSI-7977	9
Non-Nucleoside		BI207127	13
Host Targeted Agents			
Cyclophilin		Alisporivir	3
Immunomodulatory		PEG-Interferon λ1a	2
Caspase		IDN-6556	1
Host Proteins in Viral Fusion			4
Protein Kinase R (PKR)		Nitazoxanide	1

The enhanced efficacy of new triple drug antiviral regimens is most dramatic for previously difficult to treat patient populations such as African Americans, patients with unfavorable

rs1297978600 IL28B CT or TT genotypes or those previously treated patients with only partial responses (> 2 log drop in viral load by week 12 but never HCV RNA negative) or with relapse

Table 3
Sustained Virologic Responses after Triple Therapy of Genotype 1, Chronic Hepatitis C

Patient Population	Boceprevir/PR	PR Control	Telaprevir/PR	PR Control
Treatment Naïve, SVR:				
Overall	63%	38%	75%	44%
Non-African American	67%	41%	79%	48%
African American	42%	23%	58%	25%
IL28B CC	82%	78%	90%	64%
IL28B CT	65%	28%	71%	25%
IL28B TT	55%	27%	73%	23%
Prior Therapy, SVR:				
Relapser	75%	29%	86%	22%
Partial Responder	52%	7%	59%	15%
Null Responder	NA	NA	32%	5%
Severe Adverse Events:	10-15%	8%	9-15%	7%
Adverse Events More Frequent with Triple Rx	Anemia Dysguesia		Rash, Anemia Anorectal	

P=Pegylated Interferon alfa, R=Ribavirin

after initial on therapy response (see table 4)(17). In each of these patient populations, use of protease inhibitor containing triple drug regimens doubles or triples the rates of response seen with prior PEG-IFN and Ribavirin regimens(17). Among treatment naïve patients with favorable IL28B rs1297978600 CC genotypes, triple therapy regimens add little to overall therapeutic efficacy and, because of much higher drug cost (AWP of Incivek/telaprevir $49,000) may be viewed as non-cost effective(17). However, as detailed in table 4, such individuals will, in most cases achieve very high SVR rates after only 24-28 week courses of therapy and thereby avoid the additional side effects of PEG-IFN and Ribavirin that occur during the last 20-24 weeks of 48 week PEG-IFN and Ribavirin regimens(17).

Table 4
Many Genotype 1, Chronic Hepatitis C Patients are Eligible for Abbreviated Courses of Response Guided Therapy with Protease Inhibitor, PEG-Interferon and Ribavirin

	Boceprevir/PR RGT (% 28 week)	Telaprevir/PR RGT (% 24 week)
All Treatment Naive	50	65
Non-African American	54	68
African American	20	47
IL28B CC	89	78
IL 28B CT/TT	52	57/45

P=Pegylated Interferon alfa, R=Ribavirin, RGT=Response Guided Therapy

The patient subgroup with the lowest SVR rate after 48 weeks of triple drug therapy are those patients who have exhibited a null response to interferon defined by a < 2-log decline in baseline viral load after the first 12 weeks or a < 1 log decline after 4 weeks of PEG-IFN and Ribavirin therapy. Only 32% of prior interferon null responders achieved SVR after 48 weeks of therapy with PEG-IFN and Ribavirin therapy supplemented with 12 weeks of telaprevir therapy(54). Because of drug – drug interactions and insufficient clinical experience, these DAA's are not approved thus far for use with HAART in HIV/HCV co-infected patients. In addition, since the recently approved DAAs are only approved for use with both PEG-IFN and Ribavirin there are many categories of HCV mono-infected patients who are not eligible for these new therapeutic regimens(3, 17). Such patients include patients with contraindications to ribavirin (those who are pregnant or have advanced CKD) or with contraindications to type I interferon therapy such as autoimmune disease, uncontrolled depression or other psychiatric illness, decompensated liver disease (Child Turcotte Pugh Score > 6), or decompensated cardiac or pulmonary diseases(3, 17).

Both new DAAs are associated with drug induced side effects over and above the protean side effects observed with PEG-IFN and Ribavirin therapy (see Table 3)(17). While serious, grade 3 and 4 adverse events and or adverse events leading to therapy discontinuation occur in only about 10-15% of patients, side effects of moderate severity afflict a much higher percentage of patients. Thus, approximately half of patients on Telaprevir containing regimens experience skin rashes and pruritus, 36% have anemia with Hgb < 10 g/dl (vs. 17% on PEG-IFN and Ribavirin alone) and 25-30% will experience various forms of anorectal discomfort. Fatal or life-threatening cases of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Stevens - Johnson syndrome have been reported but fortunately occur in < 1% of individuals(17). The cumulative incidence of anemia (50% with Hgb < 10 g/dl) and neutropenia (25%) is higher for Boceprevir containing regimens than control regimens as is the incidence of dysgeusia (35-44%), but the incidence of skin rash is no higher than for PEG-IFN and Ribavirin (15-20%)(17). In both triple therapy regimens the interferon induced side effects of fatigue (50-60%), insomnia and irritability (20-35%) continue to be common as is the risk of depression(17).

Thus, while recently approved HCV NS3/4A protease inhibitor containing regimens are more effective for genotype 1 infection than prior regimens, such therapy is associated with myriad side effects and fails to achieve an SVR in a significant fraction of patients. For these reasons, while practice guidelines advocate use of these agents as the standard of care in genotype 1 HCV infected patients with significant evidence of progressive liver disease(17), use of triple drug therapy in patients with less severe liver disease (stage 2 fibrosis) is a subject of debate and clinical judgment and use in patients with stage 0-1 fibrosis is felt to be contraindicated(17, 62). The rationale for deferring antiviral therapy of genotype 1 patients with less than stage 3 (bridging) fibrosis is based on expectations that by 2014-2015 improved antiviral regimens will be available. As detailed in table 2, there are > 50 new antiviral agents in various stage of development for therapy of chronic hepatitis C(53).

Several additional NS3/4A serine protease inhibitors already have demonstrated apparent advantage over current DAAs in Phase II or preliminary Phase III trial data due to improved pharmokinetics allowing once daily administration, improved efficacy (SVR rates > 80% when added to PEG-IFN and Ribavirin regimens), fewer side effects and/or somewhat higher barriers to viral resistance (macrocyclic structure)(53). In addition, two categories of drugs not yet on the market, nucleoside inhibitors of the HCV NS5B viral polymerase and inhibitors of the human cyclophilin proteins required for viral replication, appear to have exceptionally high barriers to viral resistance(53, 63). Furthermore, a unique, inhibitor of the HCV NS5A replication complex

has been reported to have unprecedented efficacy in treatment of genotype 1 HCV infected individuals with prior null response to interferon containing regimens(64-66).

In contrast to the < 35% SVR rate observed with use of currently available triple drug regimens in therapy of HCV genotype 1 null responders, inclusion of the NS5A replication complex inhibitor Daclatasvir (BMS-790052), in a quadruple drug regimen also utilizing PEG-IFN, Ribavirin and a NS3/4A protease inhibitor (BMS-650032) achieved SVR in 10/10 null responder patients (9 genotype 1a, one 1b) in a small pilot study initially reported by Lok, A, et al at the EASL annual meeting in the spring of 2011(64). Another 11 patient arm in this trial was treated with a two-drug, interferon free regimen containing only Daclatasvir and the BMS-650032 NS3/4A protease inhibitor. This interferon free protocol achieved SVR in 2/2 genotype 1 b null responders and 2/9 genotype 1a null responders (see Table 5). This dual DAA regimen was repeated in another small, 10 patient phase II study enrolling genotype 1b infected Japanese null responders to prior interferon based therapy(65). 9/9 patients completing a 24 week course of Daclatasvir (BMS-790052) + NS3/4A protease inhibitor (BMS-650032) achieved an SVR. The 10th patient discontinued therapy after 8 weeks due to elevated liver enzymes but was still HCV RNA negative 24 weeks later. Thus, while much larger phase III studies must be completed to assess the full side effect and efficacy profile of these new DAAs, these early experimental results indicate that sustained virologic responses can be achieved in even highly interferon resistant patients with use of interferon free, two drug oral DAA regimens.

Additional studies assessing efficacy of interferon-free regimens, have used a uridine analog, nucleoside polymerase inhibitor, PSI-7977 in combination with ribavirin in 12 week interferon free regimens in therapy naïve genotype 2 and 3 HCV infected patients(67, 68). Two different groups of investigators have now completed treatment of a total of 35 patients in prospective 12 week trials of this two drug regimen and have reported the results in abstract format at the 2011 EASL(68) and the 2011 AASLD meetings(67), respectively. One patient was lost to follow-up after day 1 of the protocol. All 34 remaining patients completed the 12 week therapeutic protocol and achieved an SVR. Even more impressive is the very low rate of side effects reported in patients receiving these interferon free regimens and the absence of any detected viral breakthrough/resistance in patients taking only PSI-7977 and ribavirin(67). PSI-7977 has also exhibited efficacy in treatment of genotype 1 HCV infection(69). In another phase II study in which PSI-7977, 400 mg per day was added to PEG-IFN and Ribavirin for therapy of genotype 1 HCV infection in a 24 week protocol, 98% of patients completing at least 8 weeks of therapy and 43 of 47 patients overall achieved an SVR (69). In this study, no adverse events occurred at a higher rate in the triple drug arm than in the dual PEG-IFN and Ribavirin therapy arm and once again, no evidence of viral breakthrough or resistance to PSI-7977 was observed.

Table 5
Results of Phase II Studies Demonstrating Eradication of
HCV Infection following Interferon-Free Antiviral Therapy

DAA Regimen	Genotype, Rx History	# Enrolled	# with SVR
Daclatasvir (BMS-790052) + BMS-650032 X 24 wks (64, 65)	1a, Non-Responder	9	2 (22%)
	1b, Non-Responder	11	11*(100%)
PSI-7977 + Ribavirin X 12 wks (67, 68)	2 or 3, Naive	35	34 (97%)

*One patient discontinued therapy after 8 weeks but remained HCV RNA free > 24 weeks later

Pharmasset, Inc., the small 80 employee company that discovered and developed PSI-7977 announced the initiation of large, phase III trials of PSI-7977 + ribavirin therapy of genotype 1, 2 and 3 HCV infections in November, 2011 with expressed hope of marketing this drug in 2014. Later the same month, Gilead Sciences, Inc. announced an agreement to purchase Pharmasset and the patent rights to PSI-7977 for nearly $11 Billion(70).

Thus, after 2 decades of HCV antiviral therapy based on only two classes of relatively non-specific drugs, a large number of new DAA and non-DAA drugs are entering late phase clinical trials. The first two DAA drugs to be approved already offer significant therapeutic advantage for genotype 1 infected patients with advanced fibrosis and in relatively urgent need of therapy. For patients and their physicians who wish to defer therapy of less advanced disease, results of phase II studies have produced abundant promise of even more effective, 12-24 week, interferon free oral regimens. Once highly effective interferon free DAA regimens with minimal side effects are approved for marketing, it is predicted that the spectrum of patients who are candidates for therapy will expand greatly to include most of the patients currently excluded from therapy by contraindications to interferon or ribavirin use. In addition, the CDC has recently submitted for peer review(7) a proposal to add the entire 1945-1965 U. S. birth cohort to the list of persons who should be routinely tested for HCV infection. It is estimated that less than half of HCV infected persons know of their infection and/or have pursued medical care(5), and less than half who are diagnosed have received therapy(71). Therefore, such universal screening, if adopted has the potential to identify an even larger population of HCV infected individuals who might benefit from therapy.

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