Therapy of Hepatitis C: Clinical Application and Drug Development

The burden of hepatitis C is increasing in both developed and developing countries and there is an urgent need to improve the detection of people infected with the virus and to improve access to effective treatment to reduce mortality from chronic infection, warned leading experts at a recent EASL/AASLD special conference on hepatitis C therapy attended by more than 800 clinicians and researchers from around the world.

Professor Heiner Wedemeyer (Hannover Medical School, Germany), a member of the organising committee, said:

“This meeting is extremely important and timely as the use of current therapy and development of novel therapies is very challenging. Our review of the ‘state of the art’ across all aspects of hepatitis C will have a major impact on the development of treatment guidelines, clinical trial design and reimbursement policies. One key discussion point is the question if and when interferon-free treatment regimens will become available, which may change the entire landscape of HCV treatment. We are in a time of complete paradigm shift as to how to treat chronic hepatitis C.”

“HCV is a major global health issue and the worldwide prevalence is increasing,” warned Dr. Steven Wiersma, from the Tanzania Field Study, Centers for Disease Control. He reported on a systematic review and model-based meta-analysis of all studies reporting prevalence of antibodies to hepatitis C.

• Results showed that number of people testing positive for anti-HCV antibody increased from 2.3% (> 122 million) in 1990 to 2.8% (> 195 million) in 2005.

• Regions with particularly high rates of anti-HCV+ included North Africa and the Middle East, where rates were over 3.5%.

He cautioned that this is a conservative estimate, and the true prevalence is likely to be even higher. Previous World Health Organization (WHO) figures based the burden only on acute HCV infection. “But the major burden is the sequelae of chronic infection, including cirrhosis and premature deaths,” he said, calling for more resources to be allocated to HCV prevention and treatment based on its global impact.
Intravenous (IV) drug use remains the major route of HCV transmission in North America and Europe, with studies showing prevalence rates of 60-80% in current and former IV drug users. “There is an ongoing high rate of new HCV infections in IV drug users, particularly in the first year of drug use where the rate is 6-39% in European countries,” Professor Thursz reported. Healthcare-associated transmission is the major route of HCV in less economically developed countries, with one of the major risks being re-use of needles and syringes by medical practitioners and blood transfusions also being a common cause of infection. This results in very high HCV prevalence in many developing countries. “We need to improve healthcare practices to reduce this burden,” Professor Thursz said.

If all countries used screening alongside the deployment of new treatments, hepatitis C could be halved, according to a modeling study in six European countries reported by Sylvie Deuffic-Burban, INSERM, Lille, France. She concluded that new treatments that can reduce transmission of HCV and therefore reduce the burden of HCV disease might save costs in the long-term.

“Hepatitis C is currently the only form of hepatitis with no prophylactic vaccine that can prevent infection,” pointed out Dr. John Ward, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention, Centers for Disease Control, USA. “Despite a reduction in incidence, transmission continues and may even be increasing, based on CDC reports with a second-wave or people aged 15-24 affected, due to injection drug use,” he said. “And healthcare-associated infection accounts for 40% of cases globally.” Dr. Chris Walker, Ohio State University, USA, summarised the challenges and current status of HCV vaccine development. He reported that first phase II trials are now underway.

The role of peg-interferon/ribavirin in 2012 and beyond

Peg-interferon/ribavirin without direct antiviral agents has a limited role in treating HCV in the future, predicted Professor Geoffrey Dusheiko, University College London, UK. Tracing the use of recombinant interferon-alpha in HCV since its first approval in 1991, he noted that developing pegylated interferon-alpha improved the pharmacokinetics and pharmacodynamics and that adding ribavirin increased the rate of SVR from 20% to 40-50%. “But there is considerable variation in patient response and despite years of use we still don’t understand the precise mode of action,” he said, adding that side-effects and contraindications make it a difficult drug for some patients.

Despite its limitations, Professor Dusheiko considered that the last two decades of experience with interferon in HCV has provided many important therapeutic lessons for developing therapies in the future. The first is that SVR equates to cure, establishing this as the goal for HCV therapy. “Most importantly, the idea that you can cure HCV has paved the way for direct antiviral agents.” Use of interferon has also showed the importance of preventing the progression of fibrosis in HCV. He suggested that it is likely to continue in two settings: in IFN-sparing regimens and in quadruple IFN-containing regimens.
One year of triple combination therapy

How effective is new triple combination therapy - adding a protease inhibitor to INF and ribavirin - in clinical practice? 

Dr. Paul Kwo, Indiana University, USA, reviewed trial results and clinical experience. “Both boceprevir and telaprevir have dramatically improved SVR compared to interferon/ribavirin,” he told the meeting. The ADVANCE study showed a marked improvement in SVR adding telaprevir compared to control (75% vs 44%) and SPRINT-2 showed a 28% increase in SVR adding boceprevir to IFN+RBV. He suggested that all HCV patients are potential candidates for triple therapy but careful monitoring is needed in those with advanced fibrosis who are more at risk for treatment-related adverse events.

What is the frequency and severity of HCV therapy side-effects in real life clinical practice? 

Dr. Christophe Hézode, Hôpital Henri Mondor, Créteil, France, warned that the safety record of triple therapy is poor but this has to be balanced against its good virologic response. “The majority of patients should be treated, but cautiously,” he suggested. Particular care is needed in patients with high-risk complications, including cirrhosis - with the French real-life CUPIC study of telaprevir in patients with HCV and cirrhosis showing severe adverse events in 48.6% of patients. He noted that life-threatening complications such as severe infection are not uncommon in patients with advanced cirrhosis and that 2-3% of this highly selected cohort died during treatment.

Drug-drug interactions are emerging as a major issue with the array of new agents being developed for the treatment of HCV – particularly those affecting the cytochrome enzymes that metabolise many commonly prescribed medicines. Professor David Back, University of Liverpool, UK, suggested that clinicians need to be aware of these interactions and resources developed to alert people to potential drug interactions and provide advice on their management.

Drug interactions with IFN/ribavirin were limited, but the introduction of direct acting antiviral agents has greatly increased the problem. Professor Back suggested that clinicians need data on key drug interactions for HCV patients, inviting people to add data to a website he has developed to share information on this (www.hep-druginteractions.org).

HIV-HCV co-infected patients – even in the HAART era – show faster progression to cirrhosis and increased liver-related mortality compared to HCV patients without HIV, warned Professor Juergen Rockstroh, University of Bonn, Germany. “Unfortunately, only about 25% of co-infected patients in European cohorts and 11% of the VA cohort in the US ever receive HCV treatment,” he reported. “There is a tremendous need to improve treatment in this challenging patient population.”

The role of triple therapy in other special patient populations, including pre- and post-transplant, haemodialysis and immunosuppressed patients, is currently unclear because of lack of data, said Dr. Xavier Forns, Barcelona, Spain. SVR is lower in patients with cirrhosis, but he argued that it is worth aiming for undetectable virus levels before transplantation. Drug-drug interactions pose a further challenge in post-transplant patients.

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Looking to the future for HCV therapy

Multiple targets for new direct and indirect acting antivirals against HCV are emerging with a growing understanding of the HCV life cycle, suggested Professor Darius Moradpour, Switzerland, as he took delegates on a tour through the virus’ replication pathway. “Each step offers a new target for drug development, giving us a very rich pipeline.” After a slow start in HCV research because researchers were unable to culture the virus in vitro for many years and there is no easily available animal model recent years have seen ‘fantastic breakthroughs’ he said. Understanding of the HCV life cycle has enabled the development of agents targeting viral entry into the cell, translation of the viral genome into proteins and viral assembly and release.

Sustained virologic response in HCV translates into both short- and long-term benefits, according to the longest follow-up study yet to assess treatment. Dr. Chris Koh, from the Liver Diseases Branch at NIDDK-NIH, Bethesda, USA, reported results from the study of the first 103 patients achieving SVR treated at the centre with interferon+-ribavirin, starting in 1984. They were followed for up to 22 years after SVR with non-invasive markers of disease activity and fibrosis. Results showed that 94% of patients maintained a virological response and markers of liver disease improved over time. Only three patients relapsed, giving a 10-year relapse rate of 5.7%. The study was one of more than 100 abstracts reporting original data during the conference.

Delineating the mechanism of viral clearance in HCV is an important part of understanding how relapse might occur after treatment. “HCV infection is curable because it’s dependent on the continuous presence of a metastable membrane-bound replication complex,” Professor Stanley Lemon, University of North Carolina at Chapel Hill, USA, explained during an update on mechanisms of HCV clearance. Other viral infections, such as HIV and Herpes simplex, archive genetic material in cell nuclei but this does not happen with HCV. The mechanisms that stop the virus spreading include adaptive immunity, innate immunity achieved by natural killer cells and interferon alpha, beta and lambda responses, reduced viral fitness and cellular RNA decay pathways.
New HCV drugs in development

“We have come a long way with interferon treatment since it was first introduced in 1991 to the use of pegylated interferon as part of triple HCV therapy today. Some are predicting therapy will be interferon-free. But we need all the tools we can get to improve the management of HCV and novel interferons and IFN inducers may have an important role in some patient subgroups,” said Dr. Michael Manns, Medical School of Hannover, Germany. He suggested that interferon-based therapies have several potential advantages compared to direct antiviral agents:

• No viral resistance
• Comparatively low cost
• Vast clinical experience
• Potential use in other viral infections such as HBV.

For the future, INF-based therapy may be appropriate for easy to treat patients, but new interferons have to be developed that are much safer and better tolerated than current options.

Newer NS3/4A protease inhibitors in combination with peg-IFN and ribavirin achieve high rates of SVR with simpler dosing schedules and generally better tolerability than older agents, according to Dr. Michael Fried, University of North Carolina, USA. He said that two years of clinical experience with the currently available PIs have shown that ribavirin is required for achieving SVR, rapid virological response is associated with highest SVR and adverse events can generally be managed but that certain populations are less responsive. New PIs in development include simeprevir and faldeprevir (phase 3) and asuneprevir and ABT-450/r (phase 2), mostly with peg-INF + RBV backbone. Trials so far show encouragingly high rates of SVR and generally good tolerability, but we have to wait for more data, he concluded.

“It’s becoming clear that nucleoside/nucleotide analogues provide a very strong backbone for future HCV therapies,” argued Dr. David Nelson, University of Florida, USA. They work by causing premature chain termination during viral nucleic acid synthesis. The active binding site in the target – NS5B RNA-dependent RNA polymerase – is highly conserved across HCV genotypes, conferring pangenotypic activity and there is a high barrier to resistance. Three agents are currently in development: sofosbuvir (phase 3), mericitabine (phase 2) and ALS-2200 (phase 2), while some others have been put on hold due to toxicity.

“Sofosbuvir (previously GS-7977) will be the most important compound during the next 2-4 years,” predicted Professor Wedemeyer. He noted that sofosbuvir therapy was successful in various IFN-free regimens and may also help to shorten IFNa-based therapies. “However, we have learned over the last few months that there will be no ‘one-size-fits-all’ regimen with sofosbuvir.”

Non-nucleoside inhibitors of HCV RNA polymerase have no role in monotherapy and limited role in triple therapy, but they may be useful in quadruple therapy, suggested Dr. Paul Pockros, La Jolla, USA. Reviewing the available data, he noted that these agents have low to moderate potency, a low barrier to resistance and are unlikely to have cross-genotype activity. “Of the 13 non-nucleoside inhibitors in development in 2008, a lot have given disappointing results, with only six remaining,” he said. Of these, Vx-222 is the most potent, achieving a 3.4 log10 reduction in viral load (at a dose of 400mg bid) and is currently in phase 2. However, some compounds may still be used in IFN-free treatment regimens if combined with other highly potent DAA.
Cyclophilin inhibitors offer the benefits of a high barrier to resistance and no cross-resistance with protease or polymerase inhibitors. Professor Robert Flisiak, Medical University of Białystok, Poland, told the meeting. They act on NS5A, NS5B and NS2 HCV viral proteins, as well as preventing HCV-mediated mitochondrial and endogenous interferon production.

Alisporivir – the most advanced agent in the class – has shown effects in treatment naïve, previous non-responders and in HIV/HCV co-infected patients. It has demonstrated antiviral efficacy against the four most prevalent genotypes (1, 2, 3 and 4). It is effective in interferon-free regimens, as well as providing additional antiviral effects in combination with peg-interferon plus ribavirin, and is well tolerated. However, it is currently on hold due to toxicity in combination with PEG-IFNa. Future trials may therefore focus on IFN-free regimens including alisporivir.

Entry inhibitors, which block the entry of HCV into cells, are at an early stage of development but proof of the concept has been demonstrated in cell culture and in vivo models, reported Professor Thomas Baumert, University of Strasbourg, France. They are pangenotypic, prevent infection with escape variants and provide a complementary mechanism of action of direct antiviral agents, demonstrating marked synergy. "They offer a very attractive antiviral strategy for the prevention of liver graft infection in patients who have undergone transplantation, as well as for difficult to treat patients and those with multiresistance," he suggested.

New HCV drugs in development continued...

Therapeutic vaccines represent a scientifically valid approach to treating HCV but there is a long way to go to optimise vaccine response, suggested Professor Heiner Wedemeyer. He questioned whether vaccines for HCV are needed at all, with all the new drugs currently in development, but suggested several reasons why they may be useful. “First, HCV is not HIV,” he pointed out. “Immune control of HCV is possible, in contrast to HIV infection.” Clinical observations show – quite remarkably – that 10-50% of cases of acute hepatitis C are cleared without treating, suggesting a major role for the immune system.

Combinations including NS5A inhibitors appear likely to address many of the current unmet medical needs in HCV, especially for patients who remain difficult to treat with currently available therapies, including those with cirrhosis and patients undergoing liver transplant, according to Dr. Stanislas Pol, Hopital Cochin, France. Reviewing the data with daclatasovir, the first agent in the class, he said it is very potent, has broad genotypic coverage and has a pharmacokinetic profile supportive of once daily dosing, making it easy to take. A recent study with quadruple therapy including daclatasovir, asapavir and peg-interferon/ribavirin has shown ‘fantastic results,’ he said, with SVR4 of 90-100% in a difficult to treat group of genotype 1 null responders. Moreover, NS5A inhibitors are part of many IFN-free treatment regimens.
Overcoming resistance and treatment failure

“Treating HCV is a very simple process. We simple have to block virus production, which requires drugs with high potency, and then maintain inhibition for the full duration of treatment, avoiding the emergence of resistant strains,” said Professor Jean-Michel Pawlotsky, University of Paris-Est, France. “The development of resistance in HCV is less of an issue compared to other viruses such as HIV, but we still need to prevent its emergence.

“We have drugs with the necessary potency. How do we use the right combinations to ensure a high barrier to resistance?” He suggested the best approach may be to combine an agent with a low barrier to resistance with one with a high barrier. Direct acting antivirals with a high barrier to resistance include:

- Nucleoside / nonnucleoside analogues, cyclophilin inhibitors
- NS5A inhibitors (1b)
- Second generation protease inhibitors
- NS5A inhibitors

Protease inhibitors, non-nucleoside inhibitors of RdRp and NS5A inhibitors (subtype 1a) all have low barriers to the development of resistance because amino acid substitutions can result in reduced antiviral activity.

New ways to search for novel anti-HCV drugs

Dr. Jake Liang, Liver Diseases Branch, NIDDK, USA, outlined how his group has been ‘thinking outside the box’ to develop novel therapies using modern technologies based on high throughput screening to screen libraries of small molecules for activity against HCV. “Forward chemical genetics enables unbiased probing of the viral life cycle and use of cell based assays should mean we develop more biologically relevant therapies,” he said. Tracing the development of these approaches, he reported the identification of five lead compounds – one targeting viral entry, one replication, and three viral assembly – using an assay suitable for quantitative high throughput drug screening.

Bringing what he considered has been an ‘outstandingly successful’ meeting to a close, Professor Wedemeyer said that clinicians have a responsibility to use current and upcoming treatments in a responsible way, making best use of limited resources to help patients. “In the end, what counts is not treatment efficacy but effectiveness at a population level. This means identifying patients to be treated, helping patients to understand the need for treatment and good adherence, educating primary care physicians about how to reduce the condition and advocating at a political level to ensure we have the resources in all countries to cure HCV.”