

Clinical Trials Design:

Experimental HCV Drugs for HIV/HCV Coinfected People

EATG Third International Workshop - Brussels I / Sitges III

November 19th - 20th, 2009 Brussels



European AIDS Treatment Group



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For further information see the workshop link:

<http://www.eatg.org/eatg/ECAB/Conferences/Brussels-I-Sitges-III-Nov-20-Brussels>

The European AIDS Treatment Group (EATG) is a NGO at the forefront of the development of the civil society response to the HIV/AIDS epidemic in Europe. The EATG is a European patient-led advocacy organisation that represents and defends the treatment-related interests of people living with HIV and AIDS. Its mission is to achieve the fastest possible access to state of the art medical products, devices and diagnostic tests that prevent or treat HIV infection or improve the quality of life of people living with HIV, or who are at risk of HIV infection. For more information, please visit www.eatg.org

Foreword

On November 19th and 20th 2009, EATG organized the Brussels I / Sitges III third international workshop: “Clinical Trials Design: Experimental HCV Drugs for HIV/HCV Co-infected People” in Brussels, Belgium.

The 2009 Brussels I / Sitges III meeting built on the success of two previous meetings focusing on access to HCV experimental drugs for HIV/HCV coinfecting people, and development of a research agenda to facilitate the process. Sitges I and II, held in 2007 and 2008, were instrumental in advancing HCV drug development in co-infected people. EMEA issued guidelines and recommendations, for HCV drug development including pre-approval studies in HIV co-infected people. Although FDA has not formally issued recommendations, they also support pre-approval studies in HIV/HCV coinfecting people. Community members contributed to these guidelines.

Some companies also initiated clinical trials in co-infected people, while others began consulting with the community to discuss their HCV early drug development programs for HIV/HCV co-infected people.

The Brussels I / Sitges III meeting continued this momentum. The objectives were to promote a multi-stakeholder discussion on how to move HCV research and clinical trial design forward for HIV/HCV coinfecting people.

The meeting was attended by approximately 50 participants:

- European and US Community Advocates from EATG, TAG, NATAP, Project Inform, HACA, ELPA, and the World Hepatitis Alliance
- Regulatory agencies (FDA and EMEA)
- Pharmaceutical companies (Abbott, Boehringer-Ingelheim, BMS, Gilead, MSD, Roche, Schering-Plough, Tibotec)
- Clinicians and Researchers, who are specialists in HIV and HCV treatment and clinical research

The morning session was centred around the following presentations:

- **Dr Filip Josephson** from EMEA presented the EMEA/CHMP guidelines on the clinical evaluation of DAA intended for treatment of chronic hepatitis C.
- **Dr Kimberly Struble** from FDA presented the FDA perspectives on clinical trial design for new HCV products.
- **Jules Levin** from NATAP presented on Early Access Programs for HCV drugs
- **Dr Stéphane Chevaliez** from the Department of Virology of the Hôpital Henri Mondor in France provided an update on the resistance to HCV Drugs & its clinical Implications.

Then, the afternoon session featured a dynamic roundtable of experts to discuss design of clinical trials for experimental HCV drugs in HIV/HCV coinfecting people.

Roundtable participants:

- **Dr. Bernard Hirschel** (Division des Maladies infectieuses, Unité VIH/SIDA Hôpital Universitaire de Genève)
- **Dr. Juergen Rockstroh** (Department of Internal Medicine I, Bonn University, Bonn, Germany)
- **Dr. Massimo Puoti** (Department of Infectious Diseases, University of Brescia, Italy)
- **Dr. Josep Mallolas** (Infectious Diseases Service, Hospital Clínic, Barcelona, Spain)

Following the roundtable, each pharmaceutical company attending the meeting was given the opportunity to comment on the discussions that had arisen during the day, and describe their plans for including HIV/HCV coinfecting populations in their clinical trials for new hepatitis C drugs. Finally the meeting ended with a very moving speech from Joan Tallada, EATG, calling for a strong multi-stakeholder response to accelerate development of safe and effective HCV drugs for HIV/HCV coinfecting population.

Following the workshop, the Community reached consensus on specific clinical questions (populations, inclusion criteria, trials design). The 'Community consensus' is presented at the end of the report.

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Agenda of the Meeting

9:30-9:45 Welcome

- Wim Vandeveldel – ECAB Chair

9:45-10:45 Presentation of EMEA guidelines (20 min)

- Speaker: Dr. Filip Josephson (EMEA)

FDA perspectives on clinical trial design for new HCV products (20 min)

- Speaker: Dr. Kimberly Struble (FDA)

Followed by a general discussion (20 min)

- Moderator: Wim Vandeveldel & Tracy Swan

11:00-12:00 Early access programs for HCV drugs

- Speaker: Jules Levin (NATAP)
- Moderator: Luis Mendao

12:00-13:00 Update on resistance to HCV drugs & clinical implications

- Speaker: Dr. Stephane Chevaliez (Department of Virology, Hôpital Henri Mondor, France)
- Moderator: Stephan Dressler

14.30-16:00 Roundtable

Clinical Trials Design: “Experimental HCV Drugs for HIV/HCV Coinfected People”

- Dr. Bernard Hirschel
(Division des Maladies infectieuses, unité VIH/SIDA Hôpital Universitaire de Genève)
- Dr. Juergen Rockstroh
(Department of Internal Medicine I, Bonn University, Bonn, Germany)
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(Infectious Diseases Service, Hospital Clínic, Barcelona, Spain)

- Chairmen: Joan Tallada and Diego Garcia

16:15-18:00 Industry feedback

- Moderators: Laure Sonnier & Stephan Dressler

18:00-18:30 Closing remarks

- Joan Tallada

Clinical Trials Design: Experimental HCV Drugs for HIV/HCV Coinfected People

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INTRODUCTION

Since the introduction of Highly Active Anti-Retroviral Therapy (HAART) in the 1990s, people with HIV are living longer. But many HIV-infected people are co-infected with hepatitis C virus (HCV), which often does not cause disease until many years after infection. As a result of HAART, people co-infected with both HIV and HCV are now living long enough to develop hepatitis.

HIV increases the risk and accelerates the rate of liver damage from HCV. End-stage liver disease from HCV is now a leading cause of non-AIDS related death among HIV-infected people in the United States and Western Europe (Weber et al., Arch Intern Med 2006).

HCV is most frequently acquired through injecting drug use. However it is now increasingly sexually transmitted among HIV positive men (Euro Surveill. 2009; vol 14(47), p19421), with prevalence increasing at alarming rates in some cities.

The current standard of care for HCV is weekly injections of pegylated (longer half-life) interferon plus daily oral doses of the antiviral drug ribavirin (Peg+RBV). The duration of treatment varies depending on HCV genotype, viral load and HIV status. In some cases, HCV treatment can permanently eradicate the virus. This is called sustained virological response (SVR), defined as no virus

being detected in the blood six months after completion of treatment.

But Peg+RBV have many side effects, making it difficult for many people to tolerate. Advances in understanding the HCV lifecycle have now led to a wave of new drug development. There are several dozen promising new direct-acting antivirals (DAAs) for HCV in clinical trials, and more in preclinical development.

These new HCV drugs will be tested first in people infected with HCV alone. People co-infected with HIV and HCV present a more complicated picture for clinical trials, as they are usually on many other medications as well, and have various degrees of immune and liver impairment, complicating the interpretation of trial results.

Currently an estimated ten per cent of people with HCV also have HIV. The co-infected community is concerned that new HCV drugs may be brought to market without trials being done among co-infected people who desperately need them. Without such trials, co-infected people and their doctors will use the drugs anyway, but

with little scientific information about how this may affect the patient's HIV status or interact with HIV drugs.

The HCV/HIV co-infected community has been meeting with the pharmaceutical industry, and the regulatory agencies that approve clinical trials, to resolve these concerns. In 2007, at a meeting in the Spanish town of Sitges, they agreed that co-infected trials would begin once doses were established by large-scale, or Phase 2, trials in HCV mono-infected people. That meeting was followed by another one in Sitges in 2008.

Now many HCV drugs are in Phase 2 and even Phase 3 trials. Given the flurry of new HCV drug development, and to continue the landmark work of the Sitges meetings, the community arranged a meeting with stakeholders in Brussels on 19 and 20 November 2009, to discuss clinical trial design and early access programs. The first day the community met to form a consensus position on outstanding issues. The following day it met with researchers, clinicians, companies and regulators from Europe and the US. This report summarises the presentations and the discussions.

SESSION ONE: VIEWS FROM REGULATORY AGENCIES



Filip Josephson
Swedish Medical Products Agency, on behalf of the European Medicines Agency, EMA

Josephson discussed the EMEA guidance on clinical trials of directly-acting antivirals (DAAs). The current standard of care for HCV is pegylated interferon plus ribavirin (Peg+RBV). Around 80 percent of patients with HCV genotypes 2 and 3 achieve a

prolonged reduction of viral levels to below the detectable level (called sustained viral response, SVR) on this treatment. But fewer than half of patients with genotypes 1 and 4 do so even after 48 weeks, and the percentage of HCV/HIV co-infected people who achieve SVR is even lower. Many patients cannot tolerate Peg+RBV. Antiviral drugs select for drug resistance; HIV anti-retrovirals (ARVs) demonstrated this. The EMEA guidance is chiefly aimed at preventing resistance to HCV DAAs.

In early trials to ascertain the correct drug dosage, some patients will get insufficient drug to wipe out HCV, which is when viruses that resist the drug are most likely to multiply. So EMEA guidelines call for Phase 2 dose-selecting studies to be done with DAAs combined with Peg+RBV, in people where resistance will do the least harm, treatment-naïve or relapsed patients without advanced fibrosis or co-infection. Although these are not the sickest patients with the most urgent need, clinical development for them should be unduly postponed.

But before starting therapy in patients who respond poorly to Peg+RBV, EMEA wants a DAA to show it can cut viral levels in less vulnerable patients. It should have cut viral loads to undetectable levels by 4 weeks (called rapid virological response or RVR); or have cut them to undetectable levels, or by more than two logs (on the order of a hundred-fold), within the first 12 weeks of treatment (called early virological response, EVR). Patients must stop if there is no EVR.

If dose selection (Phase 2) trials show a DAA plus Peg+RBV causes RVR or EVR, studies can begin in more vulnerable populations, subject to similar stopping rules. Studies of two DAAs in combination, with no Peg+RBV, can begin before these trials are fully underway.

Vulnerable populations include: patients with advanced fibrosis and cirrhosis who cannot tolerate Peg+RBV; non-responders to Peg+RBV; co-infected patients; liver transplant patients; in future, patients who have failed treatment with another DAA and Peg+RBV; and patients with genotype 2, 3 or 4 if the DAA is applicable.

We need drug interaction studies for the DAAs with methadone, antidepressants and oral contraceptives, and for co-infected patients, ARVs. DAA dosages may need to be changed for co-treatment. ARV development showed combining different

nucleoside analogues (polymerase inhibitors) may give unexpected safety and efficacy problems. As there are drugs in this class for HIV, and in development for HCV, these data should be available when DAAs are approved for co-infected people.

Phase 3 trials, the basis of marketing applications, must demonstrate better efficacy or lower treatment duration compared to Peg+RBV alone. Treatment duration cannot be cut at the expense of reduced efficacy.

Two randomised trials adding a DAA to Peg+RBV are already underway. Treatment naive patients and people who have not responded to Peg+IFN should be treated as separate populations, although people who responded to Peg+RBV, but relapsed after treatment completion 24, might be enrolled in either group, with data treated separately.

Studies will first be done with genotype 1, and in a change of EMEA policy, genotype 4 if the DAA shows promise there, with data kept separate. Once a DAA is approved, it will become another basis for comparative trials of new drugs, besides Peg+RBV.

Clinical trials will aim for SVR by week 24, with persistence monitored after licensing. Patients who do not achieve SVR should be monitored for a year for drug resistance, and to find out whether resistant strains of HCV that emerge during treatment

persist afterwards (called archiving). Safety studies will include: resistance; pharmacokinetics in people with impaired liver function; whether side effects of DAA and Peg+RBV are synergistic; and other predicted toxicities, such as mitochondrial poisoning by nucleosides.

So far EMEA has focused on trials combining a DAA and Peg+RBV. It is not yet clear how to design trials of two DAAs without Peg+RBV. These must take account of possible cross resistance between DAAs, and resistance to more than one class of drugs in patients failing therapy. There must first be drug interaction studies, doses should be optimised based on RVR and EVR, and trials should start in treatment-naive people without advanced fibrosis.

EMEA wants trials in co-infected patients, because of high rates of liver failure and low rates of response to Peg+RBV in that population. There must be drug-drug interaction trials first, including ARVs, with particular attention to nucleosides, which may have complex pharmacokinetics.

If a DAA is superior to existing treatment in mono-infected people, randomised trials in co-infected people will not be required for licensing. Single arm trials of the DAA and Peg+RBV (conducted without control groups on Peg+RBV alone) will be needed to address safety issues, to confirm adequate drug exposure to the

DAA if there are drug interactions, to confirm efficacy and see whether EVR or RVR predict SVR.

In principle these studies can stop once EVR and safety data are available, but they may be delayed by the need for drug interaction studies. Transplant patients and children will also need separate single-arm trials, but not before licensing.

The EMEA guidelines will be updated as the field evolves. They must strike a balance between protecting the most vulnerable from non-optimal drug regimens, and not hindering drug development and access for those with the most need.

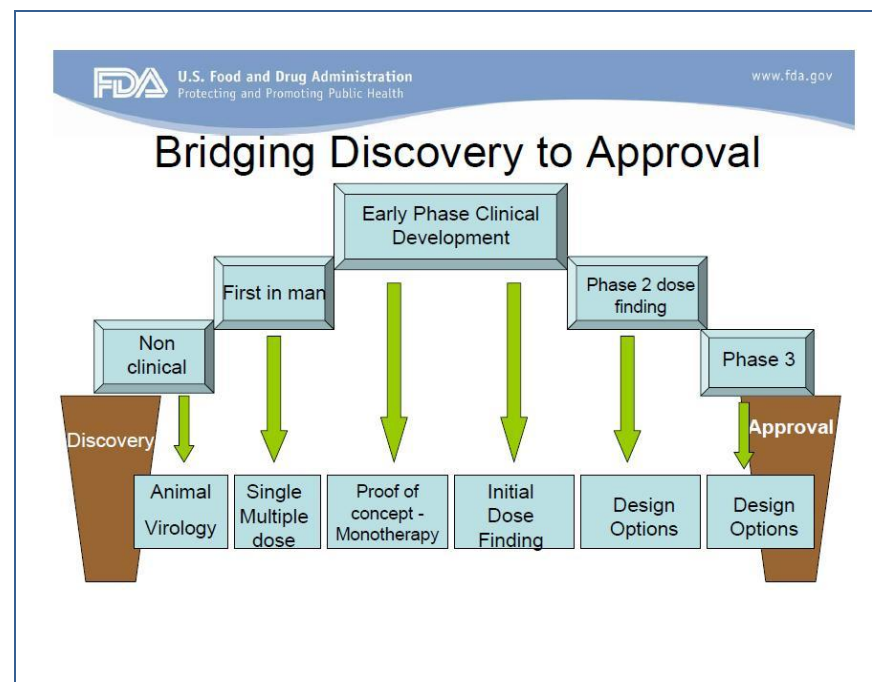


Kimberly Struble
Division of Antiviral Products, US Food and Drug Administration (FDA).

The talk is not the official view of the FDA, but current thinking on clinical trial design. Unlike EMEA, the FDA does not have guidelines for HCV drug testing, but hopes to publish draft guidance soon, after a public meeting to get comments.

Trials proceed from proof-of-concept (basic efficacy) to dose-finding, Phase 2. FDA expects these to begin in treatment-naïve patients, followed by the treatment-experienced, but it can make case-by-case exceptions. They should include representation for

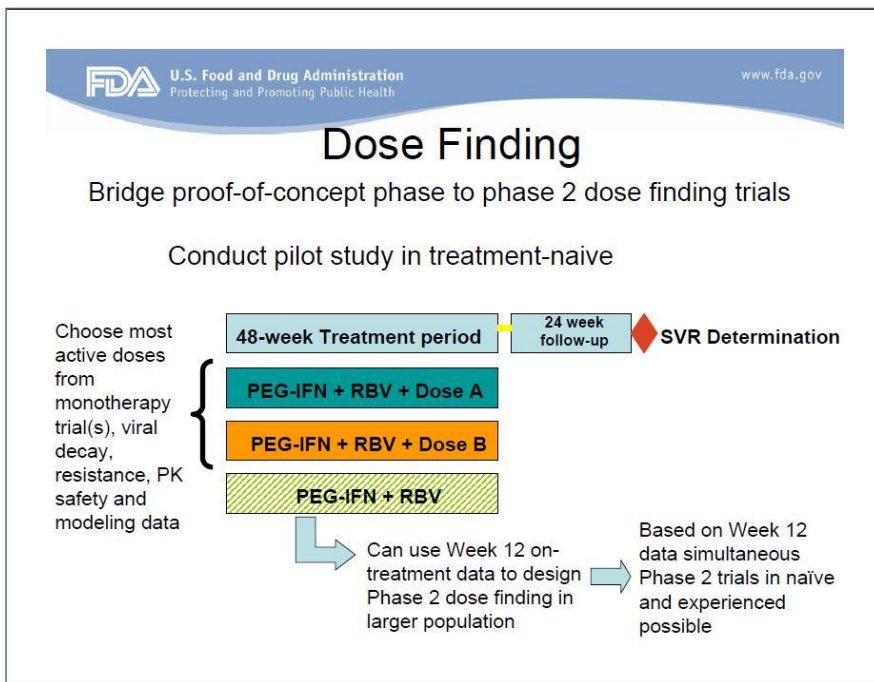
gender, race, age and body weight. FDA wants patients with compensated cirrhosis (who still have liver function) to take part in Phase 2 and 3 trials, as well as people with the most urgent need if the necessary data is first obtained.



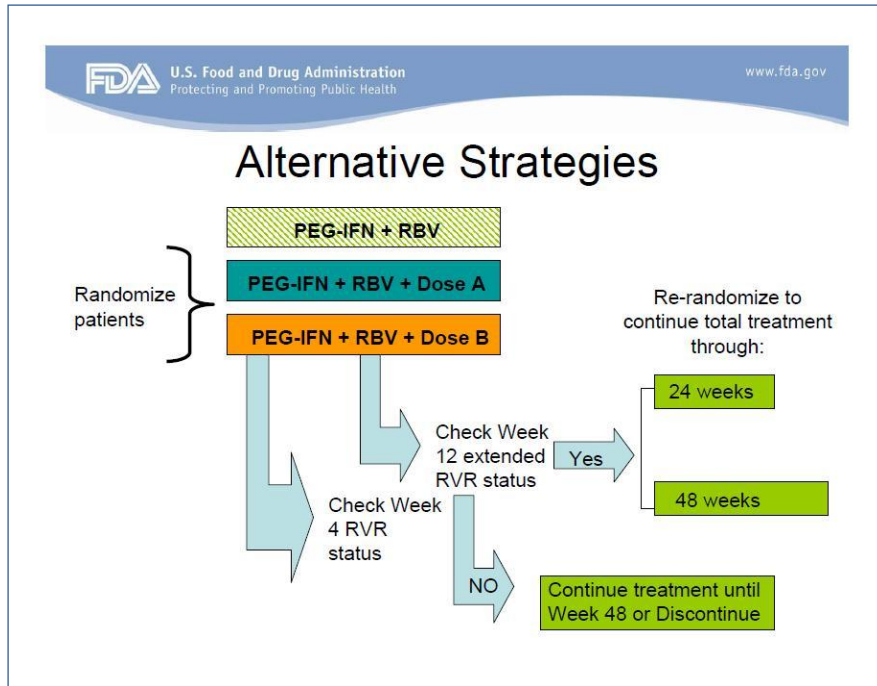
They will begin with trials of the DAA alone for up to three days, to minimise resistance. These will observe pharmacokinetics, safety, the decay of HCV RNA, and emergence of resistance.

Then two of the most active doses will be chosen, and one will be given to each of two randomly-chosen groups of treatment-naive patients along with Peg+RBV. They will be compared to another on Peg+RBV alone, for 48 weeks with a 24 week follow-up to determine SVR persistence. If there is sufficient response by week 12, further Phase 2 trials can be launched immediately in both treatment-naive and experienced people.

Animal experiments will help find the optimal duration of therapy. It is a misconception that the FDA wants 3-day trials in humans, then 2-week, 4-week, 12-week and only then 48-week trials. The intermediate trials are done only when there is not enough animal data to support longer trials. FDA wants companies to have enough animal data to do initial trials that are as long as possible, unless the side effects outweigh the benefit. The duration of therapy must balance the risk of insufficient response and relapse on shorter treatments, with the risk of resistance and toxicity on longer ones.



In trials randomising patients to Peg+RBV alone or with different doses DAA, RVR and EVR should be monitored with stopping rules as appropriate. If people achieve EVR (viral reduction by 12 weeks), they might be randomly assigned to continue the full 48 weeks, or only 24 weeks. If people have not responded by this point they may continue, or be stopped, which may be especially prudent in those on Peg+RBV alone. SVR data at 24 weeks will be needed from Phase 2 trials to ensure effects are lasting, and to calculate sample sizes for Phase 3 trials.



Competitive pressure notwithstanding, cutting corners on earlier trials may harm overall drug development if unexpected problems arise. These could even require starting over. There are many strategies for Phase 2 and 3 trials: different doses, duration, lead-in on Peg+RBV, etc. Strategies may differ for different drug classes. FDA is open to alternative designs. Once the first DAA is approved, future trials will compare new drugs to it. Subjects who achieve SVR must be followed for at least 3 years to ensure durable response,

determine whether subsequent detection of HCV is relapse or re-infection, and evaluate liver health.

Use of two or more DAAs without Peg+RBV is strongly encouraged, to benefit include non-responders to Peg+RBV, people who cannot take Peg+RBV due to decompensated liver disease, severe anaemia or intolerance, transplant and decompensated cirrhosis patients, and others who respond poorly to Peg+RBV, including people of African descent and the HCV/HIV co-infected.

The two DAAs should ideally have different mechanisms of action, and there should be preliminary data on each agent separately, and on combined antiviral activity in culture and in animals, viral resistance and cross-resistance. The FDA needs at least three months of animal data on each agent separately, but not in combination, to support a three-month combined study in humans. A longer combined study requires data for each agent separately, for six months in non-rodents, and nine months in rodents. This is a change: in the past combined trials were required in animals before they were done in humans, but these provide no more useful information than separate trials. The FDA also needs anti-HCV activity and safety data in humans before approving trials, as well as drug-drug interaction studies if interactions are possible.

Two or more DAAs might be given for less than two weeks to treatment-naive patients followed by 24-48 weeks of Peg+RBV. Longer durations with or without interferon and/or RBV in treatment-naive or experienced people should be accompanied by HCV viral load monitoring and stopping rules if there is little response. Combined therapy before liver transplant should be tested for prevention of infection of the transplanted liver.

Trials need to show that each agent contributes. Modified factorial designs might include Peg+RBV alone, with each of two DAAs, and with both of them, to tease out what each drug contributes. Pilot studies should evaluate drug and dose combinations in different patient populations with or without Peg+RBV, with early decisions to continue or expand the trial numbers depending on response.

Data on DAA drug-drug interactions, and pharmacokinetics in patients with hepatic impairment, are needed early in order to study patients with liver transplant, decompensated cirrhosis, or HCV/HIV co-infection. Studies in people with reduced liver function must show whether doses of DAAs need to change, and can help in extending trials to transplant patients. This allows patients with hepatic impairment to enrol in Phase 2 and 3 trials.

The FDA strongly encourages companies to include data from trials in co-infected people in New Drug Applications. This should include drug-drug interaction with the most common ARVs, safety data for

co-infected people taking the drug for the entire length of recommended treatment, and some efficacy data. Labelling will describe efficacy and drug interactions in the co-infected.

To expand the approved use of a DAA to co-infected people, a trial must include at least 300 people. It can be a single-arm trial without a control group on Peg+RBV alone, if the DAA has proven effective compared to Peg+RBV in mono-infected people. End points should include SVR at 24 weeks after treatment ends, safety including any loss of ARV efficacy, progression of liver disease, transplant and death. In people with decompensated cirrhosis, multiple DAAs will be needed, and single-arm trials will be accepted to support approval of the drug for that indication.

Early access programmes for DAAs as Investigational New Drugs should be done early in development, but will depend on company sponsorship. FDA cannot mandate them, but approves of them if there is enough data to establish a reasonably safe and effective dose. These should start after Phase 3 trials are enrolled, so enrolment for early access will not compete with enrolment for the trial. Even earlier access may be possible for individuals or groups of 100 patients or less. The FDA is open to different ideas for providing access.

The FDA has a hepatitis listserv on safety and regulatory issues in hepatitis A, B and C, including product approvals, labelling changes,

safety warnings, and notices of upcoming meetings and proposed regulatory changes. Go to www.fda.gov and type hepatitis in the onsite search engine.

Discussion

Community members asked how the regulatory agencies will promote early access programmes for investigational drugs in populations with unmet needs. Apart from (as one put it) shaming companies into it, the agency representatives said they ask companies to expand access at each phase of development, provided they have enough information to keep from doing more harm than good. Patients, especially non-responders to Peg+RBV and those with greatest need, must take two or more drugs to avoid the mistakes that were made with ARVs, when patients took two drugs but only one was effective (functional monotherapy), and it rapidly selected for resistant virus. EMEA, like FDA, cannot require companies to back early access programmes, but encourages the studies of drug interactions and correct dosing in co-infected people required to provide such access.

The FDA is required to hold a public hearing of all stakeholders before allowing early access, and the meeting must be announced in the US Federal Register 60 days beforehand to allow comment. It is possible but far from certain that this will happen in early 2010.

Community members noted that hearings must happen soon, because companies are planning their clinical trials now, and similar hearings in 1994 were crucial for early access to ARVs.

What would be a robust enough response to DAA in mono-infected people to warrant a single-armed trial in the co-infected? Josephson said the 90 per cent increase in response seen to telaprevir and boceprevir in Phase 2b trials is certainly enough. Struble said FDA would want to see improved rates of SVR balanced with toxicity. Combined trials of two or more DAAs without Peg+RBV can start once trials of the DAAs with Peg+RBV have demonstrated RVR and EVR, but need not await SVR. A co-infected trial can start while a larger Phase 2 trial in the mono-infected is still underway, as long as drug interaction and dose-selection studies have been done, but it may be hard to design without some data on SVR.

The FDA co-infected trial requires 300 patients because safety information from 300 to 500 people is considered enough to

expand an indication, in this case from mono- to co-infected, so 300 is a benchmark; more may be needed depending on results.

Community members asked about substitutes for liver biopsy in assessing trial participants. EMEA accepts non-invasive alternatives if the company can show it gives the information required. A non-invasive test might be enough to exclude patients with severe cirrhosis from a trial, for example, while biopsy may still be needed to evaluate changes among cirrhotic patients during a study. The FDA does not accept non-invasive tests. Companies may collect validating data, but FDA now requires biopsy three years or less before trial enrolment. It is not required for 3-day trials, but it helps in evaluating safety.

Community members said they wanted as many drug interaction studies as possible to be done before drug approval, including opiate substitutes, as 70 per cent of co-infected people use or have used illegal drugs. DAA interactions with methadone and heroin must be studied or trials will exclude many co-infected. It was noted that people on maintenance already have good compliance. Regulators agreed interaction studies were needed, but patients on methamphetamine or cocaine pose problems as these drugs share metabolic pathways with DAAs.

How should trials include people with decompensated cirrhosis, or transplant patients? Will there be additional trials for people with

specific problems? Agency representatives felt information on such groups would be valuable, and that people with decompensated cirrhosis who cannot tolerate Peg+RBV should be included in trials of combined DAAs, but the details have not yet been discussed.

Will early co-infected trials include people on ARVs, and if not, when will they? Some ARVs should have minimal interaction with DAAs, so maybe trials could begin without waiting for all the interaction studies. Josephson said he would bring this up in discussions at EMEA. ARVs have shown many unexpected interactions, but EMEA will not demand interaction studies for all ARVs before allowing studies in co-infected people - although they might initially be limited to people only on certain ARVs.

Community members noted that the situation for co-infected people is more complex than when ARVs were being developed, so the way people were given expanded access then may not apply now. More vulnerable patients and their doctors should be able to discuss early access with the regulatory agencies once data emerges in trials with less vulnerable patients.

Must trials with co-infected people use the same dosages as mono-infected trials? FDA was open to different doses. Some expressed concerns that adverse events in co-infected people, and those with other co-morbidities, might derail drug development, but Struble

noted that FDA has broad experience of early access from ARV development, and events would be viewed in individual context.

Erythropoiesis-stimulating agents are used to counter the anaemia caused by treatment. Their effect on achieving SVR with DAAs should be evaluated in a prospective trial.

The community noted that in the next few years many mono- and co-infected people will die, while trials took years. Many should be given a chance sooner. The regulatory representatives said trials of combined DAAs without Peg+RBV would be needed as early as possible in such patients. But giving people with decompensated cirrhosis two DAAs required interaction and pharmacokinetic studies in people with liver damage, so patients would not be massively under- or overdosed, doing more harm than good.

SESSION TWO: EARLY ACCESS PROGRAMS AND VIEWS FROM THE COMMUNITY



Jules Levin – NATAP

Community members suggested a small task force of people from the regulatory agencies, companies and the patient community might be formed to track fast-changing developments and facilitate compassionate use, but Jules Levin of NATAP felt legal and commercial impediments made this impossible. The US community,

however, has set up a small committee to talk with individual companies about their HCV drug development in both mono-and coinfection. Every company present committed to meet the committee in early 2010. European community members said they would put together a group like the US task force, and hoped to get doctors and researchers on board as well. Community members also discussed forming a combined US-European group.

Levin said he appreciated companies' commitment to developing lifesaving drugs for HCV and wanted them to work with the community to balance safety, efficacy, profits and access.

Early access is harder for co-infected people than it was for ARVs: people vary more, in extent of liver damage, and risks of decompensation and drug resistance. How do we design early access in different patient populations while protecting companies? Regulators must be flexible in balancing safety, access and development, and not throw a drug out for every small safety issue. We need to discuss open label studies where doctors collect data while allowing early access.

If people are about to die they might not care if they become resistant to one class of drugs. There is a risk of drug resistance if people on Peg+RBV plus a DAA don't respond to Peg+RBV, but this could be tested with a Peg+RBV lead-in first. There are potential interactions between protease inhibitors for HCV and HIV. Early pharmacokinetic studies will accelerate everything.

When we have three different drug regimens, in industrialised countries nearly 100 per cent of patients will be cured, drying up the market for companies, Levin felt. But there are infected people elsewhere. What will keep companies in the HCV field? In the US many HIV services are paid for by government, but that won't happen for HCV. Who provides patient assistance, psychiatric evaluations, and therapies for the non-insured in countries without public health care? There will be demand for global access to the drugs. Who will pay?

Tracy Swan of the Treatment Action Group noted that in the US, government AIDS programmes give away Peg+RBV, but few get access because they can't get liver biopsy, viral load analyses, or the sick leave and child care needed to complete 48 weeks of therapy. A company-sponsored trial might not show the way out of this situation. The community should meet with companies to

discuss how to pay for care programmes, including care of side effects, psychiatric if needed.

Companies may not do interaction studies or clinical trials of their drugs with those of other companies. What if the best drugs in two classes belong to two companies: will they do joint trials? Will early access programmes allow combinations across company lines?

Company representatives said working only with the company's own molecules is "not how we do business" any more: in the last 3 years there have been collaborative studies between companies across the hepatitis field, combining different companies' molecules. If one company's drug can get SVR faster combined with another company's drug, there would be collaborations.

But we can't do trials combining two DAAs that are best in their classes immediately, as we won't know which drugs those are until Phase 2 and 3 trials are done, and by then the drugs will already be close to approval. So how soon will regulators allow mixing and matching, as with ARVs? Or will drugs be approved only in the combinations in which they underwent Phase 3 trials? Mixing and matching might happen faster with early access programmes.

SESSION THREE: CURRENT RESEARCH ON RESISTANCE

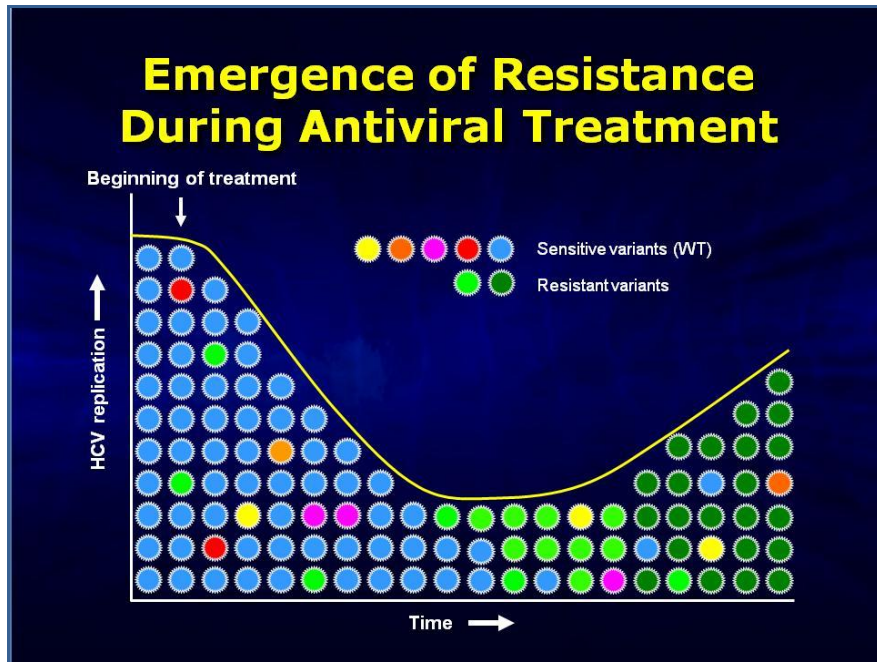


Stephane Chevaliez
Virologist, Hôpital Henri Mondor, Paris, France.

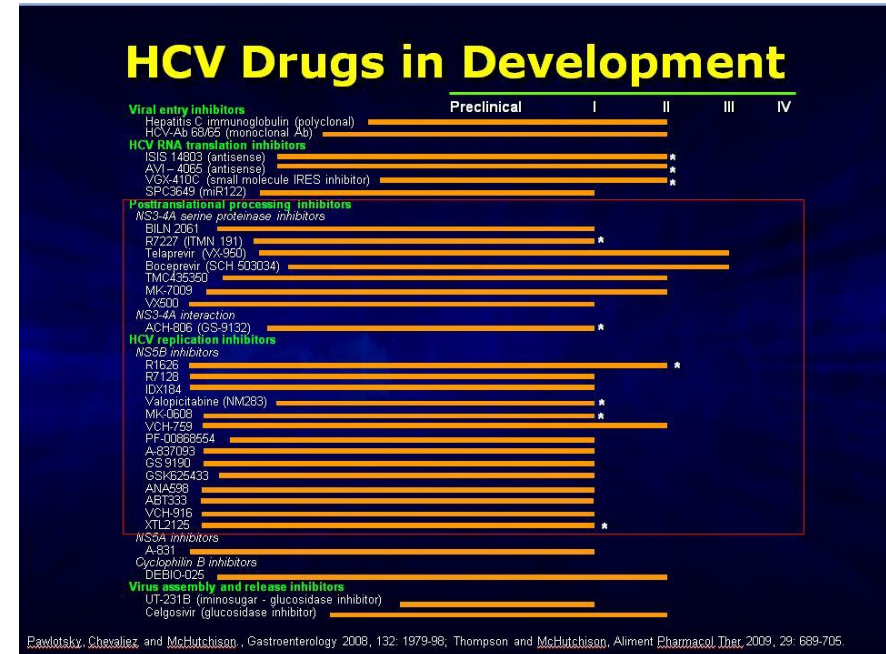
Unlike HBV and HIV, HCV doesn't integrate with the genome, meaning it is curable. If Peg+RBV cut the amount of virus in the blood to undetectable levels for 24 weeks after the end of treatment the person achieves sustained virological response (SVR).

But SVR is not achieved in about half of cases with genotype 1 and a fifth with genotypes 2 and 3. Intrinsic resistance to interferon affects mainly the early response to treatment; ribavirin prevents later relapse. But failure of this treatment is not due to selection for strains resistant to interferon or RBV.

DAA's, however, do select for such strains, in which mutations alter the drug target on the virus and stop the drug binding. Like all RNA viruses, HCV exists in the body as a "quasi-species", or swarm of mutants. All the single-point mutants and 10 per cent of the double mutants that resist DAA's already exist in small numbers in all patients, and are selected for by treatment. Breakthrough, in which HCV levels rebound after an initial drop, occurs as the drug-resistant mutants multiply and replace the drug-sensitive wild-type virus.



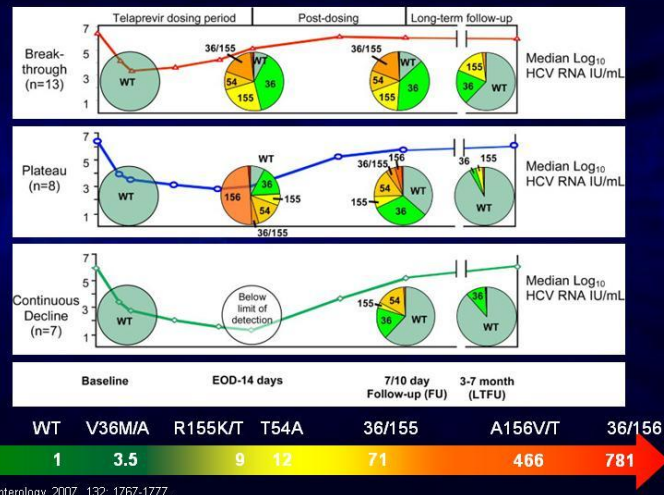
Viral factors that affect the development of resistance include the rate of replication, the effect of the mutation on the virus's fitness, and the half-life of infected hepatocytes. Host factors include compliance with treatment and immune status. Pharmacological factors include the drug's potency, the genetic barrier to resistance – how many mutations a virus needs to resist the drug – and how much drug reaches infected cells. Drug plasma levels are higher in patients who reach EVR than in patients who breakthrough or plateau. DAAs in development attack various stages of viral translation, replication and assembly.



The currently most advanced DAAs inhibit the virus's NS3 protease. Amino acid substitutions in the protease confer resistance, and cross-resistance to all other NS3 protease inhibitors.

Resistance cuts the efficacy of telaprevir by a 10^3 to 10^4 after 7-14 days of treatment. If patients are grouped according to their viral response – breakthrough, plateau or EVR - their HCV exhibits several patterns of amino acid substitution, mostly at four loci, which confer different levels of resistance.

Dynamics of NS3 Protease Variants according to the Virological Response

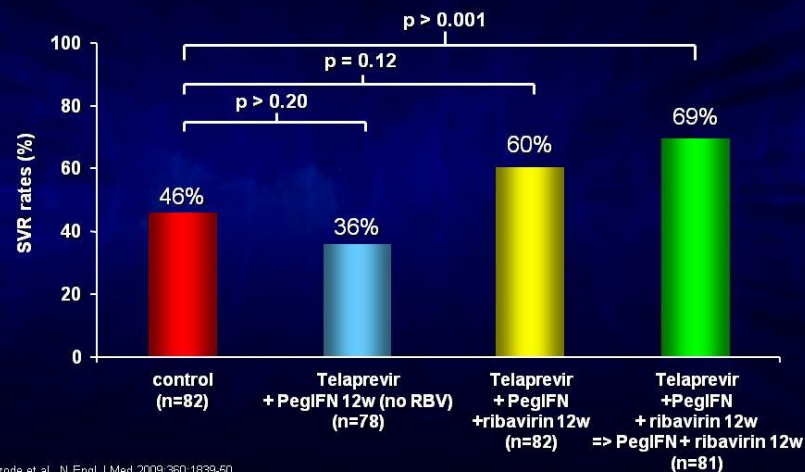


The wild type virus is more fit than resistant mutants: after treatment stops the wild type re-asserts itself and resistant strains decline, but persist. In patients continuing therapy, they cause breakthrough.

In the PROVE-2 trial of telaprevir, 320 treatment-naive European patients with genotype 1 were put on one of 4 regimens with the following results:

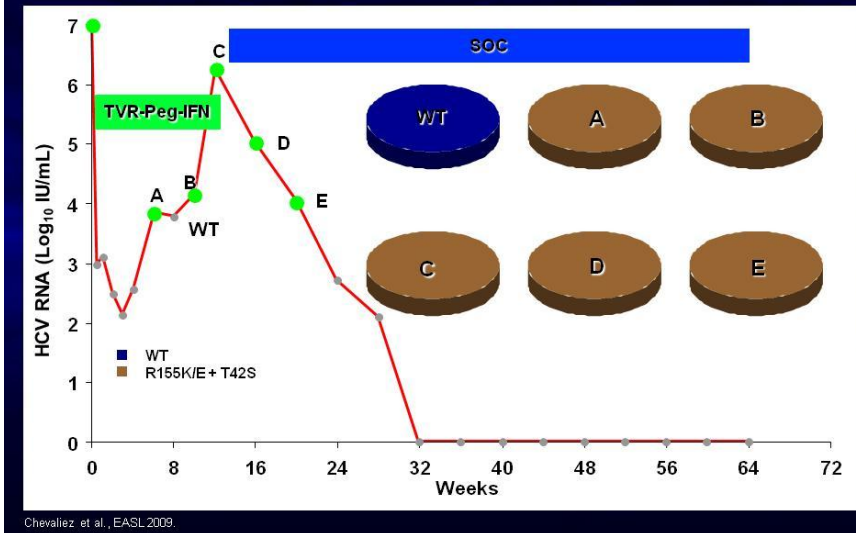
- 48 weeks Peg+RBV: SVR 46%
- 12 weeks Peg+RBV plus telaprevir, then another 12 weeks Peg+RBV: SVR 69%
- 12 weeks Peg+RBV plus telaprevir : SVR 60%
- 12 weeks telaprevir with interferon but no RBV: SVR 36%

PROVE-2 Trial (Phase II) Sustained Virological Response



Telaprevir failed to substitute for RBV, mainly because of an eightfold higher breakthrough rate compared to telaprevir combined with, then followed by Peg+RBV. Resistance mutations emerged during this breakthrough. In one such patient who didn't achieve SVR, numerous resistant variants emerged but did not permanently replace the wild type virus. In another who did achieve SVR in spite of this breakthrough, wild type virus was replaced to the level of detectability, but by only two resistant variants.

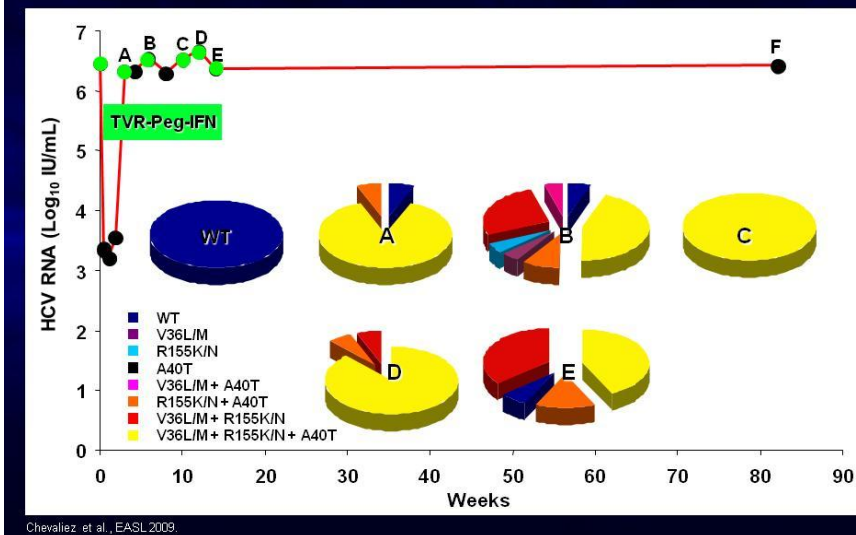
PROVE-2 Trial (Phase II) Dynamics of NS3 Protease Variants



Telaprevir or boceprevir monotherapy rapidly selects viruses with resistance mutations. All are less fit than wild type, and confer cross-resistance to all NS3/4A protease inhibitors. Emergence of these mutants is associated with failure of therapy, and they may persist afterwards, but importantly, the mutants are sensitive to Peg+RBV.

Polymerase inhibitors are of two types. Nucleosides bind the main binding site of the enzyme that replicates the HCV virus's RNA genome. Resistant strains must carry mutations in this delicate piece of viral machinery, hence are not very fit. Non-nucleoside inhibitors do not attack the enzyme's binding site, so resistant mutants are more fit. Only three mutations are known that confer resistance to nucleosides, 17 that confer resistance to non-nucleosides.

PROVE-2 Trial (Phase II) Dynamics of NS3 Protease Variants



In chimpanzees, 38 days of the nucleoside MK-0608 cut HCV replication a hundred-fold, but after treatment virus rebounded due to selection of a resistant mutant.

Debio-025 binds to cyclophilin, a host protein that aids HCV replication, and inhibits replication of genotype 1, 3 and 4. After two weeks of monotherapy patients had a 3.7 log reduction in viral levels, and the drug has shown an additive effect with Peg+RBV. But a mutation conferring resistance emerged in two patients on monotherapy.

So there has been resistance to DAAs *in vitro* and *in vivo*, and it occurs often and early in monotherapy. Failure of Peg+RBV plus DAA to clear HCV is associated with the selection of resistant viral mutants. Further research should exclude monotherapy: DAAs must be combined with other antivirals that at least have an additive effect, and do not evoke resistance that cross-reacts.

Discussion

HCV/HIV co-infected people have higher HCV viral loads than mono-infected people. In theory more virus means more risk of resistance, but there is no data on this in co-infected people on DAAs yet, nor on the sequence in which HCV drugs should be given to minimise resistance. Longer drug half-lives might overcome some resistance problems, but we will need salvage protease inhibitors for patients who develop resistance.

It is not yet clear if resistance persists. Patients who develop resistance to telaprevir may be re-treated with telaprevir plus Peg+RBV. Importantly, some HIV protease inhibitors have a weak activity against HCV, and it is not yet clear if this might induce resistance to HCV protease inhibitors. Clinical reference labs will have to be equipped to rapidly identify resistant strains. Some companies are working on such detection kits.

SESSION FOUR: ROUNDTABLE ON CLINICAL TRIALS DESIGN



Jurgen Rockstroh, Universitäts-Klinikum, Bonn, Germany

Josep Mallolas, Hospital Clinic, Universitat de Barcelona, Spain

Bernard Hirschel, Hopitaux Universitaires de Geneve, Switzerland

Massimo Puoti, University of Brescia and AO Spedali Civili, Brescia, Italy

All reported a growing epidemic of acute HCV infection, and low treatment rates for HCV/HIV co-infected people outside specialist clinics. In 2003 some 10 per cent of co-infected across the 30 countries of the WHO European region received Peg+RBV; in 2008

that was still only 25 per cent, partly due to lack of reimbursement in Russia. In Western Europe about half of co-infected people get treated, and half of those respond.

The clinicians were asked which co-infected group they thought should take part, if a company could do only one clinical trial of a DAA. They suggested treatment-naive patients with advanced fibrosis and HCV genotype 1, and as this is an unmet medical need, they also suggested including people who have relapsed but are known to respond to Peg+IFN, because they almost made it once and might achieve SVR with a DAA as well. Non-responders to Peg+RBV on that plus a DAA would effectively be on DAA alone, and resistance would ensue.

There are now many ARVs that are not metabolized by the cytochrome P450 enzyme system in the liver, so trials could include people on HAART as this should not interfere with the pharmacokinetics of the DAA.

The representatives of FDA and EMEA said this might be acceptable, but it would depend on the DAA being tested. Roche is

testing DAAs in mono-infected people who have not responded to Peg+RBV, but they are not the first group to be tested. Before giving someone a last chance at a cure in such a trial, data from mono-infected trials must determine the dose.

The clinicians said they might not get much input into trial design because of contact networks: hepatitis is handled by gastroenterologists, who generally don't talk to HIV specialists, although HIV specialists have more experience conducting drug trials. Industry could break this barrier by developing broader contacts, encouraging partnerships across specialties, and fostering regional networks. Non-HIV specialists are "scared of HIV patients": as a result, drug trials exclude people with HIV for no clear reason. As a result doctors are now using drugs for hepatocellular carcinoma, a complication of hepatitis, with no idea how they interact with ARVs.

Companies said trials in all sub-groups are needed. The community wants major trials to include relapsers, and small open label studies after the main trials are enrolled to include people with the most need. Prospective participants might be screened for the IL28 genetic marker which may predict response to interferon.

There are few co-infected relapsers in the US as most co-infected aren't treated – there a lead-in on Peg+RBV might be useful to detect complete non-responders who should not subsequently go

on to functional mono-therapy on DAA, and risk resistance. Specialised training for clinicians is important for trials: in Barcelona it made the difference between all or no co-infected people withdrawing from trials at different hospitals.

The doctors expressed frustration over delays in co-infected trials. If DAAs are licensed with little information apart from effects in relatively healthy treatment-naïve, mono-infected people, doctors will use them off-label in sicker people with no idea about dosages, drug interactions or risk to HIV management. They asked the companies to prevent this situation.

Trials starting in co-infected people now are accepting people with CD4 levels below 200 but over 100, and controlled HIV, with undetectable viraemia. A history of HIV-related opportunistic infections does not exclude participation, but a current one does. It is not clear if participants must be HIV treatment-naïve, but the doctors said they would welcome data from people on HAART. HIV should be followed weekly in trial participants. Two HAART regimens could be tested for interactions with DAA to allow things to get underway faster, without waiting for a dozen interaction studies. But Struble from the FDA felt that to include patients on optimised HAART regimens, extensive interaction tests were needed.

If HCV protease inhibitors make HIV resistant to HIV protease inhibitors, some patients may have few other ARVs to fall back on. Doctors felt we should get on with co-infected trials of HCV drugs without delaying too long for interaction studies as many co-infected people are on ARVs that should not interact. Only about 20 per cent of the co-infected are on last-chance ARVs with few other options. Community members felt that for some people it is ethical to take these risks because otherwise they will die, and they will generate data for others.

The doctors supported non-invasive alternatives to liver biopsy. European guidelines include an algorithm for working out when these are warranted. Currently liver function is initially assessed using different non-invasive techniques. If those show clearly what state the liver is in, that is enough, but in some 30 per cent of cases the result is not clear. Those cases, therefore, go to biopsy. But, the doctors noted, the use of different blood markers which measure fibrosis and fibroscan saves lots of biopsies. Fibrosis progresses fast in the co-infected, with a quarter of patients progressing two stages in two years. It is unrealistic to biopsy that often. Whatever stage of liver disease co-infected patients are at initially, they will need treatment fast regardless, so assessment may be pointless.

The doctors felt there was prejudice against non-invasive techniques like Fibroscan because it is a European, not a US device, and the hepatitis world is used to biopsy. But it can scan a patient every six months and show when treatment is needed, and it scans the whole organ and not just a small part of it, with the sampling error that involves. The question of whether to use biopsy may become moot when HCV treatment is available for all patients regardless of liver condition. For now the doctors agreed non-invasive methods were sufficient to detect and exclude cirrhotic patients from trials.

Some participants in trials could have serious psychiatric disorders. Doctors felt people with uncontrolled disorders should delay HCV treatment, because of the risk of consequences such as suicide. Half of patients starting Peg+RBV also take antidepressants, which helps compliance. Interaction trials with opiate maintenance drugs are needed, but the most complex interactions may be with transplant drugs, especially immunosuppressants. Controlled trials in these patients are difficult as there are so few of them, maybe 250 in Germany in 10 years.

SESSION FIVE: VIEWS FROM THE PHARMACEUTICAL INDUSTRY

Representatives of pharmaceutical companies developing DAAs all made a brief statement.

Tibotec: was glad the regulatory agencies were present, and supported a small joint working group with the community. It has two protease inhibitors now in Phase 2b trials, plus drug interaction studies including methadone. The Phase 3 trial of telaprevir with US partners Vertex has started. A small trial in co-infected patients, some on HAART and some not, will be opened in 2010.

Merck-Schering: The two merged two weeks ago. The boceprevir Phase 3 trials are fully enrolled, and recruitment has begun in a co-infected trial. The merger enlarged the antiviral pipeline, which includes another protease inhibitor, and polymerase inhibitors. Collaboration and drug-drug interactions studies are crucial.

Roche: just merged with US firm Genentech, so its HCV pipeline drugs now have new names: RG7128 and RG7227. Roche wants co-infected trials as soon as possible after mono-infected, to include treatment-naive and treatment-failed patients.

Gilead: also appreciated hearing regulators. Its new drugs include protease, polymerase and caspase inhibitors, all at early stages. It plans interaction studies and early access programmes, and noted that “the community creates opportunities for us to listen”.

Bristol-Myers-Squibb: is working on NS5A and NS3 protease inhibitors, a polymerase inhibitor and a novel gamma-interferon.

Boeringer-Ingelheim: normally doesn't discuss early drug development policies openly because it is family owned and has no share-holders – but it has broken that rule for HCV. It has a promising protease inhibitor, is doing interaction studies and is drafting a protocol for a co-infected trial, including looking at the CD4 levels they will require of participants. The company predicts “a few more years” before their protease inhibitor reaches the market, but says “working with others companies is not a problem for us.”

Abbott: has three DAAs, one protease inhibitor and two polymerase inhibitors, and is starting drug interaction studies with

all three. ARV monotherapy in the mid-90s had a devastating impact we must avoid with HCV. Co-infected studies should include prior relapsers and other non-responders to Peg+RBV. As need warrants, it will explore early access. This meeting is the only one where regulators, the community, companies and researchers discuss these issues. There aren't enough hepatologists in the world to provide the flood of treatment that will follow the availability of small molecule HCV drugs; we must make the Infectious Diseases Society of America and others embrace this treatment.

Discussion

Community members said they have wanted a clear commitment by companies to work with them for many years, and hoped a joint focus group on drug development for HCV might be launched soon. They are used to being involved in the early stage of drug development and have problems with confidential rules for trials protocols. They will partner with companies to support more risky designs.

There will be no new declarations like Sitges I, because the Sitges 2 declaration took a long time to hammer out, and is no longer needed because progress is being made. If informal meetings create more momentum and consensus we can go back to that.

MEETING CLOSURE



Joan Tallada gave a final message: “This meeting has attracted more interest than expected from companies, and we are glad they sent people who can make decisions. In 1991 I became an AIDS activist. We fought for our lives, including people who are no longer here. We should be proud of what we achieved in the late 1990s. Then in 2004 I realised that because of HCV, again people were dying. So we have to try. Since our first meeting, some friends and colleagues have died. We have a personal and ethical commitment as citizens, not just as regulators or scientists, to save people’s lives. That is the ultimate reason for this meeting and meetings to come.”

Following the workshop, the Community reached consensus on specific clinical questions (populations, inclusion criteria, trials design etc). The Community consensus is presented in the next section.

The organizers: Laure Sonnier, Wim Vandevelde, Diego Garcia, Joan Tallada, Tracy Swan



CONSENSUS FROM THE COMMUNITY REPRESENTATIVES ON HCV DRUG DEVELOPMENT FOR COINFECTED POPULATION

BRUSSELS I / SITGES III MEETING November 20th, 2010

Clinical trials

1. The community wants sponsors to do more than one co-infection trial per molecule, to explore safety and efficacy in people by HIV status (ie CD4 cell count), HCV genotype (when applicable), severity of liver disease, presence of co-morbidities etc. We encourage companies to fund a portfolio of studies in HIV/HCV co-infected people that address clinically relevant questions, prior to approval/marketing, and health authorities to support them
2. The risk of resistance should be minimized by avoiding virtual monotherapy. A lead-in period may be useful in some populations, for characterizing interferon responsiveness.
3. People should have access to broad and clear information to weigh the risk/benefit of entering both trials and open label studies/compassionate use programs.
4. Early pharmacokinetic studies of DAAs should be carried out as soon as possible, in order to permit wide open-label and compassionate use access.
5. Early trials must include people on HAART unless known drug-drug interactions make this impossible.

6. Efforts should be made to combine treatment naïve and non-naïve in the same trial. When possible, trials should be stratified, so that treatment naïve and relapsing people can be studied at the same time. The community suggests the use of a parallel track to make drugs available to people with urgent need for new drugs, this option would not be available until enrolment in formal trials is complete.

Participation in clinical trials

7. Particular subgroups (women, people with co-morbidities, people on methadone, buprenorphine, or heroin maintenance programs and people with severe disease) should be included in trials.
8. Although the community understands the importance of liver biopsy, we will continue to advocate for research on less invasive techniques to assess liver status. We believe that biopsy can be replaced with non-invasive tests in certain circumstances: to determine the presence or absence of cirrhosis, and in populations where it is felt to be too risky, such as people with haemophilia. However we consider that biopsy is so far, the best method for characterizing liver damage and inflammation.

Inclusion criteria

On inclusion criteria, the community would like three sets of trials:

9. - Box 1: Telaprevir or boceprevir plus Peg+RBV in treatment-naïve co-infected people, and relapsers with a CD 4 cell count of ≥ 100 , well controlled HIV, and a liver status which does not contraindicate the use of pegylated interferon. Additional data can be collected through open label compassionate use for people at high risk of liver failure and/or transplant candidates and recipients. Specific conditions of open label/compassionate programs should be discussed between the community and each drug developer, depending on drug characteristics and interaction profile; both companies and regulatory agencies should ensure that these data are collected in a timely manner.

- 10.** - Box 2: Participation should expand to a larger group of treatment-experienced co-infected people: those who did not reach SVR or had to stop treatment due to side effects or personal circumstances. These trials are for people who respond to Peg+RBV, so they will not be at risk of receiving virtual monotherapy. Null responders are not included in this category.
- 11.** - Box 3: Trials of two DAAs without Peg+RBV in people outside those two categories (i.e people with advanced liver disease where Peg interferon is contraindicated and non responders to SOC). Compassionate use should also be available for this community.
- 12.** All three should start at the same time. If only one is possible, 1 and 2 should merge.



Participants List

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