A new era for screening and treatment of hepatitis C:

a public health challenge

SPLIT, CROATIA

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draft

Objectives

The Viral Hepatitis Prevention Board (VHPB) organized a meeting in Split, Croatia (14 and 15 November 2013) for public health experts, clinicians, policy-makers, and representatives of patients associations and the pharmaceutical industry to discuss prospects for prevention and control of hepatitis C in the light of the expected imminent licensing of new and better treatments.[a]

Context

An estimated 170 million people in the world are infected with hepatitis C virus (HCV)[1] , with about 15 million people in the WHO European Region positive for HCV RNA[2] and more than 4 million chronic hepatitis cases in the USA. Some 10 million injecting drug users (60% of the total) are thought to be infected, and 4-5 million people are co-infected with HIV and HCV[3].

The prevalence rates of HCV infection vary across the world. In high-income countries in Europe, the rates range between 0.4% and 3.5%[4]. Elsewhere they can be higher, ranging up to about 15% of the general population in Egypt[5]. The incidence rate overall in Europe has remained fairly steady over the past few years, but different geographical patterns are apparent with varying rates within countries and across regions. Rising rates or recent increases were reported from some countries and regions, for instance Australia, Canada (rural areas), USA (in particular also in rural areas) and Uzbekistan. Data are incomplete, and there is considerable under-reporting.

The main routes of transmission are through injecting drug use (including the sharing of non-injecting equipment) and nosocomially (mainly through syringe use); globally, the latter accounts for many HCV infections. Modelling studies indicate that the epidemic of HCV-related chronic liver disease, including hepatocellular carcinoma, will continue to rise until peaking around 2032.

About three quarter of acute HCV infections become chronic; some lead to no clinical or only mild disease, whereas 10 to 20% of patients develop severe liver disease, including cirrhosis and hepatocellular carcinoma, and death. Late diagnosis results in an increased number of admissions to

[a] The presentations at the meeting are accessible as PowerPoint slides on the VHPB web site: www.vhpb.org.

hospital and high costs of treatment. Most people infected with HCV are unaware, undiagnosed and untreated.

Hepatitis C has been described as the silent killer. Its mortality is substantial: currently, the number of deaths is estimated at more than 350,000 globally each year and the rate is rising.[6]

Screening and testing

The steady improvement of treatment of hepatitis C over the past two decades has been used to justify screening for HCV infection. The rationale for testing people who inject drugs for HCV infection is clear and accepted. The argument for large-scale screening is complicated, however, by the fact that not all infections lead to clinical disease, that existing treatments can have serious side effects and are complex to administer, and that not every diagnosed patient has access to treatment. Differing views on the value of screening when there is no access to treatment were aired at the meeting.

Sadly, most guidance for testing consists mainly of a recommendation to test members of a list of risk groups rather than a fully defined and costed programme. Little has been done to measure the quality of performance of screening programmes, and existing programmes have shown limited effectiveness.

Recognizing that at least 45%-60% of people living with HCV infection in the USA were unaware of their HCV infection status, the Centers for Disease Control and Prevention (CDC) introduced in 2013 an age-based screening strategy consisting of a one-time test for HCV infection for everybody born between 1945 and 1965.[7] The rationale was that most people infected with HCV in the USA were born in that generation and were infected through injecting drug use or unscreened transfusions. This unique programme, which has received legislative mandate in some states, is additional to the existing recommendations for testing on the basis of risk and medical indications and has been well accepted. The cost is covered by health insurance. The initiative's cost-effectiveness is equivalent to that of other screening programmes but depends on treatment costs and rate of treatment take up. It is in its early days, and questions remain about its applicability to other countries.

The traditional approach to laboratory testing has been to use an immunoassay followed by a confirmatory test. With advances in testing, the question can be asked whether it would be better and more effective to conduct simultaneous tests on pooled blood, for example in a large screening

setting (such as blood donors) or targeted group (for instance, baby boomers). Testing in itself requires resources but they are insignificant compared with the costs of treatment.

New technological approaches may help to expand access to testing and treatment. Two examples mentioned were the use of dried blood spot sampling and rapid, low-cost point-of-care tests. The latter can also be used for monitoring the response to treatment (including measuring viral load) but arguments about their value remain.

Treatment

Current therapies

Since the mid-1980s when treatment with interferon was introduced, the addition of ribavirin, the use of pegylated interferon and triple combination therapy with direct-acting antivirals (telaprevir and boceprevir, approved in Europe and the USA in 2011) have dramatically raised cure rates.[8] Current therapy is also lowering the mortality rates for hepatocellular carcinoma. Treatment regimens vary with genotype, with cure rates of 70-80% against genotypes 2 and 3 and lower rates for other genotypes. Therapy with interferon-containing treatments, however, causes serious side effects (which up to half the patients with hepatitis C cannot tolerate) and incurs high costs. Triple therapy also raises concerns about drug interactions. Careful patient selection plays a crucial role in improving the safety of treatment,[9] and monitoring of effectiveness and safety in real world settings is needed. HCV-Target, an international consortium of leading HCV investigators, is collecting standardized data in a common database on patients treated with regimens that include boceprevir and telaprevir in order to evaluate the effects of triple therapy in the broader population.[10] In a similar move, the European Association for the Study of the Liver (EASL) is supporting research into improving registry data collection.[11]

Not all patients are eligible for treatment. Of those who are, many refuse (especially those with asymptomatic infections), for reasons such as consequences for quality of life, work implications, and the desire to wait for the advent of newer, safer medicines. Others do not comply with, or drop out of treatment. In the USA, it is estimated that no more than half the people infected with HCV have been tested, and that only 5%-6% of those infected have been successfully treated.[12] Overall, rates of uptake of treatment are very low.

Many health systems lack the capacity to cope with the disease. The French early access programme confirmed that HCV-infected patients with advanced liver disease should preferably be treated in

specialized centres because of the risk of severe complications, yet there are few specialists.[13] Not all gastroenterologists and infectious disease experts are willing or able to treat hepatitis C; some physicians no longer do so because of the increasing complexities. The need for education – of physicians, nurses and patients – is paramount.

The changing therapeutic landscape

Decisions on new safe, highly effective therapies were imminent at the time of the meeting, with the US Food and Drug Administration scheduled to decide on the licensing of two, sofosbuvir and simeprevir, within weeks. If approved, these would be the first interferon-free therapies for hepatitis C.[b] Many more antiviral agents, belonging to different classes and with different mechanisms of action, are in the development pipeline. They include NS3-4A protease inhibitors (like telaprevir and boceprevir), NS5B polymerase inhibitors, inhibitors of NS5A, and host-targeted agents, such as cyclophilin A inhibitors and microRNA-122 antagonists.

The greatest therapeutic hope lies in interferon-free, once daily, all-oral regimens with directly acting antivirals (with or without ribavirin), holding out the prospect of cure after treatment for 12 weeks compared with an often miserable course of 48 weeks with multiple injections every week. Challenges remain, such as low efficacy in cirrhotics and previous non-responders and against genotype 1a, and the concern that treatment in the "real world" may be more complex and less successful than in carefully controlled clinical trials; moreover, efficacy does not equate with effectiveness.

The advent of all-oral, interferon-free treatment regimens heralds a revolution in treatment, breaking down the barriers to therapy and opening the way to making treatment accessible to many more people. It should dramatically and imminently increase the number of patients being treated, but the immediate obstacle will be cost (see below). For patients in countries with limited resources, pegylated-interferon in combination with ribavirin will remain the standard of care.[c]

[b] On 22 November 2013, the FDA approved use of the HCV protease inhibitor simeprevir in combination with pegylated interferon and ribavirin for treatment of hepatitis C due to HCV genotype 1. In December 2013, the FDA approved the HCV polymerase inhibitor sofosbuvir for use with ribavirin in people infected with HCV genotype 2 or 3 and with pegylated interferon for treatment of infections with genotype 1 or 4. Applications for marketing approval for both antivirals are pending in the European Union and several other countries.

[c] The combination of pegylated interferon and ribavirin for treatment of hepatitis C was included in the Complementary List of the 18th WHO Model List of Essential Medicines issued in April 2013, with a caveat about the high level of expertise and specialized facilities needed for safe and effective use of interferons and the high cost of this treatment.

Modelling predicts that, if the same number of patients as today are treated with new therapies (and therefore higher cure rates than at present), the projected growth in disease burden can be significantly cut.[14] Moreover, if higher cure rate is combined with higher treatment rate and prevention, the burden of hepatitis C can be substantially reduced (if not eliminated) before 2030.

Prices and costs

The price of anti-hepatitis treatments will probably remain (contentiously) high for the next few years; at the time of the meeting, the cost of a 12-week course of treatment of sofosbuvir in the USA was put at US$ 84,000. In some countries the cost is reimbursed by the State or private health insurance companies, but in others it will be a substantial barrier to access. Countries with limited resources will need support to extend HCV testing and treatment. Different approaches to obtaining lower prices are available. Some countries, such as Romania, have compared the prices paid by other countries before negotiating. Other approaches include regional procurement, tiered-pricing or negotiated rebates. Meeting the substantial costs of treatment over the next few years demands urgent investigation of innovative funding mechanisms, including analysis of the success factors behind the creation of some existing models (such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, the GAVI Alliance and UNITAID).

Testing and treatment guidelines

In addition to the cost, the toxicity and complexity of hepatitis C treatment are important barriers to accessing therapy. Physicians face several strategic choices about the course of treatment after diagnosis of HCV infection. Is treatment aimed at preventing secondary transmission? Should all HCV-infected people be treated or should there be a selection process? Patient selection includes, for instance, identification of HCV genotype and determination of the extent of fibrosis (mostly still by invasive liver biopsy). Different approaches are needed for people who have never received treatment before and those who have been treated but relapse, partially respond or do not respond. Once initiated, treatment needs monitoring, for example with (expensive) tests of viral load.

At a time of rapid change in treatment, clear and updated guidelines are increasingly necessary. EASL has issued updated Clinical Practice Guidelines on the Management of Hepatitis C Virus Infection[15] and WHO has finalized its guidelines on screening, care and treatment.[16] Other guidelines exist or are in preparation, for instance those of: the European Centre for Disease Prevention and Control and the European Monitoring Centre for Drugs and Drug Addiction,[17] the European Union's HEPscreen (due 2014) and the American Association for the Study of Liver Disease and the Infectious

Diseases Society of America jointly. Those of the Netherlands[18] and Sweden[19] (update due in 2014) were presented at the meeting. As soon as all-oral triple therapy is licensed, all the existing guidelines will need to be updated.

Country experiences

The country experiences of Croatia, Netherlands, Sweden and Balkan and Mediterranean countries were presented (see VHPB website). In general they confirm the necessity of political commitment and the value of national programmes (including reimbursement of the costs of treatment), the heterogeneity of guidelines and access to treatment, and the observation that existing patients are currently deferring treatment, awaiting the advent of oral, interferon-free therapy.

In Balkan and Mediterranean countries the epidemiology of hepatitis C is changing, with the major population infected being migrants, and health systems are ill-prepared to cope with the influx. Societal factors such as the legacy of war, civil unrest, displacement, and the lack of recognition of viral hepatitis as a public health problem complicate the situation. A summit conference in Nicosia, Cyprus, in 2012 concluded with a call for action which among other things urged cooperation, communication, improved surveillance and prevention programmes, better access to treatment and more community-based programmes.[5]

Vaccines

Progress towards a vaccine for hepatitis C was summarized. Several candidate vaccines exist and small clinical trials have begun. Obstacles to development of a vaccine include the very high mutation rate and genetic diversity of HCV; the fact that neutralizing antibodies are ineffective; the need to induce humoral responses; and the lack of an animal model.[20] The prospects for success or commercial interest appear slim.

Barriers to treatment and ways to overcome them

In four break-out sessions participants discussed obstacles and potential solutions from different perspectives. Barriers are seen at all steps and levels, from policy-making and health care delivery to knowledge and attitudes of the general public and physicians. They were summed up as the four "A"s of access: Availability, Accessibility (by country or region), Affordability (price), and Acceptability (toxicity and complexity of treatment). Lack of awareness may mean lack of diagnosis, which is probably the primary barrier to treatment.[21]

Policy-makers urgently need up-to-date data on the disease burden and to recognize that a surge of cases in people infected more than 20 years ago is about to hit health systems, even though the incidence of HCV infection in people under 20 years of age is decreasing. Costs of treatment, even in rich countries, are unsustainably high and call into question the ability or willingness of insurance systems or governments to cover them, but experience from HIV/AIDS demonstrates that solutions for lowering prices exist. The need for policies is evident (too often, lack of good data provides an excuse to do nothing) and steps must be taken to eliminate the stigmatization engendered by HCV infection.

Other solutions include generation of more and better data on disease burden through seroprevalence and health economic studies. Viral hepatitis needs to be integrated into national health policies, and programmes covering prevention, screening and treatment of hepatitis C should be formulated. The challenge will be to find how to amplify a small increase in funding into a large increase in benefits for patients. Globally, action is needed to respond to the fact that most HCV infections are related to health care settings. Health authorities need to promulgate clear and frank messages, for example about the consequences of infection and chronic disease, the benefits of new treatments, and the need for prevention. Other measures proposed included the decriminalization of drug use.

Many ***patients*** are reluctant to accept interferon-based treatment, sometimes because of the misinformation they obtain through the Internet. Many others have no access to treatment because health authorities offer neither screening nor treatment programmes. The problem of access is exacerbated for disadvantaged populations, who often are unaware of their health rights, and people who inject drugs can experience difficulty in find willing care providers. Infected people may also be reluctant to identify themselves as at risk because of fear of stigmatization.[22]

Advocacy is needed, in particular through celebrities (as with AIDS) who will champion the cause of treating hepatitis C. The stigmatization associated with the link between hepatitis C and injecting drug use (especially as not all those with HCV infection are people who inject drugs) needs to be reduced. Widespread information campaigns should highlight the prospects for better and safer treatment.

Many ***health professionals*** remain poorly informed about hepatitis C and do not welcome injecting drug users as patients. Efficient service delivery is hampered by the heterogeneity of the populations

being served and the lack of coordination between different services. Few general physicians wish to specialize in the complex and rapidly evolving area of treating hepatitis C with its fragmented service delivery. No estimates have been made of the likely human resource needs to cope with existing and new treatment regimens for all those people who need treatment.

More and better educated health workers are essential. The work by support groups and others, for example to correct through social media the misinformation being promulgated on the Internet, needs to be supported and expanded. The natural history of infection and disease needs to be clarified, with standardized actions set out for all stages from diagnosis to access to treatment, cure or relapse. Care also needs to be brought closer to the patient, under specialist supervision, and combined with prevention and harm reduction measures.

Some solutions fall into the area of policy-making, for example, priority setting, training and education, and integration and coordination of viral hepatitis prevention and control in different health delivery systems. Adherence to universal precautions must be ensured in order to eliminate nosocomial transmission. Administrators need better information so as to be able to plan staffing and costing needs. For laboratory testing, rapid tests to determine the viral genotype and rapid point-of-care screening tests need to be evaluated.

For ***pharmaceutical industry*** similar barriers were identified, from lack of policies to poor data. Concern was expressed about the perceived conflict of interest between the industry's marketing activities and support for patients' organizations. Cost-effectiveness studies are generally lacking and the results of those that exist are often not understood or applied. Licensing of new medicines will not resolve the issue of reimbursement of costs. Clinical trials of new regimens would need support from third parties such as the European Union and health/sickness funds.

Solutions included better surveillance, studies on disease burden, modelling and forecasts, and health economics, including cost-effectiveness of treatment. The pharmaceutical industry could contribute to this by sharing the clinical trial data it collects. Treatment regimens need to be simplified.

The way forward

In many countries the existing limited expertise on hepatitis C could be centralized. More hepatologists are needed. Patients should be engaged in the different stages of policy-making

processes and patients' organizations created or strengthened as appropriate. Policy-makers, regulatory authorities and the pharmaceutical industry should collaborate further on issues such as trials and the data needed for licensing. Both leadership and the formulation and implementation of national and international plans, with targets and indicators for the next 10 years, would contribute greatly to the prevention and control of hepatitis C.

Much can be learnt from the experience with HIV/AIDS, including the success of advocacy and the expansion of access to treatment, the concept of treatment as prevention and the value of cost-effectiveness data for shaping policy on care and treatment. It was suggested that the VHPB may have a valuable role to play in the greater sharing of that experience.

Improved awareness and education were highlighted as needing urgent attention. Participants also identified the value of networks and partnerships between public health experts and policy-makers, clinicians, funding agencies, doctors and patients. The focus of national plans should be broadened to cover destigmatization of hepatitis C and improved prevention of transmission between injecting drug users. The potential of combining interventions such as harm reduction and antiviral treatment[23] needs further exploration. Screening programmes are needed to detect the large numbers of people who are infected but unaware of the fact; the CDC's birth cohort programme is a major step forward. Screening should be linked to action such as preventive measures and treatment. Policies need to be formulated for managing people diagnosed with HCV infection but who have no access to treatment. Such public health measures fit in with the current drive towards universal health coverage.

In the long term, the goal of controlling hepatitis C, through increased treatment and prevention, looks feasible, especially in the developed world, but it will be attained only with political will, funding, improvements in health-system infrastructure and capacity-building. In the short term, however, a crisis looms. Many patients have deferred treatment in anticipation of the arrival of new medicines. Many more will seek treatment once they know that therapy is better, more tolerable and affordable; epidemiology confirms that the number of patients with hepatitis C is going to increase.

Health authorities must prepare for what was described as an oncoming tsunami of cases. Hepatitis C is about to become a global public health emergency.

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