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Control of HCV and related disease burden in the United States

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Q. What is the burden and challenges of HCV in the US?

Chronic hepatitis C virus (HCV) infection affects more than 3 million people in the United States with more than 50% undiagnosed prevalent cases[1]. Managing HCV is critical since HCV infection can, in a small but not trivial percentage of cases, lead to chronic liver disease, liver failure, liver transplant or death [2]. The challenges in HCV management are the high prevalence of undiagnosed cases, and an increasing national economic burden which was estimated at $6.5 billion in 2011[3].

Q. Has the burden of HCV decreased following prevention and public health measures?

According to the United States' National Health and Nutrition Examination Survey (NHANES), the prevalence of chronic HCV decreased from 3.2 million in 2002 to 2.7 million in 2012 [4, 5]. It was also estimated that the prevalence of cirrhosis caused by HCV infection increased among Americans from 6.6% in 1990s to 17% in 2012[6]. Several simulation and predictive studies indicated that the prevalence of HCV would continue to decrease due to newly approved HCV therapies and the inclusion of one-time screening for individuals born between 1945 and 1965, the age cohort with the highest HCV prevalence according to HCV screening guidelines. These studies also predicted that the number of patients with cirrhosis, liver cancer and need for liver transplants due to HCV infection will peak in 2020[3,7,8]. This increasing trend could be due to the aging of peak HCV prevalence cohort as well as low diagnosis rates, which leaves many infected individuals prone to advancing to later stages of the disease, when older generation HCV therapies would not be as effective. However, the recently approved HCV therapies could suppress the burden of advanced liver diseases in the next decade.

Q. How will the availability of all-oral regimens contribute to fighting HCV in the near future?

The launch of newly approved all-oral interferon-free HCV therapies, such as sofosbuvir, simeprevir, ledipasvir, elbasvir and grazoprevir, and a 4-drug regimen (paritaprevir, ritonavir, ombitasvir and dasabuvir) revolutionized HCV treatment[9-11] and increased SVR rates to as high as 98%[12, 13]. These agents are superior to traditional interferon-based therapies, which previously were the mainstay of HCV treatment, in that they require shorter treatment duration, have fewer adverse effects, and can be administered to a broader treatment population.

Q. What barriers have to be overcome to achieve HCV eradication in the US?

With the availability of new therapies, most HCV-infected individuals could be cleared of the virus, but several challenges are present from a public health point of view to decrease HCV burden and associated mortality. The first challenge is decreasing the undiagnosed number of HCV cases. The importance of expanding HCV screening beyond risk-based parameters and the 1945-1965 birth cohort have been highlighted in research studies due to its impact on reducing unknown HCV transmissions and increasing rates of treatment that prevent patients from advancing to end-stage complications. Increasing HCV screening rates among individuals, however, would increase the demand for treatment and leads to the second challenge: although new HCV therapies are highly effective,

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their high prices present barriers to care for individuals and healthcare payers. The cost of a 12-week course of treatment with new therapies ranges between $54,000 and $94,000 in the United States. Although large healthcare institutes and federally funded programs such as Medicare and Medicaid, tailored to providing medical care to elderly, low-income families with children, and disabled individuals, would receive rebates and discounts from manufacturers, they spent billions on HCV therapies in 2014[14, 15]. Facing budgetary constraints, most Medicaid programs require prior authorization criteria and offer limited HCV treatment coverage to patients with advanced stages of the disease. Other private insurance providers and Medicare advantage plans also require prior authorization for HCV therapy, and higher insurance premiums in order to provide treatment coverage.

Q. Does treatment capacity influence HCV treatment uptake?

The third challenge in tackling HCV burden in the Unites States is treatment uptake among diagnosed individuals and treatment capacity in terms of the availability of hepatologists to test for treatment authorization and administration. The expansion of overall treatment capacity in the United States and treatment uptake among individuals would prevent most HCV cases from advancing to end-stage liver disease. In conclusion, of all present challenges, healthcare policy-makers in the United States would face difficult decisions to balance cost and public benefit of HCV treatment. The earlier expansion of HCV screening and treatment uptake among individuals in all HCV stages would incur a huge economic burden at present time, but delaying the treatment would incur more cost as untreated individuals progress to advanced HCV stages, along with passing the economic burden to federal government and tax payers when patients age into Medicare. As the prevalence of HCV is decreasing in this decade, screening rates, treatment coverage and cost are the most important factors to affect the future burden of HCV in the United States.

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The success of the HBV vaccination program in China

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Q. Professor Qu what was the hepatitis B burden in China in the era pre-vaccination?

Hepatitis B virus (HBV) infection is one of the leading causes of morbidity and mortality in China, primary liver cancer (PLC) and cirrhosis being the long-term major adverse outcomes of chronic HBV infection[1,2]. In the Chinese population, most chronic infections with HBV are acquired early in life, often during the perinatal period. In 1992 before the national HBV vaccination program was launched, the rate of serum surface antigen (HBsAg) positivity, due to chronic HBV infection, was 9.67 % in the 1-4 age group, i.e. as high as in the general population (9.75%)[3]. In response to WHO recommendations on the prevention of chronic HBV infection and PLC[4], China implemented the universal immunization of newborns by integrating HBV vaccination into the Expended Program of Immunization (EPI), beginning in January, 1992 with 3 doses of vaccines paid by the family[5].

Q. Has the HBV burden in China been modified following vaccination?

Qidong County, with a population of 1.1 million and about 13,000 births each year in 1980s, is a rural area with high chronic HBV prevalence and high incidence and mortality of liver diseases as compared to China as a whole[6, 7]. In order to validate safety and efficacy of plasma-derived HBV vaccines before launching the national immunization program, the Qidong Hepatitis B Intervention Study (QHBIS) was conducted in the period 1983-1990[5, 8, 9], a window period when the vaccine was not available in any rural areas of China. In this study, where approximately 80,000 newborns were randomly assigned to vaccination or control groups, follow-up studies of vaccinated and not-vaccinated cohorts of age 5-6 years and 10-11 years showed a 75% immunity efficacy of the vaccination in reducing HBsAg seroprevalence[5]. In 30-year follow-up studies, more than 72% efficacy of neonatal vaccination against chronic HBV infection in adulthood was achieved, with evidence that neonatal vaccination conferred a protective efficacy of 84% against PLC and 70% against mortality due to severe end-stage chronic liver disease[10].

Q. What obstacles had to be overcome in the implementation of the national vaccination program?

The most challenging issue was to provide enough safe and effective HBV vaccines to meet the yearly requirement of immunizing 20 million newborns and high-risk individuals. The Minister of Public Health favored techniques for manufacturing both plasma-derived and recombinant HBV vaccines from Merck and Co., making plasma-derived vaccine available in the late 1980s whereas a recombinant vaccine was manufactured in early 1993[5]. In 1997 the plasma-derived vaccine was entirely replaced by the recombinant vaccine nationwide, yet owing to the family payment of the HBV vaccines, the vaccination coverage in rural areas was lower than in urban areas [5, 11]. Hence, from 1st January 2002 the vaccination program was integrated into the national EPI program, with the vaccine being provided entirely by the government. With support from Global Alliance on Vaccine and Immunization the HBV vaccination program extended quickly to reach the resources poor areas of China.

Q. What was the outcome in terms of efficacy of the vaccination program?

The nationwide HBV serosurvey conducted in 2006 showed that HBsAg seroprevalence was 0.96% in the population aged 1-4 years, 2.32% in those aged 5-14 years, 5.4% in persons aged 15-19 years, and more than 8.0% in individuals aged 20-59 years [12]. In 2014, the HBsAg seroprevalence declined to 0.32% in the 1~4 age group, 0.94% in the 5~14 age group and 4.38% in those aged 15~29 years [13]. Nationwide neonatal HBV vaccination dramatically decreased the HBV infection in children and young adults.

Q. Was catch-up vaccination effective in preventing chronic HBV infection in unvaccinated adults living in the endemic areas?

In the period 2000-2001 with increased supply of the recombinant HBV vaccine, the unvaccinated children born in Qidong County after 1986 were eligible to receive a 3-dose catch-up vaccination whereas those in the vaccination group were eligible for receiving a one-dose booster [10]. In the years 2010-2013 when all the participants enrolled in the QHBIS reached adulthood and more than half of them agreed to undergo HBsAg determination, more than 72% efficacy of neonatal vaccination against chronic HBV infection in adulthood was achieved. However, efficacy of catch-up

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vaccination received at age 10-14 years was 19% only in reducing HBsAg seroprevalence in adulthood [10], highlighting the crucial importance of HBV vaccination in neonates in highly endemic regions.

Q. How long will vaccinees remain protected against HBV?

Neutralizing anti HBs antibodies conferred by vaccination tend to wane after 10-15 years, overt and occult HBV infection being documented in individual adult vaccinees raising the question whether an adolescent booster is considered necessary [14,15]. In the QHBIS cohort, individual participants received a 3-dose vaccination within 24 hours for the first dose, one month and six months after birth for the second and third dose, respectively, while a bounce of adolescents received an additional booster dose. During adulthood, the risk of becoming chronic HBsAg carriers for participants who were born to HBsAg-positive mothers and received the adolescent booster did decline significantly compared to those not receiving an adolescent booster (hazard ratio = 0.68) [10]. Among first-generation vaccinees who have stepped into adulthood, the HBsAg prevalence was 6.35%-6.47% in men aged 25-39 years living in the rural areas of China [16]. It should be noted however, that HBV is likely to breakthrough in young adults loosing immune memory to HBsAg, particularly when risky behaviours are engaged. Indeed, sexual transmission of HBV is predominating in low endemic areas [17, 18], suggesting that one booster dose is worthwhile in adolescent and adult vaccinees at-risk.

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Benefits of Directly Acting Antivirals (DAA) in HIV/HCV coinfected patients

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Q. In the era of DAA, can persons living with Human Immunodeficiency Virus (HIV) Infection still be considered a "special population"?

In the era of interferon-alfa therapy of Hepatitis C Virus (HCV), persons coinfected with HIV were the quintessence of the special populations because of the low efficacy and safety of HCV treatment, the rapid progression of the disease and the interactions between anti-HCV and antiretroviral drugs. The scenario has been subverted by the success of DAA HCV regimens in both patients with and without HIV coinfection. Yet HIV/HCV coinfected patients continue to be a population with unique characteristics requiring special attention, owing to the high rates of prevalent and incident HCV infection with highly published rates of HCV re-infection following a sustained virological response as well as the burden of drug interactions requiring the collaborative expertise of HIV and HCV clinicians. This explains why we are eagerly looking at novel drugs and treatment strategies (such as short duration treatment) to be assessed in patients with HIV/HCV coinfection.

Q. Has the impact of HCV eradication added an "extrahepatic" value in persons living with HIV?

A large proportion of coinfected individuals has extrahepatic complications that may be indirectly or directly related to HCV, including autoimmune and/or lymphoproliferative disorders, and cardiovascular, renal, metabolic, and central nervous system manifestations. Chronic activation of the immune system and systemic inflammation, hallmarks of both infections, may significantly contribute to extrahepatic comorbidities of HCV in this population. There is substantial evidence that successful antiviral therapy might reduce both hepatic and extrahepatic manifestations of HCV infection in patients coinfected with HIV/HCV.

Q. How does HCV eradication impact on the course of HIV infection and on the efficacy and safety of antiretroviral treatment?

The high rates of success will eliminate concerns about increased risk for antiretroviral-related hepatoxicity in those with HCV infection and potentially increase CD4 T-cell recovery induced by antiretroviral therapy.

Q. Given the high incidence of HCV among HIV patients with high-risk behaviours will DAAs help in curbing this epidemic?

In the past, treatment of HCV infected people did not result in reduced incidence of HCV transmission within this high-risk population. Patients who are actively engaged in such high-risk behaviours such as active injecting drug use often are not deemed ideal candidates for interferon-based treatment because of concerns related to adherence and reinfection risk. However, targeting high-risk populations is exactly what is required in terms of public health policy if incidence rates are to be reduced. All-oral regimens provide a treatment option that can be safely and broadly utilized in high-risk populations with the benefits of curing even individual patients who are unfit to interferon, and addressing broader public health concerns related to HCV. This extends to men who have sex with men, particularly those with HIV infection, who engage in high-risk sexual behaviours that have been associated with HCV exposure. There is a potential opportunity to reduce the total burden of HCV in both of these communities with the use of all-oral regimens, thereby protecting the individual from long-term liver disease and reducing the population risk of HCV exposure. This approach is consistent with the 'treatment as prevention' model of antiretroviral use and has been considered as a model for HCV treatment

Q. Are there still unresolved issues in the treatment of Hepatitis C infected persons with HIV?

Two barriers need to be overcome when treating HIV/HCV coinfected patients – drug-drug interactions and the risk of HCV reinfection. Drug-drug interactions between antiretroviral medications and DAAs are likely to occur resulting in substantial modifications of serum concentrations of the drugs involved. In turn, these changes may lead to increased toxicity or diminished efficacy, not to speak about development of drug resistance. These interactions should be taken into account not only in healthy controls but also in patients treated for both diseases in randomized trials and in real life. Another distinctive epidemiological feature of HIV/HCV coinfected patients is the higher observed number of HCV reinfections occurring in either i.v drug users or MSM, with rates as high as 7.8 and 15.2 per 100 patient years of follow-up . The most likely culprit are unchanged sexual behaviours and other risk behaviours in combination with the emergence of national and international networks of HIV positive men preferentially having unprotected sex with HIV partners (i.e. serosorting) . Therefore, in-depth quasispecies analysis should be performed to reliably distinguish between HCV relapse and reinfection in those patients who are diagnosed with a relapse in current clinical trials, with the aim of preventing development of HCV resistance mutations in DAA treated patients. Recently, the first case of transmission of a DAA-resistant variant of HCV from a patient who was treated with telaprevir to his sexual partner was described. Increasing DAA use in combination with high rates of HCV reinfection has the potential to result in accumulation of HCV DAA-resistant variants that could ultimately impair future DAA treatments.

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How we are going to reduce prevalence of HCV in Poland

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Q. Professor Flisiak, is Poland aiming to eradicate HCV?

Currently, we are not able to eradicate any infectious disease without a specific vaccine because we are not able to diagnose HCV in all infected individuals and to cure all patients with cheap and efficient medications. However, with the availability of highly effective all-oral regimens we will certainly reduce the prevalence and clinical complications of HCV significantly.

Q. Can you tell us how HCV has been treated in Poland to date?

In Poland HCV treatment is reimbursed by Narodowy Fundusz Zdrowia (the NFZ - National Health Fund) according to the therapeutic program approved by the Health Ministry, until 2015, this therapeutic program reimbursed triple therapy containing boceprevir or telaprevir to a limited number of genotype 1 infected patients with advanced fibrosis, who failed previous interferon-based dual therapy or were treatment naïve with IL28B genotype TT. As a result, about 20% of patients had potential access to triple therapy and a large majority of patients were still treated with a suboptimal combination of pegylated interferon alfa (PegIFN-alfa) and ribavirin (RBV). Furthermore, elastography had not been approved as the method to evaluate hepatic fibrosis.

Over the last recent years, the Polish Expert Group for HCV has had opportunities to discuss access to hepatitis C treatment with the Health Ministry. This likely led to the new edition of the NFZ therapeutic program, which started in May 2015 and provided reimbursed simeprevir (SMV) containing triple therapy for all genotype 1 and 4 infected patients without limitations related to hepatic fibrosis (even in patients without fibrosis), previous treatment history and irrespective of IL28B status. Importantly, elastography became the approved method to evaluate hepatic fibrosis

Q. Have all-oral anti-HCV regimens become available in Poland?

Starting from July 2015 the first interferon-free regimens with ombitasvir/paritaprevir/ritonavir (OBV/PRV/r) combined with dasabuvir (DSV) and RBV were approved for reimbursement to all individuals infected with HCV genotypes 1 or 4. In September, the second interferon-free combination containing asunaprevir (ASV) and daclatasvir (DCV) for genotype 1b was included in the NFZ therapeutic program as a move to enhance market competition. Finally, in November sofosbuvir (SOF) for possible combination with RBV(and PegIFN-alfa) in genotypes 2-6, and SOF/ledipasvir (LDV) in genotype 1 were approved for reimbursement. However pricing remains a barrier, where the number of treated patients remains on the same level as in the era of interferon-based therapy. According to available sales and tender data, we can assume that in 2015 almost 5000 patients at least started therapy for chronic HCV including 3000 who received interferon-free regimens, mostly OBV/PRV/r±DSV±RBV. Positive changes in the perception of HCV issues by authorities was probably due to the stable composition of Health Ministry officers for almost eight years that allowed discussion with the same people. Therefore, final benefits from new therapeutic options and cost-efficacy analyses were well understood, and resulted in the new therapeutic program without unnecessary and strict limitations.

Q. What is the burden of HCV in your country and what are the plans to reduce HCV-related mortality?

According to estimates based on the recent epidemiological studies we can assume that about 200 000 individuals in Poland are infected with HCV. To achieve >90% reduction of HCV prevalence by 2030 it will be necessary to diagnose and treat 15 000 patients annually with efficacy exceeding 90%. The current level of 5000 individuals both diagnosed and treated can result in a 30% reduction within the next 15 years. Despite the availability of interferon-free regimens, there is still limited access to treatment owing to the annual financial cap established for each treating center by NFZ resulting in waiting lists. This could be solved with an increase of funds dedicated to HCV therapy that has happened in recent years together with a further decrease of costs for new therapeutic options, that are expected to be registered this year and in 2017. Unfortunately, increasing the number of treated patients highlighted the problem of insufficient staffing. Therefore, to achieve a 3-fold increase of individuals treated annually it will be essential to increase the number of physicians and nurses involved in HCV management.

Q. Are you planning to target HCV through mass screening programs?

The next step for HCV elimination in Poland will be identifying undiagnosed cases. To this end, in mid-2015, a national program for HCV elimination was submitted to the Health Ministry by National Consultants for Infectious Diseases and Polish Group of HCV Experts. This program assumes wide access to highly efficient therapy and anti-HCV testing of populations identified in Poland as at high risk for HCV infection that include:

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- recipients of blood transfusion before 1992
- intravenous drug users (ongoing and past)
- hospitalized more than 3 times during life time
- history of imprisonment
- tested for HIV infection
- demonstrated elevated ALT
- diagnosed or suspected of any hepatic disorder

Unfortunately, we have not received any response from the Health Ministry.so far. Even with efficient, cheap, safe and user -friendly medication, significant reduction of HCV prevalence does not seem to be possible without national screening and prevention programs supported by the health authority and the national health insurance system. Consequently, we hope to continue the positive dialogue with the health authority that has been successful in creating access to anti-HCV treatment in recent years.

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Health Related Quality of Life for patients with Hepatitis B and Hepatitis C Infection

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Hepatitis B and C are among the most common causes of chronic liver diseases worldwide. Chronic hepatitis B (CH-B) and C (CH-C) have significant clinical impact on patients' lives with potential for development of cirrhosis and its complications leading to increased mortality. Additionally, both chronic hepatitis B and C affect patients' health related quality of life (HRQL) and patient experience. In this context, understanding the impact of CH-C and CH-B from the patient perspective is important. The following report discusses the different tools used to measure HRQL and other patient reported outcomes as well as what we have learned about the impact of hepatitis C and B and their treatments on the outcomes that are important to patients.

Introduction:

Hepatitis C virus affects millions of people around the world and is the predominant cause of chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC) in the Americas, Europe, Japan and the Middle East. [1] On the other hand, hepatitis B virus (HBV) is widespread throughout Asia, especially in China, and is a major cause of cirrhosis and its complications, including HCC in Asia. [2]

Q. Why should one consider measuring health related quality of life? What information does the measurement provide that the healthcare provider does not obtain during a patient's clinical visit with their physician?

The clinical outcomes of HCV and HBV do not always provide information about the patients' experience with their disease. Insight into how these diseases and their respective treatments affect patient-reported outcomes (PROs), such as health-related quality of life (HRQL), is imperative to understand the full impact of these diseases on patients' health and well-being. In fact, PROs provide information that may assist the providers in managing patients' expectations of their care and may potentially improve their adherence to treatment.[3,4] Further, HRQL measures may help provide the healthcare provider with a more thorough understanding of the social constraints and determinants of a patient's disease. [3,4] Actually, under the healthcare reform laws in the United States, measuring patient reported outcomes, as surrogate markers of patients' experience, has become a mandated recommendation. Further, on a national level, gathering PRO information helps to inform healthcare policy makers to better understand the true burden of disease. [5] In the following paragraphs, we describe some of the most common instruments used to measure PRO's in patients with HBV and HCV infection.

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Q. What tools are available to measure health related quality of life?

Patient reported outcome (PRO) is defined as a report that comes directly from patients about their health without any modification by anyone. Although the term HRQL and PRO's are often used interchangeably, PROs do include other outcomes reported by and important to the patients. Other alternative terms commonly used to define a patient's perspective (self- report) of their physical, mental and social functioning include health status and well-being. [6] In general, HRQL tools or instruments are divided into General Measures (Generic Instruments) and disease specific instruments. [7]

The most commonly used generic instrument to measure HRQL is the Short Form-36 version 2 (SF-36v2). [12] This tool measures eight HRQL domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). The total score from 0-100 with higher values corresponding to a better health status. There are also two summary scores which summarize the physical and mental health components of the SF-36: the Physical Component Summary score (PCS) and Mental Component Summary score (MCS). The SF-36 scales and summary scores are calculated using the QualityMetric Health Outcomes Scoring Software 4.5 (Lincoln, RI, USA) and the 2009 United States (U.S.) population norms.[8]

Other generic instruments used to measure HRQL include the Sickness Impact Profile (SIP) and the Quality of Well-being Scale (QWB). The SIP tool measures a change in behavior as a consequence of illness. It contains 136 items covering 12 categories/activities of daily living including: sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness behavior, emotional behavior, and communication. Higher scores reflect greater dysfunction. An aggregate psychosocial score is derived from four categories, and an aggregate physical score is calculated from three categories. [7,9]

The QWB-SA investigates health oriented symptoms and functioning. Symptoms are measured using questions that ask about the presence or absence of different symptoms or conditions. A patient's functioning is assessed by questions investigating functional limitations over the previous three days for 3 domains: mobility, physical activity, and social activity. The domain scores are combined into a total score that provides a numerical point-in-time expression of well-being ranging from zero (0) for death to one (1.0) for optimal functioning. [7]

There are also several liver disease-specific tools used for measuring HRQL in patients suffering from chronic liver disease. The Chronic Liver Disease Questionnaire (CLDQ) is a validated instrument developed specifically for assessment of HRQL in chronic liver disease patients. [10] It includes 29 items and 4 HRQL scales: activity and energy (AE), emotional (EM), worry (WO), and systemic (SY). [10] These scales are averaged for a total score that ranges from 1-7 with higher values representing better HRQL. [10] A hepatitis C-specific version has also been developed and validated (CLDQ-HCV) which consists of 5 scales measuring: Activity/Energy (AE), Emotion (EM), Worry (WO), Systemic (SY), and CLDQ-HCV total (CLDQ-Tot). [11] Both CLDQ and CLDQ-HCV are now widely used throughout the world to assess HRQL for patients with liver disease and HCV. [12] Additionally, a disease-specific HRQL instrument for patients with Non-alcoholic Fatty Liver Disease (CLDQ-NAFLD) has recently been developed and validated [13]

Other tools include the short form liver disease quality of life tool (SF-LDQOL) which is comprised of 36 disease-targeted items representing 9 domains, symptoms of liver disease, and the effects of liver disease. The SF-LDQOL has been shown to correlate highly with SF-36 scores, symptom severity, disability days, and global health. [7] The Post–Liver Transplant Quality of Life (pLTQ) Instrument is a relatively new measurement tool developed to measure health related quality of life in post- transplant patients. The tool includes 32 items covering 8 domains (Emotional Function, Worry, Medications, Physical Function, Healthcare, Graft Rejection Concern, Financial, and Pain) and is stable over time. [14] The Hepatitis Quality of Life Questionnaire™ Version 2 (HQLQv2™) is a two-part survey designed to assess the functional health and well-being of patients with chronic hepatitis C. It includes the SF-36v2® Health Survey and 15 additional questions measuring other health concepts relevant to assessing the impact of hepatitis (e.g. health distress, positive well-being) as well as other disease-specific concepts (e.g. hepatitis-specific functional limitations, hepatitis-specific distress). [7] This tool was developed to help patients and clinicians monitor the effects of hepatitis C and treatment. [9,11] The Liver Disease Symptom Index 2.0 (LDSI 2.0) uses 18 items to measure symptom severity and hindrance in the past week. [7] The LDSI provides complementary information to the information gleaned from the SF-36 so, the LDSI 2.0 is considered an additive tool when measuring HRQL in those with liver disease. [7]

Patients with HCV and HBV infection are known to suffer from disease associated fatigue which impacts their work productivity. [3,11] The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) is the most commonly used tool to measure fatigue with the other known fatigue tools used occasionally with liver disease known as the Fatigue Severity Scale (FSS) and the Chronic Fatigue Screener (FSS)[6,7]. The Work Productivity and Activity Index (WPAI) Questionnaire is used to measure the effect of the disease on patients' ability to work. [6,7]

The FACIT-F is a 40-item questionnaire used to evaluate fatigue and its impact upon daily activities [6,7]. The tool measures four well-being domains (physical (PWB), emotional (EWB), social (SWB) and functional (FWB)) and one fatigue subscale domain (FS). These five scales together add up to the total FACIT-F score which ranges from 0-160 with higher values representing better well-being.

The WPAI questionnaire evaluates a patients' impairment in their daily activities and work productivity associated with a specific health problem. [6,7] Studies which have used the WPAI ask questions about the specific impact of their disease on their work productivity and ability to perform their daily activities. The work productivity is measured only in those who are employed at the time of being asked to complete the questionnaire. The WPAI is made up of two domains: absenteeism and presenteeism which is defined as the amount of time at work that one is unproductive as a result of their disease. The activity impairment domain investigates impairment in all other daily activities outside of work and is completed by all patients regardless of their employment status. Unlike the other PRO instruments discussed, higher WPAI scores are equal to lower work productivity or activity. In fact, the minimum possible value of 0 represents no impairment in work productivity or daily activities while the value of 1 represents complete inability to work or perform those activities. [6,7]

Finally, one of the practical applications of quality of life assessment is their use in economic analysis. In economic analysis, the quantity of and quality of life are measures used to determine whether an intervention is economically feasible. In fact, the gold standard for cost-utility assessment is quality-adjusted years of life gained or lost (QUALY's).

Health Utility Assessment (HUA) is the method used to obtain quality of life adjustments and is either determined through direct assessment (time-trade-off or standard gamble techniques) or through indirect assessment which uses questionnaires designed to estimate patients' preferences for a state of health and quality adjust outcomes. [6,7] The three questionnaires most commonly used to obtain the HUA are the Short Form-6D

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(SF-6D), the Health Utilities Index (HUI), and the EuroQol-5D (EQ-5D). [6,7]

The SF6D is developed by using scores from The SF-36v2® or the SF-12v2® Health Survey. The HUI I which is comprised of two scales, HUI2 and HUI3, which together describe almost 1,000,000 unique health states made up of a generic comprehensive health profile system and a generic HRQL utility scoring system. The HUI3 is usually used as the measure for primary analyses since it has population norms as part of its measurement. HUI2 offers distinct, independent attributes including self-care, emotion that focuses on worry/anxiety, and fertility. The two systems are independent but complementary. As mentioned, the HUI3 is used as the primary utility measurement while the HUI2 is used for secondary/ sensitivity analyses. [6,7,8]

Finally, the most commonly used health utility tool in the European community is the EQ-5D. The original version of the EQ-5D (EuroQol) had 14 health states in 6 different domains; however, the current version consists of five dimensions (EQ-5D): mobility, self-care, usual activities, pain/discomfort, anxiety/depression and is measured on one of five levels of severity: no problems, slight problems, moderate problems, severe problems or unable to perform the activity. For scoring, each dimension stands on its own merit so the scores are not combined together for a cardinal score rather each score is recorded separately, for example, 11111, which means there are no reported problems in any of the five areas. [6,7] The EQ-5D is used in a substantial number of clinical and population studies due to its ability to be converted to one generic monetary value useful to many European countries. [6,7]

Q. What have we learned from the use of these tools?

After discovery of HCV and understanding its impact on clinical outcomes, there has been a great deal of interest in better understanding the impact of HCV on HRQL and other PROs. In this context, we know that HCV infection impairs patient's physical, mental, and functional health.[15] In particular, HRQL research has provided insight into the higher reports of fatigue, depression, and decreased work productivity among patients infected with HCV when compared to the non-HCV population. Additionally, the severity of liver disease further impairs HRQL[15]. Furthermore, there is substantial evidence that treatment with peglyated interferon and ribavirin HCV treatment can severely impact HRQL and work productivity. On the other hand, the new direct acting agents (DAA's) free of both interferon and ribavirin can improve PROs. In fact, this improvement can occur as early as 2 weeks into treatment across all age groups and stage of liver disease. In addition to HRQL, the new regimens improve work productivity. In fact, among the US working population, an annual societal cost of $7.1 billion has been estimated in lost wages due to low worker productivity related to HCV. On the other hand, improvement in worker productivity after HCV cure with these new regimens leads to $2.7 billion savings over a 1-year time horizon. [16]

In contrast to HCV, there are fewer studies assessing PROs in patients infected with HBV. Nonetheless, studies have shown that HRQL in patients with HBV is significantly lower than the general population, and patients with other liver diseases (except for HCV) after controlling for the stage of disease. Patients with HBV experience impairment of HRQL related to physical functioning and fatigue domains that can affect their work productivity. [17] Although interferon-based therapy can have a negative impact on these patients' HRQL, there are not published data specifically on the impact of the oral nucleotide or nucleoside analogues for treatment of HBV. In contrast, HBV prevention with vaccines may improve HRQL and is considered cost-effective. Nevertheless, this issue needs additional research.

Conclusion

Chronic hepatitis B and C negatively can negatively impact patients' HRQL and other PROs. Although some studies have reported no significant HRQL differences between HBV and HCV, most studies suggest that patients with HCV experience more impairment of HRQL. Although the old interferon-based regimens for HCV severely impact PROs, the new all oral regimens for HCV, not only have very high cure rates but also have positive impact on these patients' HRQL. More research is needed to understand the full impact of HBV and the oral treatment for HBV suppression on PROs and HRQL domains.

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