CONQUERING C – GOING BEYOND CURE

Summary of presentations from the Gilead Satellite Symposium, held at the International Liver Congress™ 2015, the 50th Annual Meeting of the European Association for the Study of the Liver, Vienna, Austria, 24th April 2015

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Disclosure: All the authors have been speakers for Gilead Sciences Europe Ltd. Stefan Zeuzem has provided consultancy and participated in speakers' bureaus for Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, and Merck. Nezam H. Afdhal has received research support for hepatitis C virus studies from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Merck, and Vertex Pharmaceuticals; has been a consultant and/or has participated as an advisory board member for AbbVie, Achillion Pharmaceuticals, Echosens, Gilead Sciences, GlaxoSmithKline, Janssen, Kadmon Corporation, Ligand, Merck, Springbank Pharmaceuticals, and Sandhill Scientific; holds stock or stock options with Springbank; and is currently the editor of the *Journal of Viral Hepatitis*. Marc Bourlière has consulted and advised for Bristol-Myers Squibb, Merck, Roche, AbbVie, Gilead, Janssen, and MSD, and also advised for Vertex. Graham Foster has received funding from AbbVie, Achillion Pharmaceuticals, Alnylam Pharmaceuticals, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead Sciences, Merck, Novartis, Roche, Spring Bank Pharmaceuticals, and Tekmira Pharmaceuticals. Charles Gore is currently the President of the World Hepatitis Alliance in Switzerland. Jean-Michel Pawlotsky has received research grants from Gilead Sciences and served as a scientific advisor for Abbvie, Achillion, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Idenix, Janssen, Merck, Novartis, and Roche.
Acknowledgements: Writing assistance was provided by Dr Juliet Bell of apothecom scopemedical Ltd.
Support: The HCV satellite symposium at EASL 2015 was a medical education event. The publication of this review article was funded by Gilead Sciences Europe Ltd., including medical writing assistance. The views and opinions expressed are those of the authors and not necessarily of Gilead Sciences Europe Ltd.
Citation: EMJ Hepatol. 2015;3[2]:42-51.

MEETING SUMMARY

Prof Zeuzem opened the symposium by acknowledging that there is a new era in hepatitis C virus (HCV) treatment, due to the availability of efficacious treatments that could eradicate the disease. Prof Pawlotsky outlined recent advances in the field of HCV and discussed the European Association for the Study of the Liver (EASL) Recommendations on Treatment of Hepatitis C 2015, which were released at the congress. These recommendations prioritise the available HCV treatments in Europe, from treatment-naïve to treatment-experienced patients and in the context of patients with various stages of HCV disease, and highlight the need to remain vigilant for possible drug–drug interactions (DDIs) between HCV direct-acting antiviral agent (DAA) treatments and regular pharmaceutical medications. Dr Bourlière then described the remaining challenges in HCV relating to treatment of certain patient populations, such as those with advanced disease and specific contraindications. Prof Foster presented the real-life challenges of treating

a patient population that can have heterogeneous characteristics and presented the recent outcomes of nationally implemented programmes for HCV. Mr Charles Gore, a patient advocate, described the World Health Organization (WHO) policies in HCV and highlighted that government lobbying by physicians and patients was required to improve awareness and prioritise HCV treatment. Prof Afdhal then summarised the current impact of HCV on productiveness and patient outcomes, and spoke about the benefits of patient access programmes in expanding the pool of patients who can be treated along with the cost implications of the global eradication of HCV. Finally, Prof Zeuzem emphasised how HCV is currently perceived as a lower global priority compared with other viral diseases and that lobbying will be required to demonstrate how investments into the treatment of HCV patients would dramatically reduce the prevalence and long-term costs of the disease.

Conquering C – Looking Beyond Cure

Professor Stefan Zeuzem

There is a need to treat HCV-infected adults due to the increased risk of premature death[1] and curability of the chronic viral disease.[2-6] The efficaciousness of DAAs on mortality, morbidity, and sustained virological response (SVR) rates >90% have been demonstrated in recent clinical studies.[2,5-7]

Real-world data have also demonstrated the effectiveness of such treatments and their successful transition from a trial to a clinical setting.[8] However, the translation of SVR to long-term outcomes and eradication of the disease may present some challenges. Patients with advanced stages of HCV infection can be treated successfully; however, long-term surveillance is still required for hepatocellular carcinoma (HCC).

Although new treatments for patients with HCV have ushered in a new era where the disease can be eradicated, this is dependent on certain aspects such as treatment access, policy changes, and patient factors that include existing disease status.

Conquering C – Solutions For All Patient Types

Professor Jean-Michel Pawlotsky

The goal of therapy is to cure HCV infection, preventing complications including compensated or decompensated cirrhosis, HCC, severe extra-hepatic manifestations, and death. The EASL Recommendations on Treatment of Hepatitis C 2015 defined the HCV therapy endpoint as SVR with undetectable HCV RNA (≤15 IU/ml), 12 or 24 weeks after the end of treatment.[9] The simple life cycle of HCV has resulted in effective treatments that are well tolerated and can be grouped into four classes: protease inhibitors that inhibit polyprotein processing (i.e. the maturation of viral proteins), nucleotide analogues and non-nucleoside inhibitors of the HCV RNA-dependent RNA polymerase that affect HCV replication, and non-structural protein 5A (NS5A) inhibitors that both indirectly inhibit viral replication and block the assembly and release of the virus.[10]

Efficacious treatments are available and the EASL Recommendations on Treatment of Hepatitis C 2015 now highlight the need to prioritise specific groups of patients, due to the current cost of certain medications and the large number of individuals with an indication for HCV therapy (Table 1).[9] The EASL recommendations describe treatments for patients with a high severity of HCV disease, clinically significant extra-hepatic manifestations, or debilitating fatigue. Patients with specific risk factors should also be prioritised treatment for HCV, including HIV or hepatitis B virus (HBV) co-infection and those at higher risk of transmitting HCV (people who inject drugs, men who have sex with men with high-risk sexual practices, and prisoners).

Recently approved DAAs in the EU include sofosbuvir (SOF), a nucleotide analogue that is active against all genotypes (GT), simeprevir (SIM), a protease inhibitor against GT1 and 4,[11-13] and daclatasvir (DCV), a pan-genotypic inhibitor approved for GT1, 3, 4, 5, and 6.[11] A fixed-dose combination of ledipasvir (LDV)/SOF active against HCV GT1 and 4 has been approved by the European Medicines Agency, while the 2015 EASL recommendations also advise the use of LDV/SOF for GT5 and 6.[9,14] A combination of ombitasvir (OMB)/paritaprevir (PTV)/ritonavir (RIT) should be prescribed for GT1 and 4, which can be combined with dasabuvir (DSV) for GT1 patients.[14-16] A variety of recommended treatment options according to HCV GT are shown in Figure 1.[9]

Table 1: Treatment prioritisation of patients with hepatitis C virus according to recommendations from the European Association for the Study of the Liver.

Treatment priority	Patient group
Treatment should be prioritised	- Patients with significant fibrosis (F3) or cirrhosis (F4), including decompensated cirrhosis - Patients with HIV co-infection - Patients with HBV co-infection - Patients with an indication for liver transplantation - Patients with HCV recurrence after liver transplantation - Patients with clinically significant extra-hepatic manifestations - Patients with debilitating fatigue - Individuals at risk of transmitting HCV
Treatment is justified	- Patients with moderate fibrosis (F2)
Treatment can be deferred	- Patients with no or mild disease (F0-F1) and none of the above-mentioned extra-hepatic manifestations
Treatment is not recommended	- Patients with limited life expectancy due to non-liver-related comorbidities

From Jean-Michel Pawlotsky, presentation at the Gilead Satellite Symposium, held at the International Liver Congress (ILC), Vienna, Austria, 24th April 2015.
HBV: hepatitis B virus; HCV: hepatitis C virus.

IFN-free regimens	HCV genotype
Sofosbuvir + RBV	2, 3
Ledipasvir/sofosbuvir (±RBV)	1, 4, 5, 6
Ombitasvir/paritaprevir/ritonavir + dasabuvir (±RBV)	1
Sofosbuvir + dimeprevir (±RBV)	1, 4
Sofosbuvir + daclatasvir (±RBV)	All
Ombitasvir/paritaprevir/ritonavir (±RBV)	4
IFN-containing regimes	
PEG-IFNα + RBV + sofobuvir	All
PEG-IFNα + RBV + simeprevir	1, 4

Figure 1: Treatment options for patients with hepatitis C virus (HCV), according to recommendations from the European Association for the Study of the Liver.[9]
From Jean-Michel Pawlotsky, presentation at the Gilead Satellite Symposium, held at the International Liver Congress (ILC), Vienna, Austria, 24th April 2015.
IFN: interferon; PEG-IFNα: pegylated interferon alpha; RBV: ribavirin.

Treatment recommendations are provided as numbered options to address the needs of all patient types, with various criteria to inform the selection of each specific DAA regimen, such as HCV GT (including GT subtype for some options), severity of liver disease, patient comorbidities, the DAA pharmacokinetics profile, DDIs, and the patient's prior treatment experience. For the interferon (IFN)-free fixed-dose combination of LDV/SOF with or without ribavirin (RBV), treatment recommendations for patients with GT1 apply across a broad range of patient characteristics,[9] including non-cirrhotic and certain cirrhotic patients,[17,18] patients with compensated cirrhosis who are treatment-experienced or treatment-naïve,[19,20] and those who are HIV–HCV coinfected. OMB/PTV/RIT+DSV with or without RBV can also be used for patients with GT1 (subtypes 1b and

1a) both with and without cirrhosis, with studies showing SVR rates of >90% in patients who had GT1, cirrhosis, and were either treatment-experienced or treatment-naïve.[20] IFN-free regimens can also be used in HIV–HCV coinfected patients as per HCV monoinfected patients, as described by Osinusi et al.[21]

Patients with compensated cirrhosis and who had failed prior treatments were treated with LDV/SOF+RBV and demonstrated high SVR rates >95%,[19] as well as those with GT1 and decompensated cirrhosis (SVR rates >85%).[22,23] Post-transplantation patients with a fibrosis score between F0–3 or with Child-Turcotte-Pugh (CTP) Stage A, and HCV recurrence, were given LDV/SOF+RBV and showed an SVR rate of 96% after 12 weeks of treatment.[22,24] SVR rates were reduced in patients with CTP Stages B and C who were prescribed the treatment regimen of LDV/SOF+RBV. Treatment-naïve patients with GT4 displayed an SVR rate of 95% in a recent Phase II trial when prescribed LDV/SOF,[25] while patient populations with GT4 who were treatment-naïve or treatment-experienced and had not shown any cirrhosis presented with 100% SVR after 24 weeks of treatment with OMB/PTV/RIT.[26,27]

Although the efficacy of some treatment regimens has been established in certain patient populations, remaining treatment challenges include options for patients with severe chronic kidney disease or end-stage renal disease.[9] DDIs can also present difficulties when treating certain patients taking prescribed and/or over-the-counter medications, therefore guidance from EASL and drug interaction charts from the website of the Department of Pharmacology, University of Liverpool[28] may assist in the determination of an optimal treatment regimen. However, physicians should remain vigilant for any adverse events that may result from certain treatment combinations. Furthermore, recommendations for patients who have failed an IFN-free regimen are based upon indirect evidence, and real-life studies will again be useful for the confirmation of efficacious treatment strategies. Current re-treatment regimens should contain SOF and RBV along with one or two other DAAs for a duration of 12 or 24 weeks.[9]

In summary, IFN-free therapies have provided physicians with a curative and tolerable toolbox with which to treat patients with HCV. Remaining challenges include how to implement treatment strategies in the most optimal, effective, and cost-effective way as well as how to treat certain patient populations, such as those who have failed IFN-free regimens.

Conquering C – Solutions For Advanced Disease

Doctor Marc Bourlière

The translation of SVR improvements into a curative treatment for patients requires consideration of several factors, which include the stage of fibrosis. HCV accounts for one-in-four cases of cirrhosis or HCC in the global population, rising to 90% in certain high-incidence populations such as in Egypt or Japan.[29] A US-based study found that compared to matched patients without HCV, mean Fibrosis-4 scores doubled during the first 4 years after HCV infection.[30] Subsequently, 18% of this population developed cirrhosis within 10 years of having HCV, highlighting the need for early treatment. It has recently been established that achieving an SVR is associated with significantly decreased risk of mortality, and reduced risks of HCC and requirement of liver transplant (Figure 2),[31] and studies have shown that the risk of disease progression is also linked to fibrosis stage.[32] Achieving SVR is therefore not sufficient to prevent HCC in patients who are already cirrhotic; ongoing monitoring is then required.

As described above, recently available DAA combinations have enabled the treatment of patients who are compensated cirrhotic and also in some decompensated patients. The treatment regimen of OMB/PTV/RIT+DSV and RBV showed an SVR of 89–100% in patients with GT1 who were compensated cirrhotic,[15] and the regimen is also recommended for cirrhotic patients who have GT1a or 1b.[15,16,20,33,34]

A post-hoc analysis of data from seven clinical trials has shown that laboratory parameters improve along with SVR for a treatment regimen of LDV/SOF that was prescribed with or without RBV to patients who were treatment-naïve or treatment-experienced and with compensated cirrhosis.[19] A similar safety profile was reported in non-cirrhotic patients. Albumin, bilirubin, alanine aminotransferase levels, the international normalised ratio, and platelet counts significantly improved along with SVR in these patients, indicating early benefits for the compensated cirrhotic patients. A correlation of improved laboratory parameters

with SVR was also shown in cirrhotic GT1 patients who had previously failed protease inhibitor triple therapy and were treated with LDV/SOF, with or without RBV.[35] The SOLAR-1 study also demonstrated improved rates of SVR (>85%) with decompensated CTP B and C patients who were receiving LDV/SOF+RBV, with an improved Model for End-Stage Liver Disease (MELD) score after 12 and 24 weeks.[23] Improvements in SVR, laboratory parameters, and MELD score were observed in post-transplantation patients using the same treatment regimen after 12 and 24 weeks.[24] Results were similar in the SOLAR-2 study of pre and post-transplantation patients where a high rate of SVR was achieved,[36] demonstrating the immediate benefits of treating patients with severe HCV disease.

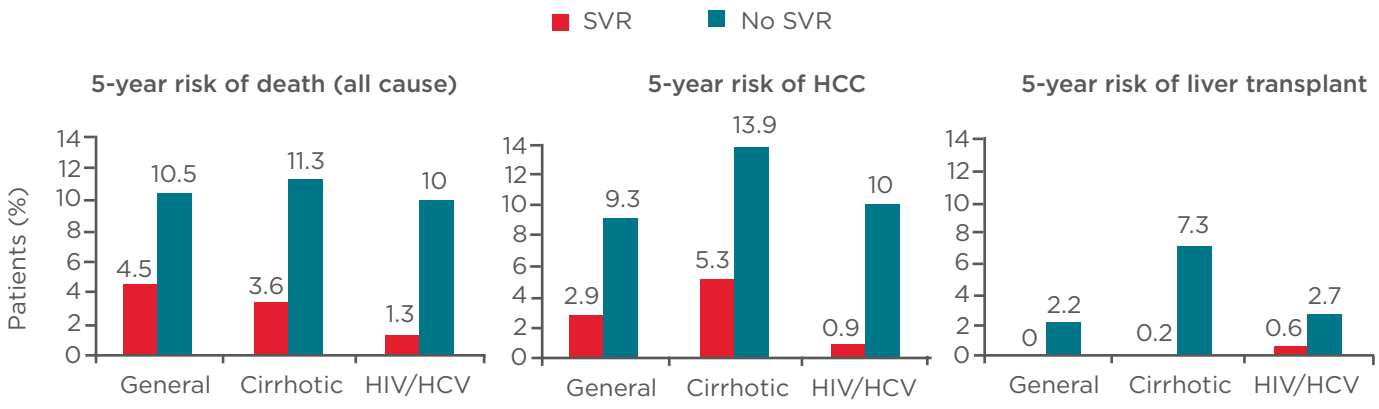
Moreover, in the SOLAR-2 trial, 48% of the patients who had been initially classed as CTP C at baseline were reduced to Class B and 5% to Class A at Week 4 of follow-up.[36] Furthermore, of the patients in CTP Class B at baseline, 35% were CTP A by the end of treatment. This beneficial effect of treatment on the CTP class has also been reported for the regimen of DCV with either SOF or SIM, both with and without RBV. Results in GT1 post-transplantation patients showed significant improvements in MELD and CTP scores as well as the stabilisation of laboratory and clinical status.[37]

In conclusion, treating patients as early as possible to ensure that cirrhosis does not occur and selecting treatments with an optimal efficacy for a particular patient profile should result in the ideal outcome. Although there have been positive outcomes and improved liver function in patients with a higher severity of HCV disease, the ideal situation would be to treat patients as soon as possible.[38]

Conquering C – Solutions For Real Life

Professor Graham Foster

Although the recent EASL recommendations serve as an invaluable user guide for HCV and advocate the use of IFN-free therapies, there can be some complications with implementing the guidance in routine clinical practice.[9] While it is agreed that patients should be treated as early as possible, treatment access may not allow for therapies to be administered until the disease has reached a later stage. However, patient factors that include comorbidities, diabetes, obesity, and alcohol problems can also contribute to the exacerbation of HCV disease, and clinical advice can therefore contribute towards lessening these issues.



- Achieving SVR was associated with:
  - 62-84% reduction in all-cause mortality
  - 68-79% reduction in risk of HCC
  - 90% reduction in risk of liver transplant

Figure 2: Sustained virological response is associated with reduced mortality, hepatocellular carcinoma, and liver transplant, as reported by a meta-analysis of 129 studies of IFN-based therapy in 34,563 patients with hepatitis C virus.[31]

From Marc Bourlière, presentation at the Gilead Satellite Symposium, held at International Liver Congress (ILC), Vienna, Austria, 24th April 2015.

IFN: interferon; SVR: sustained virological response; HCC: hepatocellular carcinoma; HCV: hepatitis C virus.

Table 2: A summary of the possible drug–drug interactions that can result from certain treatment combinations.[11–16,28,75–78]

	Victim of DDI	Perpetrator of DDI	DDI potential
Telaprevir	Substrate for CYP 3A4, P-gp	Inhibits CYP 3A4, P-gp & OATP 1B1/2	High
Boceprevir	Substrate for aldoketoreductase, CYP 3A4, P-gp, BCRP	Inhibits CYP 3A4 & P-gp	High
Ombitasvir, paritaprevir, dasabuvir, ritonavir	Inhibits CYP 3A4; substrate for CYP 3A4, CYP 2C8, OATP 1B1/3, P-gp & BCRP enzyme inducer	Inhibits CYP 3A4, OATP 1B1/3, OATP 2B1, OCT 1, BCRP, P-gp, UGT 1A1, CYP 2C19	High
Simeprevir	Substrate for CYP 3A4, P-gp & OATP 1B1	Inhibits OATP 1B1 & P-gp; mild inhibitor of CYP 1A2 & gut CYP 3A4	Moderate
Daclatasvir	Substrate for CYP 3A4 & P-gp	Inhibits OATP 1B1, OCT 1, P-gp & BCRP	Moderate
Ledipasvir/sofosbuvir	Substrate for P-gp & BCRP	Inhibits P-gp, BCRP, gut CYP 3A4 & UGT 1A1; induces CYP 3A4 & UGT 1A1	Low
Sofosbuvir	Substrate for P-gp & BCRP (affects prodrug but not active metabolite)		Low

From Graham Foster, presentation at the Gilead Satellite Symposium, held at the International Liver Congress (ILC), Vienna, Austria, 24th April 2015.
BCRP: breast cancer resistance protein; CYP: cytochrome P; OATP: organic anion transporter polypeptide; OCT: organic cation transporter; P-gp: P-glycoprotein; UGT: uridine 5'-diphospho-glucuronosyltransferase; DDI: drug–drug interaction.

To facilitate patient outcomes further, treatment regimens can be adapted around the lifestyle of the patient to improve adherence, with consideration given to possible DDIs (Table 2).[28] Patient drug histories are very pertinent and over-the-counter medications such as St John's Wort should be assessed, alongside any existing prescription medications. The reduction in complexity and duration of newly available oral therapies compared with previous therapies may also assist with patient adherence,[39] as well as extending the range of patients who can be treated to include those with a milder form of HCV if authorised by the healthcare provider.[38]

Although there is a larger selection of efficacious treatments available that enable a greater proportion of patients to be treated, the order of prioritisation of these patients still requires agreement. The uptake of DAA regimens during 2014–2015 has varied between countries, with physicians in the USA switching to SOF+SIM or SOF+RBV as soon as possible.[40] SVR rates in an observational study by the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) were >80% after the 12-week treatment regimens in patients with GT1 and who included cirrhotics and non-cirrhotics, with some patients having previously experienced decompensation or treatment failures. SVR rates in GT2 patients were 90% after 16-week regimens.[41] Another benefit of the DAA treatments in a real-world setting is the low discontinuation rates observed (<4%).

Overall, there is a trend of fewer IFN-based therapies and an uptake of DAA in both cirrhotic and non-cirrhotic patients.[40] Germany and France have also shown increased treatment rates compared with the UK, with 16 and 12 patients treated per 100 prevalent cases compared with 3 patients, respectively.[42,43] Treatment strategy across the UK has centred on treating the most urgent patients, including those on a transplant waiting list and/or with CPT B and C.[44] Interestingly, high percentages of SVR (>80%) have been shown in a cohort of real-life patients with GT1 who were

treated with LDV/SOF with or without RBV, as well as those treated with SOF+DCV with RBV. Although the SVR was lower in patients with GT3 at around 60–70% after treatment, other patients who were predominantly GT2 and 4 demonstrated SVR rates ≥85%.[44]

Real-life patient cohorts also demonstrated improvements in MELD after 60 weeks of therapy, as well as the removal of some patients from the transplant waiting list and patients with ascites having no symptoms after no detection of the HCV. The treatment of patients with SOF plus RBV ± peginterferon alpha is recommended for certain patients across all GTs with chronic HCV in the UK, while recommendations for SIM plus RBV ± peginterferon are provided for patients with GT1 and 4.[45] Although there have been promising results from national patient cohorts, the prioritisation of patients with HCV for treatment after those with a high severity of disease requires agreement.[46] It has been suggested that patients who show a high risk of disease transmission should be targeted after those of a higher severity, in order to contain the epidemic of HCV. The final patient cohort treated with the new oral therapies would be those with milder disease states.

In summary, current recommendations have been very useful in guiding treatment decisions with oral therapies and matching patients to the optimal therapies according to their lifestyle, GT, simplicity, and treatment access. However, the next challenge in the area of HCV will be to decide which patient groups would receive the greatest benefit from oral therapies, for which real-world clinical data will be important.

Conquering C – Solutions From the Patient's Perspective

Mister Charles Gore

One of the challenges of making efficacious treatments available for people living with HCV is the limited budget allocation for viral hepatitis by governments, compared with other infectious diseases such as HIV. This is despite the greater mortality from viral hepatitis, as reported in 2013.[47,48] Furthermore, few countries have national hepatitis strategies and there is an uncertain political will that seems to be linked to the associated stigma, resulting in a major impediment to a strong advocacy movement.

However, there is a global drive to improve hepatitis treatment. In 2014, the World Health Assembly adopted the resolution WHA67.[49] This resolution called for governments to put comprehensive national plans in place for the prevention, diagnosis, and treatment of hepatitis, and asked the WHO to assess the feasibility of eliminating HBV and HCV with a view to set targets and devise a monitoring system. As a result, the WHO has developed a Global Hepatitis Strategy and proposed targets of 90% of those with HCV to be diagnosed, 90% of those who are eligible to be treated, and 90% of these patients to be cured by 2030.[50]

Although patient advocacy is essential in lobbying governments to allocate more spending to HCV, physicians not only need to lend their support, but must also become actively engaged advocates for improvement in access to highly effective HCV treatments. Results from strong lobbying would include a higher prioritisation of HCV, increased prestige to the area, and more funding, as well as increased support, equipment, and research opportunities. Alongside epidemiology and economic reports to support the clinical and cost-effectiveness of national HCV treatment strategies, highlighting the emotional aspects of HCV infection and media involvement are required to effectively justify the multiple benefits of HCV treatment to governments.

Conquering C – Solutions To Address Access

Professor Nezam H. Afdhal

Current healthcare costs for HCV are increasing due to long-term effects such as HCC, liver decompensation, and the requirement for liver transplantations,[51,52] which have a median (range) annual cost of €109,075 (€38,594-€326,233).[53] Although SVR has been associated with a reduction in liver-related mortality and HCC,[5,54] as well as lower associated costs and improved quality of life,[55,56] the implementation of treatment access for all patients can be difficult.

Previously, only around 11% of patients with HCV in the USA were treated and 6% would show an SVR.[46,57] There are still global barriers to HCV treatment that include affordability and the healthcare systems available. The stigma of HCV disease combined with unwilling providers, a lack of screening, the location of clinics, and

a heterogenous population of patients can cause challenges when implementing treatment programmes.[58-60] Although targeted screening programmes have been effective at improving the detection and referral of patients with HCV, 40-85% of infected persons may not be identified depending on the location and current screening practices.[61,62]

A previous challenge of healthcare systems in treating patients with HCV was the complexity and expense of IFN treatments.[61] However, the improved efficacy of current treatments has shown a higher rate of SVR non-detection, with subsequently lower numbers of patients who require retreatment and a lower overall cost per SVR.[51,52,63] Modelling has shown that global implementation of the DAA treatments could cause HCV to be classed as a rare disease within 22 years.[64] Increasing DAA treatments to 165,000 patients per year by 2018 in the USA would eliminate the disease and cost under US$10 billion (as per calculations performed in 2014).[51,52] As 82% of patients with GT1 and moderate Stage 2 or cirrhotic diseases in the USA were treated with LDV+SOF between October 2014 and March 2015, treatments are being implemented in some areas and for patients with moderate-to-severe disease activity.

As well as the roll-out of DAA treatments across the USA, treatment access programmes have been developed in other countries. A Gilead HCV access programme has been set up with the aim to invest in long-term collaboration with governments, to implement public health plans, and to support treatment strategies.[65] Egypt has the highest global HCV prevalence of 9.8% of the population, of whom 90% are GT4 and 10% are GT1.[66-70] A 5-year action plan has been agreed upon to target around 300,000-350,000 patients per year with a 90% SVR, which could lead to eradication of the disease within 15 years and significantly reduced cirrhosis, HCC, and mortality.[66] Georgia has also implemented an eradication programme over 3-5 years along with the Centres for Disease Control and Prevention and support from Gilead, which could be used as a case study for other countries.[71]

In conclusion, the burden of HCV is still present but could be reduced substantially through DAA-based therapy, which has been shown to be effective and cost-effective. Access programmes to further improve the proportion of patients with HCV who are treated could transform the current prevalence and global consequences of the disease.

Conquering C – Going Beyond Cure

Professor Stefan Zeuzem

HCV meets all the established criteria for a disease that can be eliminated, including the absence of a non-human reservoir, an environment in which the virus cannot amplify, practical interventions that can be implemented to interrupt the transmission of HCV, and a cure.[72] As the current budget allocations for HCV are lower than HIV despite the greater mortality in HCV,[73] lobbying by patients and clinicians is required to demonstrate that current interventions are cost-effective, and that diagnosis rates of patients with HCV need to be improved.

If the treatment rate of countries was increased by 10% through a 3-5-fold increase in the diagnosis and treatment of patients, the strategy could result in a 90% decrease in total infections by 2030. Firstly, specific patient populations should be targeted with the treatment strategy, focussing initially on those with a high severity of disease. Patients with a high risk of transmission, including those who are HIV/HCV co-infected, injecting drug users, and prisoners would then be targeted with HCV treatment eradication strategies.[51]

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