HEPATITIS C VIRUS INFECTION AND ALCOHOL:

CHALLENGES AND OPPORTUNITIES!

Bristol-Myers Squibb

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Accordingly, more people than ever before will be eligible to receive such treatment which, while cost effective, will pose affordability challenges. It is essential that any barriers placed in the way of people being considered for, receiving and gaining the benefit of therapy should be minimised. One such barrier is Excessive Alcohol Consumption (EAC). This report aims to inform service users and providers by answering the following key questions using up-to-date evidence and interpretation:

- What is the relationship between HCV infection and alcohol consumption, and what are the diagnostic implications?
- Does knowledge of one’s HCV status influence alcohol consumption?
- What do we know about the combined impact of Excessive Alcohol Consumption (EAC) and HCV Infection on liver disease progression?
- Can behavioural psycho-social interventions reduce alcohol intake in the HCV-infected person?
- Is EAC a barrier to HCV-infected people getting into therapy?
- What is the impact and likely impact, respectively, of EAC on the effectiveness of Interferon containing and Interferon free HCV therapy?
- Does EAC compromise the impact of SVR on liver disease progression?
- Does HCV “cure” motivate people who drink excessively to reduce their intake?
- How important is it to understand the respective contributions of HCV and EAC when monitoring end-stage disease outcomes?

INTRODUCTION

With the introduction of direct acting antiviral therapies for Hepatitis C that are highly effective, tolerable, have a good safety profile and are easy to administer, and more in the pipeline, this is a watershed time for all Hepatitis C service users and providers. Therapeutic advances have made it possible to contemplate a world in the future which, if not infection free, may have managed to control severe disease and mortality associated with the virus.
How many people are infected and how did they acquire their infection?

HCV was discovered in 1989. The number of people infected worldwide is uncertain but likely the true figure lies between 100 and 200 million. In the EU it is estimated that about 6 million people are living with the virus (prevalences within EU Member States (MS) range from 0.4 to 4%)\(^i\).

Generally, in northern and western EU MS, where rates of infection tend to be lower, the majority of infected people acquired their infection through injecting drug use; in contrast and generally, the majority of infected people in southern and eastern MS acquired their infection through suboptimal infection control associated with healthcare procedures\(^ii\ iii iv\).

Transmission of HCV among People Who Inject Drugs (PWID) in northern and western MS is in decline, while that among PWID in southern and eastern MS is on the rise\(^v vi\). Transmission due to poor infection control is still occurring in the EU but due to considerable improvements over the last 30 years in particular, numbers of new infections acquired this way are considered to be very much smaller than those occurring through injecting drug use\(^vi\).

How is the virus identified?

The virus is identified through the testing of blood for HCV antibodies (indicating ever having been infected) and HCV RNA (indicating current infection).

What impact does HCV have on health?

Between eight and 16% of people infected with HCV for 20 years have cirrhosis of the liver\(^viii\). Duration of infection carriage, heavy drinking and HIV co-infection increase the probability of severe liver disease\(^ix\). HCV may cause very serious illness and death from cancer or liver failure\(^x xi xii\). The virus is also associated with non-liver-related disease (including cardio-vascular, renal and neurological conditions)\(^xii xiv\).

How is HCV prevented?

No vaccine against HCV is available and it is unlikely that one will become available in the near future\(^xv\). Ensuring infection control practice associated with healthcare procedures is optimal and providing high coverage injection equipment/opiate substitution therapy for PWID are the principal means through which HCV transmission is prevented\(^v v iii xiv\). Antiviral treatment given to an infected active PWID might not only help the individual receiving therapy but also prevent onward transmission of infection; this concept is a theoretical one at present\(^xix\).
What are the benefits of diagnosis?

Three principal benefits of diagnosis are i) the potential opportunity to get treatment to clear the virus, ii) the opportunity to change behaviours which are detrimental to oneself (i.e. alcohol consumption and continued injecting) and iii) the ability to prevent onward transmission through, for example, avoiding injection equipment sharing, infected blood donation and getting treatment before pregnancy to prevent mother to child infection.

Who should be screened?

Currently, worldwide, the screening of only high risk and other selected groups for HCV (PWID) is recommended; an exception is the US which also advocates general population (birth cohort) screening. But with the increasing availability of new highly effective Interferon-free therapies, other countries will need to consider general population screening initiatives.

What is the effectiveness of HCV treatment?

For a combined cohort of genotypes 2 and 3 infection, pegylated Interferon and Ribavirin can achieve a Sustained Viral Response (SVR- i.e. HCV Clearance) of up to 80%. For genotype 1, the response is up to 70% when a first generation protease inhibitor is added. With the latest and imminent Direct Acting Antivirals, it should be possible to achieve SVR rates of greater than 90% for all genotypes and, in most instances, Interferon and Ribavirin will not be required.

Incontrovertible evidence of mortality and morbidity reduction as a consequence of SVR exists; nevertheless, the intensity of such reductions may be compromised by other toxins (e.g. excessive alcohol consumption) continuing to affect the liver and by HCV re-infection – an occurrence which is particularly applicable to PWID.

The principal barrier to infected people accessing the new therapies is, and will continue in the short to medium term to be, a financial one; while most, if not all, new therapeutic regimens will be deemed cost effective by western/resource rich country standards, they will still be costly. The challenge for Governments and the Pharmaceutical Industry is to work together to ensure that those people who desperately need therapy get it!

What do the European Association for the Study of the Liver (EASL) recommendations on the treatment of Hepatitis C, published in 2014, say about who should be treated?

The recommendations state that treatment i) should be prioritised for patients with significant fibrosis (F3 and F4 – i.e. the immediately pre-cirrhotic and cirrhotic stages), ii) is justified in people with moderate fibrosis (F2) and, iii) can be individualised for patients with no or mild disease (F0 and F1).

What do the EASL Guidelines, as above, say about alcohol?

The references to alcohol are as follows:

- “Alcohol consumption should be assessed and quantified, and specific counselling to stop any use of alcohol should be given.”
- “Alcohol consumption has an impact on treatment adherence. Patients should be advised to stop or to reduce alcohol consumption before the start of treatment. Treatment for patients not able to abstain from alcohol should be fitted to the individual, focussing on their ability to adhere to medication and appointments. Hepatitis C patients with ongoing alcohol consumption during treatment profit from additional support during antiviral therapy.”
HCV: EU STRATEGY

Unlike for alcohol, HIV and TB, no EU Strategy to reduce the harm associated with Hepatitis C (and B) exists. In 2013, the European Centre for Disease Control (ECDC) established a Task Force to develop a Framework (EU Hepframe) for the control and prevention of Hepatitis B and C in the EU but this initiative stalled following an initial meeting in that year.

Small initiatives such as the development of an Implementation Guide and the establishment of a web-based communication platform on how to tackle Hepatitis C has been promoted by a small number of MEPs but any concerted strategy on Hepatitis C is still missing. Nevertheless, much good advocacy work has been done by the European Liver Patients Association (ELPA), the Viral Hepatitis Prevention Board (VHPB) and the Hepatitis B and C Public Policy Association.

In the context of i) an estimated 6 million chronic HCV infected people living in the EU, ii) only a minority of infections having been diagnosed, iii) the very high propensity for the general, and particularly injecting drug using, populations to drink heavily, iv) the increasing availability of highly effective Interferon free antiviral treatments and, v) the enormous cultural, social, wealth and healthcare provision heterogeneity among EU MS, an EU Hepatitis C (and B) Strategy is vital.

ALCOHOLIC LIVER DISEASE: BACKGROUND

Alcohol consumption accounts for 3.8% of the world’s mortality; in Europe, the proportion is 6.5%, the highest for any WHO region. The burden of compensated alcoholic cirrhosis (i.e. a cirrhotic liver which is still functioning) in Europe is not well understood but it is evident that eastern European countries tend to have higher rates of alcoholic liver disease than western ones. Temporal variations also occur; over the last three decades, alcoholic liver cirrhosis mortality has declined in many western countries and in Hungary and Romania, but increased in several eastern countries and in the UK, Ireland and Finland.

Europe has the highest per capita consumption in the world with 15% of individuals (58 million) drinking excessively (greater than 40g/day in men and greater than 20g/day in women).

The risk threshold of alcohol consumption for the development of liver cirrhosis is contentious with recent analyses indicating that some people who drink below recommended thresholds (e.g. in the UK: per week, 14 units (112g) for women and 21 units (168g) for men) are not necessarily safe**. It is very likely, however, that the risk, respectively, of women and men who drink less than 70g and 140g/week, developing liver cirrhosis is virtually non-existent and the risk of cirrhosis only starts to very considerably increase (more than four-fold compared to that for non-drinkers) at levels of greater than 30g/day***. That said, the more and longer one drinks, the greater the chance of cirrhosis. The risk of patients with alcoholic cirrhosis developing hepatocellular carcinoma after five years is about 10%.

The European Association for the Study of the Liver (EASL) recommendations on alcoholic liver disease include the following:

- Drinking habits of patients need to be routinely screened by physicians with tools which have proven their reliability (e.g. AUDIT Tool).
- In patients with alcoholic liver disease, persistent alcohol intake is associated with disease progression; therefore, the most effective recommendation for these individuals is total alcohol abstinence.
- Brief motivational interventions should be routinely used in the medical management of alcohol use disorders.
- In alcohol dependence without alcoholic liver disease, Disulfiram, Naltrexone and Reamprisate, combined with counselling, reduce alcohol consumption and prevent relapse.
- In patients with advanced alcoholic liver disease, recent studies suggest that Baclofen is generally well tolerated and effective to prevent alcohol relapse **.*
In 2006, the EU launched a Strategy to support MS in reducing alcohol-related harm. While it is recognised that a single uniform policy relevant to all MS is neither possible nor desirable, a concerted action at EU level is considered crucial to complement national actions, to tackle cross-border issues, to increase exchange of information and to identify and benefit best practice.

In December 2012, an assessment of the added value of the Strategy was published by the EU Commission. The following are selected achievements attributable, at least in part, to the Strategy:

- Most MS have updated and strengthened their alcohol strategies over the past six years, building on evidence-based measures and moving in the directions outlined in the EU Strategy.
- Most MS have strengthened policies on the availability of alcohol since 2006, including age limits.
- Actions to reduce exposure to alcohol during pregnancy have included voluntary warning label schemes and awareness-raising targeted at health professionals.
- Statutory restrictions in alcohol advertising are in place in most MS as well as self regulation and responsible practices in alcohol marketing.
- All but two MS have established a maximum blood alcohol content for driving of 0.5mg/ml or less.
- Advice targeted at harmful drinkers is provided by professionals within health services in three-quarters of MS.
- But there are concerns about monitoring as indicated in the following statement:
- “Few cross-sectional EU indicators or longterm statistics are currently available on trends related to the ultimate goal of EU Strategy reductions in alcohol-related harm.”
What is the relationship between HCV infection and alcohol consumption, and what are the diagnostic implications?

Among people who have acquired their HCV through non-injecting drug using routes – and in most parts of the, particularly resource-poor, world this means through suboptimal infection control practices such as the re-use of unsterile needles and syringes – it is unlikely that their alcohol consumption is any different from that of the equivalent age and sex matched general population.

Among both active and ex-PWID, however, the relationship with, particularly excessive, alcohol consumption is very strong; accordingly, the relationship between HCV and EAC is considerable in parts of the world where injecting drug use is the dominant risk factor for infection.

It is estimated that between 10 and 60% of PWID are heavy drinkers and that between 2 and 50% of patients with an alcohol problem (average 16%) have chronic HCV. In the context of the new highly effective HCV therapies becoming available and the well recognised synergistic effect of HCV and EAC in liver disease progression, it is crucial that individuals who drink to excess should be encouraged to be tested for HCV so that therapy can be considered; though costly, the relatively easy eradication of one liver toxin makes sense. Likewise, all HCV infected individuals should be questioned robustly about their alcohol consumption.

What do we know about the combined impact of Excessive Alcohol Consumption (EAC) and HCV Infection on liver disease progression?

Cumulative EAC causes liver disease (fibrosis, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma) and the greater the excess, the greater the risk of developing advanced disease. Chronic HCV infection causes liver disease and the longer infection is present, the greater the risk of developing disease. Having both risk factors – cumulative EAC and cumulative chronic HCV infection – further increases the risk of developing liver disease and the rate of liver disease progression.

There remains uncertainty about the level of alcohol intake which starts to convey an increased risk of developing liver disease among people with chronic HCV. Incontrovertible evidence indicating that very heavy alcohol use (greater than 50-55g alcohol/day) conveys a greatly increased risk of severe liver disease exists. At the milder end of the consumption spectrum, (less than 30g/day), however, some studies indicate an increased risk of developing liver disease among people with chronic HCV while others do not. A systematic analysis of numerous studies (a meta-analysis) concluded that HCV infected heavy drinkers (30-80g/day) were 2-3 times more likely than HCV-infected non-heavy drinkers to develop cirrhosis. It is unclear how long heavy drinkers have to abstain from alcohol before its negative effect is neutralised.

Assessing the impact of mild to moderate alcohol use in chronic HCV-infected people is challenging because they often under-estimate (rarely over-estimate!) the amount they drink and most studies on liver disease progression in HCV-infected people include alcohol consumption as one of the many factors under investigation; accordingly, the question(s) asked tend to be rudimentary. Quantifying alcohol consumption over a lifetime is hugely challenging and analysing such data in this context is usually a very crude process which does not account for variations in the amount of alcohol consumed over time and other influential characteristics of consumption such as whether or not alcohol was consumed only at mealtimes.

Does knowledge of one’s HCV status influence alcohol consumption?

The greatest benefit of an HCV-infected person knowing their status is the opportunity to be assessed for treatment and then, if appropriate, treated. Next on the list, but arguably nearly as important, is the opportunity to reduce to as low a level as possible the rate of liver disease progression through reducing/stopping alcohol consumption; this message is a vital one in the context of the post (positive) test discussion – and one which, likely, is variably conveyed in terms of intensity and accuracy.

But does knowledge of HCV status change alcohol consumption? Few studies have been undertaken and those involving PWID either show no, or a small, change. Among non-PWID, however, considerable changes towards a safer lifestyle have been observed. These findings are similar to those associated with the impact of psycho-social interventions among HCV-infected people who engage in EAC – i.e. the more chaotic the lifestyle, the less likely the chance of any change! (see below).
Can behavioural psycho-social interventions reduce alcohol intake in the HCV-infected person?

Because of the additional risks conveyed by EAC to i) the development of liver disease in the HCV-infected individual and, ii) HCV treatment, referral and administration, it is important that everything possible is done to help such people reduce drinking.

Among PWID, the group most likely to have both HCV and a history of EAC, few studies to gauge the effectiveness of behavioural interventions in reducing alcohol intake have been performed; further, the quality of some of these has been suboptimal. Accordingly, caution needs to be taken in making any conclusion about the effectiveness of such interventions in this population. Some data, however, do indicate that appreciable reductions in alcohol intake occur in the short-term but are not necessarily sustained.

Among an HCV-infected population of mostly non-PWID, there is some robust randomised controlled trial evidence demonstrating that the intervention – Motivational Enhancement Therapy (four sessions lasting 30-45 minutes) – has an impact.

Recently published WHO guidelines on Hepatitis C concluded that moderate-quality evidence exists for alcohol reduction interventions reducing consumption among people with chronic HCV infection who consume moderate-to-large amounts.

Is EAC a barrier to HCV-infected people getting into therapy?

HCV-infected people who drink to excess are less likely to be referred for HCV therapy assessment and, if referred, less likely to commence on therapy than those who do not. The main reason for this is the concern among health professionals that people who do drink to excess and continue to do so, are less likely to adhere to treatment administration and thus less likely to achieve the optimal benefit of therapy; such concerns are more based on clinical intuition than on a strong evidence base.
Does EAC impact on the effectiveness of HCV Therapy?

There is evidence that people who have drunk excessively but who stop drinking or reduce their drinking to lower levels (less than 24g/day) in the six months before treatment and during it, do just as well on therapy as those people who have never drunk more than mildly.

All observations to date apply to interferon containing regimens which are lengthy, usually administered in secondary care settings and associated with adverse effects; with the ever-increasing availability and potential access to more tolerable interferon free treatment options it is likely that adherence will be less of a concern, even among individuals who are unable to limit their heavy drinking.

Such reduction/abstinence is usually only achieved through a multi-disciplinary support package delivered by many including alcohol addiction and HCV specialists. People who also have ever injected drugs and/or who have poor social circumstances (e.g. homeless) are less likely to respond to such support.

Does HCV “cure” motivate people who drink excessively to reduce their intake?

It is possible that the joy sustained by people who clear their virus galvanises them into improving their lifestyle. A number of anecdotes of people whose HCV clearance has been followed by improvements in alcohol consumption have been recorded; however, no robust evidence addressing this question exists.

It is also possible that the process of treatment assessment, administration and evaluation per se – a process which, with interferon containing regimens, extends to around two years of engagement with doctors, nurses and other specialists – has a beneficial post-treatment influence on alcohol consumption but, again, the evidence is anecdotal. The likely rapid move towards short interferon free regimens administered in primary care settings to individuals whose lifestyles are generally more chaotic due to such lifestyle being less of an impediment to treatment eligibility means that an evaluation of the potential risk of EAC and/or injecting drug use (and thus the possibility of reinfection) compromising the benefit of therapy needs to be undertaken.

Does EAC compromise the impact of SVR on liver disease progression?

HCV-infected people who clear their virus experience a dramatic decline in liver disease-related hospitalisation; however, even among those who have not already advanced to cirrhosis when therapy is administered, the extent of liver disease may not always return to general population levels. This, likely, is due to other “behavioural” conditions associated with HCV; for example, EAC among PWID is particularly common. To realise the full benefit of antiviral therapy, it is important that support for people who engage in EAC is provided before, during and after successful treatment.

How important is it to understand the respective contributions of HCV and EAC when monitoring end-stage disease outcomes?

The ultimate aim of any HCV infection/disease programme of interventions is to prevent serious morbidity and mortality caused by this infection. Arguably, the most important HCV infection/disease monitoring outcomes are end-stage liver disease, hepatocellular carcinoma and death. The monitoring of such outcomes informs the extent of the problem and its trajectory, and also permits the evaluation of the effectiveness of interventions to prevent infection/disease. In the past, monitoring of end-stage outcomes only told us about what happened decades before as a consequence of the long incubation period of HCV and the relative ineffectiveness of therapy among infected people with advanced disease. However, with the availability of new highly effective antiviral therapies which can halt and indeed reverse HCV disease progression among individuals who have advanced disease, the monitoring of such outcomes tells us about the effectiveness of certain current interventions, namely the diagnosis of infected people with advancing disease and their access to therapy.

Theoretically, it will now be possible to control the number of HCV-infected people presenting with liver failure. Knowing what proportion of such cases are also associated with EAC is vital in interpreting the effectiveness of HCV-related interventions. For example, a recent study undertaken in Scotland estimated that a third of all HCV-infected cirrhotics would not have progressed to cirrhosis if they had not been heavy drinkers.
In 2008, Scotland launched a Hepatitis C Action Plan to improve prevention, diagnosis and treatment services for people infected and at risk of infection. Since then, nearly £100 million of dedicated funding has been invested in preventing HCV infection and related disease over and above existing NHS resources. Major improvements in the diagnosis rate (39% to 55%), treatment initiations (450 to 1000/year) and infection incidence (1500 to 750 transmissions/year) have occurred as a consequence of a concerted effort to tackle one of the country’s greatest public health problems (Health Protection Agency and Professor D. Goldberg, unpublished).

Arguably, the greatest achievement to date is the establishment of a highly trained workforce with specialist nurses at its heart and a web of national and local multi-disciplinary networks to co-ordinate and manage service development; this infrastructure places Scotland in an outstanding position to take advantage of the new highly effective antiviral therapies.

Recognising the high prevalence of EAC among HCV-infected past and current PWID who comprise greater than 90% of the country’s 37,000 chronically infected people, actions promoting the support of people with alcohol and drug addictions through the patient pathway were incorporated into the Plan. Of particular note was the stipulation that all National Health Service Boards (14) in Scotland had to have, or be affiliated to, a multi-disciplinary Managed Care Network for Hepatitis C; in addition to Hepatitis C specialists, representatives for patients, the prison service and alcohol/addictions were required to serve on the Network. Such representation would ensure an integrated approach to Hepatitis C care, ensuring that people with addictions could simultaneously be clinically managed for Hepatitis C while being stabilised, apropos their alcohol and drug problems. It is a testimony to the effectiveness of the joined-up approach that over 80% of all people administered Interferon containing therapies in recent years have a history of injecting drug use.

The importance of tackling EAC per se and the impact of alcohol-specific interventions, particularly at a population level, on HCV infection should not be forgotten. Many European countries, including Scotland, have extremely high rates of EAC. Scotland’s alcohol strategy includes a minimum pricing initiative, to be implemented by the Scottish Government subject to legal authorisation. The links between EAC, deprivation and the cost of alcohol are now well established, as manifested by a recent reduction, contemporaneous with the economic downturn, in alcohol consumption morbidity and mortality in Scotland.

Scotland – a country with a long history of heavy alcohol consumption – is tackling the combined HCV and alcohol problem head on through its unique Hepatitis C Action Plan and its progressive alcohol strategy.
CONCLUSION
The findings of this Report highlight the importance of EAC as a barrier for Hepatitis C-infected people getting rid of their virus and improving their health. It is particularly relevant to general populations and specific population groups (particularly PWID) among whom EAC and HCV are more prevalent.

At all stages of the Hepatitis C patient pathway from diagnosis to follow-up after treatment, the evidence base — in relation to i) understanding the impact of EAC on transition through the different pathway stages and, ii) the evaluation of interventions to help people reduce or stop drinking alcohol is limited; indeed, hardly any studies undertaken in resource-poor countries among which the great majority of the world’s HCV infected population reside, were identified.

The evidence demonstrating the detrimental effect alcohol has on liver disease progression in people with HCV is compelling though uncertainty about the impact of mild drinking remains.

The key message of abstinence — articulated well in the European Association of the Study of the Liver recommendations on the treatment of Hepatitis C — is straightforward and justified; however, education does not necessarily translate into behavioural change.

As we enter the new era of antiviral therapy, a huge opportunity to eradicate one of the assaults on the livers of people who have HCV and drink excessively exists. Indeed, a history of EAC in the HCV infected person should certainly not be a barrier to accessing antiviral therapy and, arguably, should be a factor which adds weight to any case for administering such therapy as quickly as possible.

Treating HCV infection is becoming the easy bit! More challenging is the co-existing alcohol problem. Thus, it is critical that everything is done to assess and address it before, during and after treatment. Essential is an integrated model of care with individuals responsible for specific Hepatitis C clinical management (mostly, at present, HCV specialists but, likely in the future, primary care clinical staff overseen by an HCV specialist team) working alongside drug and alcohol addiction specialists. If that approach can be achieved universally, there is a better chance of ensuring that people with both alcohol problems and HCV infection get access to, and achieve optimal benefit from, the new therapies.

Recommendations

For HCV-infected people whose consumption of alcohol exceeds mild levels, the management of such consumption—before, during and after anti-viral therapy—should be taken as seriously as the management of their HCV. Such alcohol/HCV management should be undertaken using a multidisciplinary approach incorporating alcohol addiction expertise.

Countries with both a high HCV prevalence and a high prevalence of EAC, in particular, should appreciate, and then act to minimise, the potential for suboptimal regional/national EAC prevention policy (and its implementation), to compromise the impact of HCV antiviral therapy on liver disease morbidity and mortality.

Further research to better understand the impact of EAC on the successful completion of the patient journey from HCV diagnosis to HCV cure, should be undertaken; interventions to reduce appreciable EAC impact, where appropriate, should be evaluated.

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