National Clinical Guidelines for the treatment of HCV in adults

Version 2.0

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Sponsors and Authorship

The guidelines have been authored on behalf of the viral hepatitis clinical leads and MCN co-ordinators network; lead authors: Dr. John F Dillon, Prof P Hayes, Dr S Barclay and Dr A Fraser.

The development of the national guidance has been a collaboration between Scotland's clinical leads in viral hepatitis, MCN co-ordinators network, National Services Scotland and Healthcare Improvement Scotland.

Purpose of guidelines

To provide guidance to Health Board Area Drug and Therapeutics Committees on the recommended place in treatment of available HCV drugs taking into consideration SMC guidance, clinical effectiveness and price.

Use of these guidelines

This is a rapidly changing field and these guidelines will be updated on a regular basis and should be used to guide treatment choices. Where no contraindication exists, the most cost effective regimen amongst the recommended options should be chosen to maximise the number of patients who can be treated.

Background

HCV is a blood borne virus leading to cirrhosis of the liver and hepatocellular carcinoma, it affects up to 1% of the Scottish population. The Scottish government under the HCV action plan and succeeded by the sexual health and blood borne virus strategic framework have provided a world leading structure for the prevention, diagnosis, treatment and care of HCV. Rapid advances in HCV therapeutics have led to an array of anti-HCV drugs that now offer cure to more than 90% of those infected with HCV. The process of implementation of these drugs into the NHS is being guided by principles developed by the HCV Treatment & Therapies Sub-Group of the National Sexual Health & BBV Advisory Committee. The National Sexual Health & BBV Advisory Committee is chaired by the Scottish Government Minister for public health, and provides advice to the minister on the sexual health and blood borne virus strategic framework. To support this implementation it is necessary to evaluate the available evidence for the anti-HCV drugs, group these drugs in terms of their efficacy to allow them to be compared for cost-effectiveness and then a preferred regimen selected based on cost to NHS Scotland. In the absence of head to head comparisons of available regimens it has been necessary to perform an expert review of the available evidence.

Development process

The guidelines are based on the integrated outputs from three sources of evidence. A systematic review, an expert review of conference abstracts and expert opinion on these sources from a national panel of expert stakeholders. The systematic review was commissioned and funded by Health Protection Scotland and performed by staff from the University of Dundee, Health Protection Scotland, and Glasgow Caledonian University. It was performed in accordance with PRISMA guidelines and adhered to Cochrane principles. The search included all phase 2b and phase 3 trials of HCV therapy published between 1st

January 2009 and 22nd October 2014. Due to the rapid speed of change in this area and the lag between presentation of data at meetings in abstract format and the appearance of the full paper, we performed an expert review of abstracts for relevant studies presented at the November 2014 meeting of the American Association for the Study of Liver Diseases, the most recent major international conference at which HCV therapy data is likely to be presented. Two expert reviewers reviewed abstract submissions to the meeting and extracted relevant abstracts for presentation at the meeting of the national panel of expert stakeholders. This most recent review was based on an additional expert review of the most recent literature literature.

Principles

The guidelines are focussed on the efficacy of the drugs and will inform which are the most efficacious. Where there are no head to head studies we have used meta-analysis techniques to show relative efficacy and over lapping efficacy, to allow decisions on choice of drug to be made. Cost effectiveness is dependent on the cost of the drug and the cost of delivering the drug, which was beyond the remit of this guideline. However for the all oral regimens the cost of delivery is similar and if there is no statistically significant difference in relative efficacy, then the cheapest drug will achieve the lowest cost per cure and is likely to be the most cost effective. There are national pricing agreements in place for medicines covered by the guidance; NHS National Procurement will keep Health Boards and lead prescribers informed of costs.

In keeping with government policy and the preference of Health Boards only SMC approved drugs were considered for final recommendation in the guidelines.

In keeping with the principles developed by the HCV Treatment & Therapies Sub-Group of the National Sexual Health & BBV Advisory Committee, which states that patients should have an expectation that the likelihood of cure as a result of their initial treatment is at least 90%.

There is an expectation from Government and Health Boards that the most cost effective regimen will be selected for an individual patient. In each of the treatment categories below the preferred drug has been selected based on its cost to NHS Scotland from among regimens of equivalent efficacy.

Guidance

The review of the evidence shows that HCV genotype remains an important determinant of choice of regimen and chance of cure therefore the guidance is presented according to genotype. The new regimens are well tolerated with low levels of side effects and we have not differentiated between the regimens on this basis nor on duration of therapy, taking the view that they are effectively equivalent.

There is a small number of Drug-Drug Interactions (DDI) that may dictate choice of regimen and the University of Liverpool web site should be consulted for potential interactions. The issue of DDI is particularly relevant to HCV-HIV co-infection, other than the greater potential for DDI co-infected patients should be treated in the same fashion as mono-infected patients.

Genotype 1

The therapeutic advances in HCV therapy have currently been mainly in genotype 1 and we have reached a stage where we are close to the ceiling of efficacy for this genotype with regimens 97-100% effective. The systematic reviews demonstrated that there were a number of regimens that crossed the 90% threshold for efficacy. Further the reviews show that these regimens can be regarded as equally efficacious, with overlapping confidence intervals.

The regimens are listed in the table below, the durations of some regimens have been shortened from those submitted to SMC or listed in the specific product information. This is due to emerging data from the expert review of abstracts and in trials where numerical differences were not shown to be statistically different and confidence intervals were shown to overlap on meta-analysis. This suggests that these shortened regimens are equally efficacious and likely to be much more cost effective than longer duration ones, especially with the addition of ribavirin. For these guidelines the definition of treatment experienced refers to treatment with interferon and ribavirin, in future versions of this guideline as data emerges specific recommendations about treatment experience with DAAs will be made.

Genotype 1	Recommended regimens
Treatment Naive (non-cirrhotic)	**First line: Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir +/- Ribavirin 12 weeks** Sofosbuvir, Ledipasvir 8 weeks Sofosbuvir, Simeprevir 12 weeks Sofosbuvir, Daclatasvir 12 weeks
Treatment experienced (non-cirrhotic)	**First line: Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir +/- Ribavirin 12 weeks** Sofosbuvir, Ledipasvir 12 weeks Sofosbuvir, Daclatasvir 12 weeks
Cirrhotic irrespective of previous treatment	**First line: Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir, Ribavirin 12 weeks** Sofosbuvir, Ledipasvir, Ribavirin 12 weeks Sofosbuvir, Daclatasvir, Ribavirin 12 weeks

The former standard of care for genotype 1, PEG Interferon alpha and ribavirin with or without Protease inhibitors for all patients did not reach the 90% threshold for inclusion in our recommended regimens. In particular PEG interferon alpha, ribavirin and simeprevir remains a HIS / SMC accepted treatment and is available in NHS Scotland. There are predictive tools that identify sub-groups of patients who can achieve cures in excess of the 90% threshold, with this regimen. However most lack prospective validation or full publication. The cost-effectiveness of this approach as a substitute for use of second generation direct acting antivirals is yet to be demonstrated. The use of such regimens may be appropriate in selected patients, at the discretion of the treating clinician and with the informed consent of the patient.

Genotype 2

PEG Interferon alpha with ribavirin is a highly effective treatment for HCV genotype 2 with SVR rates of 90%, albeit with the side-effects of interferon. Sofosbuvir is accepted for restricted use by SMC in combination with other medicinal products for the treatment of chronic hepatitis C in adults. Use in treatment-naive patients with genotype 2 is restricted to those who are ineligible for, or are unable to tolerate, PEGinterferon alfa.

Genotype 2	Recommended regimens
Interferon eligible	**PEG Interferon alpha with ribavirin 16-24 weeks**
Interferon ineligible or treatment experienced	**Sofosbuvir, Ribavirin 12 weeks**

Genotype 3

The therapy of HCV genotype 3 has improved considerably but this genotype is now the most difficult to treat with cure rates at best of around 90%. However new drugs are likely to become available next year which promise significantly improved cure rates. Thus the best management plan for some patients with genotype 3 especially treatment naive patients without cirrhosis may be to await the approval of new drugs. The overall cure rate of genotype 3 HCV infection with PEG Interferon alpha and ribavirin is around 70%, however for those with low viral loads (<800,000 Iu/ml) and minimal fibrosis (F0-1) have SVR rates of around 90% and if they achieve RVR can have therapy shortened to 16 weeks. Daclatasvir has been approved for F3 and F4 patients by the SMC, so appears in both cirrhotic and non-cirrhotic categories. The combination of Sofosbuvir and Ledipasvir has only been approved for the treatment of Genotype 3 patients without cirrhosis who have previously failed to obtain an SVR with an interferon based regimen or those with cirrhosis, regardless of prior treatment experience. In terms of treating cirrhotic patients with genotype 3 infection randomised published trial evidence of efficacy in excess of 90% is limited, recent data from the Boson trial suggests a PEG interferon based sofosbuvir, ribavirin regime is more effective than current interferon free regimens. We note that treatment of genotype 3 cirrhosis probably will not achieve greater than 90% SVR, however this group has a great need for treatment and the intention of this guideline is that Genotype 3 patients with cirrhosis should be offered therapy, preferable with an interferon containing regimen, if it is deemed safe by the clinician. The final decision to use the current therapy should rest with the treating clinician and the patient. In those patients with cirrhosis ineligible for interferon therapy, either ledipasvir or daclatasvir regimens may be used, with some cohort data from the English early access program favouring Daclatasvir. Interferon ineligible is either intolerance of previous experience of interferon or where in the opinion of the treating clinician, there is a contraindication to interferon therapy.

Genotype 3	Recommended regimens
Low viral load, mild to moderate fibrosis	**PEG Interferon alpha, Ribavirin 16-24 weeks**
Non-cirrhotic	**First line: Sofosbuvir, PEG Interferon alpha, Ribavirin 12 weeks** Sofosbuvir, Daclatasvir, Ribavirin 12 weeks (F3 only)
Non-cirrhotic interferon ineligible (treatment experienced)	**First line: Sofosbuvir, Ledipasvir, Ribavirin 12 weeks** Sofosbuvir, Daclatasvir, Ribavirin 12 weeks (F3 only)
Non-cirrhotic interferon ineligible (treatment naïve)	**Sofosbuvir, Daclatasvir, Ribavirin 12 weeks (F3 only)**
Cirrhotic	**First line: Sofosbuvir, PEG Interferon alpha, ribavirin 12 weeks**
Cirrhotic interferon ineligible	Sofosbuvir, Ledipasvir, Ribavirin 12 weeks Sofosbuvir, Daclatasvir, Ribavirin 12 weeks

Genotypes 4 - 6

Genotypes 4-6 are uncommon in Scotland, though effective treatments are available. These should be prescribed according to local protocols or where appropriate, expert advice sought.