National Clinical Guidelines for the treatment of HCV in adults

Version 3

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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: Prof. John F Dillon, Prof P Hayes, Dr S Barclay, Dr R Fox and Dr A Fraser.

The development of the national guidance has been a collaboration between Scotland's clinical leads in viral hepatitis, National Services Scotland and Healthcare Improvement Scotland, in response to a request from the National Sexual Health & BBV Advisory Committee of the Scottish Government.

Purpose of guidelines

To provide guidance to Health Board Area Drug and Therapeutics Committees on the recommended place in treatment of available HCV medicines 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 medicines that now offer cure to more than 90% of those infected with HCV. The process of implementation of these medicines 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 medicines, group these medicines 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.

Development process

The guidelines are based on the integrated outputs from three sources of evidence. A systematic review, an expert review of recent 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 31st December 2015. 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 2015 meeting of the American Association for the Study of Liver Diseases and the April 2016 meeting of The European Association for Study of The Liver. 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.

Principles

The guidelines are focussed on the efficacy of the medicines and will inform which are the most efficacious. Where there were 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 medicines 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% and this should be achieved with minimal possible side effects.

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

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 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 the purposes of this guideline treatment experienced is assumed to be an interferon based regimen with or without a first generation PI. Currently patients who are treatment experienced with other classes of DAAs should await further evidence on the best regimen unless the need for treatment is urgent, in which case treatment decisions should be made on a case by case basis, based on expert opinion.

Genotype 1	Recommended regimens
Treatment Naive (non-cirrhotic)	Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir +/- Ribavirin 12 weeks Sofosbuvir, Ledipasvir 8 weeks Sofosbuvir, Simeprevir 12 weeks Sofosbuvir, Daclatasvir 12 weeks (F3-F4 only) **Elbasvir Grazoprevir 12 weeks***
Treatment experienced (non-cirrhotic)	Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir +/- Ribavirin 12 weeks Sofosbuvir, Ledipasvir 12 weeks Sofosbuvir, Daclatasvir 12 weeks (F3-F4 only) **Elbasvir Grazoprevir 12 weeks***
Cirrhotic irrespective of previous treatment	Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir, +/- Ribavirin 12 weeks Sofosbuvir, Ledipasvir, Ribavirin 12 weeks Sofosbuvir, Daclatasvir, Ribavirin 12 weeks **Elbasvir Grazoprevir, Ribavirin 12 weeks***

*In HCV genotype 1a elbasvir grazoprevir for 16 weeks plus ribavirin should be considered in patients with baseline HCV RNA level >800,000 IU/ml and/or the presence of specific NS5A polymorphisms

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, PEG-interferon alfa. Interferon ineligible is defined as either intolerance of previous interferon therapy or where in the opinion of the treating clinician, there is a contraindication to interferon therapy. In the absence of clear evidence patients who are treatment experienced with DAAs should await further evidence on the best regimen unless the need for treatment is urgent, in which case treatment decisions should be made on a case by case basis, based on expert opinion.

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. An NS5b inhibitor such as sofosbuvir is the back bone of interferon free regimens and this can be partnered with several NS5a inhibitors. Daclatasvir has been approved for F3 and F4 patients by the SMC, 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. Velpatasvir is a highly effective NS5a inhibitor and when partnered with Sofosbuvir is approved for all patients with HCV genotype 3. While all HCV genotype 3 patients are now eligible for interferon free therapy, some with mild disease (F0-1) may not be a priority for immediate treatment for cost reasons, for such patients, then interferon based therapy can be effective, the decision to use interferon therapy or defer treatment should rest with the treating clinician and the patient.

Genotype 3	Recommended regimens
Non-cirrhotic	**Sofosbuvir, Velpatasvir 12 weeks** PEG Interferon alpha, Ribavirin 16-24 weeks (F0-F1) Sofosbuvir, Daclatasvir, Ribavirin 12 weeks (F3 only)
Cirrhotic	**Sofosbuvir, Velpatasvir, +/- ribavirin 12 weeks** 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, based on expert advice.

Liver Transplantation

These general principles apply to other solid organ transplants in addition to liver transplantation. There may be some differences however so discussion with the parent transplant unit is important. In general, treatment before transplant is preferable as it may allow liver recovery and prevent the need for transplantation, allow patients to be aviraemic at the time of surgery and reduce the risk of fibrosing cholestatic hepatitis. However patients with significant liver decompensation do not respond as well to treatment and early transplantation is best. Universal reinfection of the liver graft occurs in patients having a liver transplant with hepatitis C.

All patients should be considered for hepatitis C treatment post hepatic transplant once their steroids are stopped (or greatly reduced) usually 3 months after transplantation. An exception might include those with fibrosing cholestatic hepatitis, which is rare, where early treatment may be beneficial. Priority should be given to those with fibrosis.

Drug interactions must be considered in all patients. This is likely to be especially important early post-transplant when multiple medicines are prescribed. Pharmacy input in this setting is essential. Otherwise patients should be treated according to genotype using the drug regimens outlined in this document as appropriate. Communication between the transplant unit and the local prescriber is paramount. Annual routine biopsies to assess the fibrosis progression in post-transplant hepatitis C patients is no longer indicated.

Drug combinations in special circumstances

The above guidelines are recommended first line treatments, approved by SMC and should be used as the standard of care. There are special circumstances such as drug resistance where alternative approaches are needed. There is a growing evidence base regarding the use of combinations of SMC approved drugs in combinations not listed above. With supporting evidence alternative regimens can be considered via local agreement in specific circumstances such as DAA treatment failures, decompensated cirrhosis, and where there is a clinical need for shorter duration of therapy.