

National Clinical Guidelines for the treatment of HCV in adults

Version 5

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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. J 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, 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 Sport), 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. For the first iteration a systematic review was undertaken, augmented by an expert review of recent conference abstracts and expert opinion 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. Subsequent to this, the guidelines have been updated to take account of newly licensed therapies and expert review of emerging data either published or presented at international liver meetings, together with published international guidelines

Principles

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. 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 relevant to the choice of some regimens and the guidance is presented according to genotype. However pan-genotypic regimens are available and in some circumstances where delay in initiation is detrimental to patient care, these may be preferred. 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 are 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 in line with emerging data. SMC approved regimens that are felt to have suboptimal efficacy for a particular indication have been removed in line with international guidelines.

For the purposes of this guideline treatment experienced is assumed to be an interferon based regimen with or without a first generation PI, or in the case of Glecaprevir/Pibrentasvir, Interferon based regimens +/- sofosbuvir, or sofosbuvir + ribavirin. For patients previously treated with Ns5a inhibitors, see the guidance below. Cirrhosis refers to compensated (Child's A) cirrhosis. Not all regimens are recommended for patients with decompensated liver disease, advice should be sought from a liver unit before treating such patients especially with protease containing regimens.

Genotype 1	Recommended regimens
Treatment naive or experienced* non-cirrhotic	<ul style="list-style-type: none"> • Elbasvir/Grazoprevir 12 weeks** or 8 weeks (GT1b F0-2) • Glecaprevir/pibrentasvir - 8 weeks • Sofosbuvir, Ledipasvir 8 (naïve) or 12 weeks (experienced) • Sofosbuvir/velpatasvir 12 weeks • Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir +/- Ribavirin 12 weeks
Cirrhotic irrespective of previous treatment	<ul style="list-style-type: none"> • Elbasvir /Grazoprevir, 12 weeks** • Glecaprevir/pibrentasvir 12 weeks • Sofosbuvir, Ledipasvir, +/- Ribavirin 12 weeks • Sofosbuvir/velpatasvir 12 weeks • Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir, +/-Ribavirin 12 weeks

*Prior exposure to Interferon containing regimens +/- first generation protease inhibitor, additionally in the case of Glecaprevir/Pibrentasvir patients exposed to Sofosbuvir with or without Interferon (but not other DAAS).

**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 the presence of specific NS5A polymorphisms

Genotype 2

PEG Interferon alpha with ribavirin is an effective treatment for HCV genotype 2 with SVR rates approaching 90%, but has an unacceptable side effect profile so is not eligible for inclusion.

Genotype 2	Recommended regimens
Cirrhotic or non-cirrhotic	<ul style="list-style-type: none"> • Sofosbuvir /Velpatasvir 12 weeks • Glecaprevir/pibrentasvir 8 weeks (non cirrhotic) or 12 weeks (cirrhotic)

Genotype 3

The therapy of HCV genotype 3 has improved considerably. In line with international recommendations and the recognised adverse side effect profile, Interferon containing regimens are no longer recommended, even in subgroups where a greater than 90% SVR may be predicted. Both Sofosbuvir/Velpatasvir and Glecaprevir/Pibrentasvir have demonstrated the ability to cure in excess of 90% of patients. Phase 2 and real world data demonstrate 8 weeks of Sofosbuvir/velpatasvir is highly effective against GT3 infection in treatment naive, non cirrhotic patients.

Genotype 3	Recommended regimens
Non-cirrhotic	<ul style="list-style-type: none">• Sofosbuvir, Velpatasvir 8 weeks (treatment naïve), 12 weeks +RBV (treatment experienced)• Glecaprevir/pibrentasvir 8 weeks (treatment naïve) or 16 weeks (treatment experienced)• Sofosbuvir/Velpatasvir/Voxilaprevir 8 weeks• Sofosbuvir, Daclatasvir, Ribavirin 12 weeks (F3 only)
Cirrhotic	<ul style="list-style-type: none">• Sofosbuvir, Velpatasvir, +/- ribavirin 12 weeks• Glecaprevir/pibrentasvir 12 weeks (16 weeks if treatment experienced)• Sofosbuvir/Velpatasvir/Voxilaprevir 8weeks

Genotypes 4 - 6

Genotypes 4-6 are uncommon in Scotland, though effective treatments are available. The most cost-effective of the SMC available medicines should be used. These should be prescribed according to local protocols or based on expert advice.

Re-treatment of Patients not cleared by DAAs

Re-treatment should be considered in all patients. Patients who adhered to therapy, who did not achieve sustained virological response, should have pre-treatment virological sequencing to identify resistance associated substitutions whose presence/absence should be used to guide treatment decisions. Treatment decisions should be made by expert clinicians or based on the advice of such clinicians. In patients who did not clear virus due to poor adherence to therapy, re-treatment should be consider if adherence is likely to be improved on the next attempt.

Sofosbuvir/Velpatasvir/Voxilaprevir for 12 weeks has SMC approval for treatment of Ns5A treatment failures.

Combinations of other licensed regimens, notably Sofosbuvir/Glecaprevir/Pibrentasvir are supported by post licensing data and European guidelines and may be considered according to patient and virological factors following MDT discussion.

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 may not respond as well to treatment and early transplantation is best. Liver transplantation when patients have hepatitis C viraemia results in universal infection of the liver graft.

All patients should be considered for hepatitis C treatment post liver 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. Where there are specific circumstances such as DAA treatment failures, co-morbid disease, especially renal failure or a clinical need for shorter duration of therapy, alternative combinations with supporting trial evidence can be considered via local agreement.