Clinical Commissioning Urgent Policy Statement
Antivirals for adults with recent onset (acute) hepatitis C (URN: 170135P)

Commissioning Position

Summary

NHS England will routinely commission antivirals for adults with recent onset (acute) hepatitis C (HCV), including the treatment of acute HCV infection in immunosuppressed adults (e.g. post transplantation patients) in accordance with the criteria set out in this document.

Information about direct-acting antiviral agents

The intervention

Direct acting antiviral agents (DAAs) act by directly inhibiting viral replication independently from the immune system. There are six main HCV genotypes, with genotype historically determining the treatment regimen. National Institute for Health and Care Excellence (NICE) has approved a number of DAAs for chronic HCV infection. This policy proposes to extend their use in acute HCV infection.

Committee discussion

The NHS England Clinical Panel considered the evidence submitted. The Panel determined that the papers submitted were high quality evidence and that the evidence base was unlikely to significantly changed by an evidence review. The need to treat individuals who are hard to reach by health services was felt to be an important consideration. The Panel agreed the recommendation that an urgent policy statement to be developed recommending routine commissioning.

The condition

Hepatitis C virus (HCV) is a blood-borne virus and its infection is often asymptomatic until the liver is severely damaged. The acute phase of hepatitis C refers to the six-month period after the time of infection. Chronic hepatitis C refers to the presence of HCV for more than six months. Chronic HCV infection is confirmed with 2 positive blood tests 6 months apart. If patients are not tested, they often present late when the liver is severely damaged. Up to 1 in every 3 people with chronic HCV infection will develop cirrhosis, in which 1 in 20 will develop end-stage liver disease (ESLD) and liver cancer (hepatocellular carcinoma, HCC).

It is estimated that approximately 113,000 people in England are living with chronic hepatitis C virus (HCV) infection. Since the acquisition of hepatitis C is often asymptomatic and people often do not know that they have been infected, it is extremely difficult to estimate the incidence of acute HCV infection. The at-risk population for HCV includes men having sex with men (MSM), intravenous drug users (IDU) and highly disadvantaged groups such as homeless people and prisoners who are ill-served by traditional health services. If not treated upon presentation the opportunity for cure may be lost and the risk of onward transmission is high.

NHS England is committed to the global ambitions to eliminate HCV and wishes to be one of the first countries to do so (NHS England, 2018). Patients with acute HCV infection are at high risk of transmitting HCV through risk-taking behaviours whilst having high levels of viraemia. Delaying therapy for 6 months risks viral spread. Early treatment of acute HCV could lead to substantial cost savings as infected people will be much less likely to infect others, leading to a rapid reduction in HCV prevalence.

Although it is estimated that around 25% of patients will spontaneously clear the virus without treatment, 75% of patients potentially risk onward transmission, and/or loss during follow-up. The goal of treating acute HCV infection is primarily to prevent viral spread and its progression to chronic HCV infection. A reduction in chronic HCV infection means fewer patients will progress to develop chronic liver damage, cirrhosis, ESDL and liver cancer. It has been shown that between 2015-2017 increased treatment of chronic HCV has resulted a 39% fall in the number of HCV-related liver transplants undertaken (Public Health England, 2019).

Current treatments

Currently, there are no licensed treatments available for acute HCV infection. Alternatively, administered treatments such as interferon and ribavirin are available, but they are difficult to administer (interferon is a subcutaneous injection; ribavirin are multiple tablets), associated with numerous side effects (some of which may be life threatening) and have poor efficacy. In practise, patients with acute HCV are asked to re-attend 6 months after infection to confirm chronicity, after which they will have access to oral DAAs for chronic HCV infection.

NICE has approved a number of DAAs for chronic hepatitis C. These include sofosbuvir (TA330), ombitasvir-paritaprevir-ritonavir-(dasabuvir) (TA365), ledipasvir-sofosbuvir (TA363), elbasvir-grazoprevir(TA413), sofosbuvir-velpatasvir (TA430), glecaprevir-pibrentasvir (TA499) and sofosbuvir-velpatasvir-voxilaprevir (TA507). Achieving cure of HCV infection is determined by whether there is a sustained virological response (SVR) defined as HCV negative 12 weeks post cessation of therapy.

Comparators

None

Clinical trial evidence

Three papers were presented for review. Papers 1 and 2 are case note reviews/case series, paper 3 is an open label, single-armed controlled trial. Treatment regimens differ in cases reviewed in paper 1 and differ between all 3 papers. The findings have been presented in tabular fashion (table 1, see appendix) to enable ease of comparison. None of the studies were randomised controlled trials.

Paper 1: Girometti et al, 2019
High rates of unprotected anal sex and use of generic direct-acting antivirals in a cohort of MSM with acute HCV infection
The Girometti et al paper was a retrospective review of case notes to determine risk factors in a group of 60 MSM attending a sexual health clinic in London. Data on behaviour in the six months prior to the acute hepatitis C diagnosis were collated. A comparison was made within the study of Human Immunodeficiency Virus (HIV) positive and HIV negative men. All HCV genotypes were found. Condomless insertive anal intercourse was noted as the most common risk factor. 49/60 men had access to treatment via a number of different methods. Five different treatment regimens of differing lengths were used (Table 1, Appendix 1). It was unclear who got what treatment from what source. There were also issues with time to treatment depending on availability of treatment funding:

- NHS (10 cases)   278 days (IQR 174-417)
- Clinical trial (15 cases)   132 days (IQR 108-155)
- On line (23 cases)   114 days (IQR 75-208)
- Overseas (1 case)   not stated

Only 36 of 49 started treatment within 180 days i.e. 13 were outside the definition of acute infection. All 49 met the end point of SVR at 8 and 12 weeks. No information was provided on side effect profile.

Paper 2: Palaniswami et al, 2018
Ledipasvir and Sofosbuvir in the Treatment of Early Hepatitis C Virus Infection in HIV-Infected Men
This was a case series of 25 HIV infected men referred to a single health clinic in New York City. All received the same treatment of 56 tablets of ledipasvir and sofosbuvir. Although that should have meant a treatment time of eight weeks, one participant took it for seven, and six for nine weeks. All met the endpoint of HCV viral load <15IU/mL more than 2 weeks after last dose. They did not wait for natural clearance but started treatment as soon as possible. Despite this theoretical approach, the average time to treatment was 18 weeks. The side-effect profile was low with no serious adverse events. All patients completed the treatment course of 56 tablets. Limitations included the fact that it was only HIV positive men and they were all assessed by a single clinical expert in the management of HCV. Little information was provided on adherence to treatment and, although some did not follow the eight-week regime, all participants completed the course. The treatment start point also saw large variations, median time from HCV clinical diagnosis to start of treatment was 18 weeks (IQR 10-27 weeks). Only genotypes 1 and 4 were eligible for the study.

Paper 3: Boerekamps et al, 2019
Treatment of acute hepatitis C genotypes 1 and 4 with 8 weeks of grazoprevir plus elbasvir (DAHHS2): an open-label, multicentre, single-arm, phase 3b trial
This was a phase 3b drug trial that recruited patients from 15 HIV outpatient clinics in Belgium and the Netherlands. 146 people were assessed, of whom 86 were enrolled into the study and 80 initiated treatment. Twenty-eight of these were on antiretroviral therapy for HIV (ART:28/80). All were treated for eight weeks with grazoprevir and elbasvir. A few patients took tablets into week 9 but 95% completed by eight weeks. All 80 patients achieved the primary SVR 12 (HCV RNA <15IU/mL) endpoint. Two serious adverse events were reported, neither of which were related to the DAA treatment (low back surgery and traumatic rectal bleed). There were 59 adverse events, none of which led to drug discontinuation. The most common was acquisition of a new STI (19/80), providing evidence of continuing risk-taking sexual behaviour and highlighting the importance of behavioural interventions to minimise the potential for HCV reinfection. Of the 28 patients on ART, 27 managed to switch to a compatible ART regimen with grazoprevir and elbasvir. One did not and did not initiate the HCV treatment. The paper made reference to NS5A polymorphism with the use of grazoprevir and elbasvir. Certain NS5A polymorphism means treatment resistance in chronic HCV genotype 1a infection, and the potential need to extend treatment time from 12 to 16 weeks. However, they used fixed eight-week schedule for all and did not test for NS5A before treatment started. Fourteen with genotype 1a had NS5A and all 14 achieved SVR12. Limitations included the fact that its long list of exclusion criteria limits generalisability. Clinicians had the option to allow patients to wait and see if they cleared the virus naturally and it was unclear as to how many patients were in this category. It is usual in the Netherlands for clinicians to wait for four weeks and then retest patients. As 14 patients in this study started treatment before four weeks, it means that some decided not to wait but it is unclear what criteria were used to allow for this. Only genotypes 1a and 4 were included.

Adverse events

Side effects profile was low, such as headache and fatigue, no adverse events led to drug discontinuation.

Additionally, a rapid evidence review for immunosuppressed adults was undertaken.
Six studies were included in this rapid evidence review. Four were small case series of patients undergoing either heart transplant (McLean et al 2019; Schlendorf et al 2018) or kidney transplant (Reese et al 2018; Durand et al 2018) with hepatitis C virus (HCV)-infected organs, who were treated with direct-acting antivirals (DAAs). Two studies were cost-effectiveness analysed. One compared patients willing to accept liver transplant with either a HCV negative liver or a HCV positive liver together with DAA treatment, with patients willing to accept only a HCV negative liver (Bethea et al 2019). The second cost-effectiveness analysis compared receiving a HCV-infected kidney transplant together with DAA treatment, with remaining on the waitlist for an uninfected kidney transplant (Kadatz et al 2018).

No studies reported clinical effectiveness, safety or cost-effectiveness for patients transplanted with HCV-infected organs who were treated with DAAs compared with patients transplanted with HCV-infected organs who were not treated with DAAs.

No relevant studies were identified which reported the use of DAAs to treat acute HCV infection in patients with HIV and with a CD4 cell count <200 cells/mm^3, or in patients who were immunosuppressed due to chemotherapy or other immunomodulating therapy.

Clinical effectiveness
Sustained virological response (SVR) after completing DAA treatment [1](three studies, n=20, n=10, n=9). SVR 12 weeks after completing DAA treatment was reported in all 20 patients who received a HCV-infected kidney transplant and treatment with elbasvir-grazoprevir (Reese et al 2018), in nine out of ten (90%) patients who received a HCV-infected heart transplant and treatment with elbasvir-grazoprevir (McLean et al 2019)[2] and in eight out of nine (89%) patients who received a HCV-infected heart transplant and treatment with ledipasvir-sofosbuvir or sofosbuvir-velpatasvir (Schlendorf et al 2018)[3]. Ten out of ten patients who received a HCV-infected kidney transplant and treatment with elbasvir-grazoprevir had SVR 12 months after completing treatment (Reese et al 2018).

Presence of detectable HCV RNA after transplant (one study, n=10). Out of ten recipients of a HCV-infected kidney who commenced DAA treatment with elbasvir-grazoprevir before transplant, HCV RNA was detectable in five (50%) on the first day after transplant, one (10%) after one week of treatment, none after 12 weeks of treatment and none 12 weeks after completing treatment (Durand et al 2018).

Undetectable HCV RNA at a defined time period after initiation of therapy (one study, n=10). Out of ten recipients of a HCV-infected heart transplant treated with elbasvir-grazoprevir, HCV RNA was undetectable in nine (90%) four weeks after initiation of therapy, and in the tenth patient (who had 3-day HCV viral load of 40 million IU/ml) nine weeks after initiation of therapy (McLean et al 2019).

Median time to undetectable viral load after initiation of DAA treatment (one study, n=9). In nine patients who received a HCV-infected heart transplant, the median time to undetectable

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[1] Defined as undetectable HCV RNA 12 weeks after completion of HCV therapy.

[2] One patient died 79 days post-transplant from complications of antibody-mediated rejection, considered unrelated to HCV infection or DAA treatment.

[3] One patient, who had a previous history of thrombosis, died of pulmonary embolus during week 7 of treatment. This was considered unrelated to HCV infection or DAA therapy.

viral load after starting treatment with ledipasvir-sofosbuvir or sofosbuvir-velpatasvir was 32 days (IQR 31 to 41 days) (Schlendorf et al 2018).

Renal function at a defined time period after kidney transplant (two studies, n=20 and n=10). Twelve weeks after completing elbasvir-grazoprevir treatment, the median (range) creatinine level in recipients of a HCV-infected kidney transplant was 92.8 (79.6 to 176.8) µmol/L (1.05 (0.9 to 2.0) mg/dL), and the median estimated glomerular filtration rate (eGFR) was 63.5 (47.8 to 69.9) mL/min/1.73 m^2 (n=10) (Durand et al 2018).

Among recipients of a HCV-infected kidney transplant treated with elbasvir-grazoprevir, median (IQR) creatinine was 103 (90 to 118) µmol/L (1.2 (1.0 to 1.3) mg/dL) 6 months after the transplant (n=20), and 98 (84 to 111) µmol/L (1.1 (1.0 to 1.3) mg/dL) 12 months after the transplant (n=10) (Reese et al, 2018). At both 6 and 12 months, these creatinine levels were significantly lower (better) than those of matched groups of patients who had been transplanted with a HCV-negative kidney with a similar KDPI score[4][5] (p<0.001 at both 6 months and 12 months). At both 6 and 12 months, the study subjects' creatinine levels were not statistically significantly different from those of matched groups of patients who had been transplanted with a HCV-negative kidney with a lower (better) KDPI score (p=0.33 at 6 months, p=0.37 at 12 months).

Among recipients of a HCV-infected kidney transplant treated with elbasvir-grazoprevir, median (IQR) eGFR was 67.5 (57.8 to 85.7) mL/min/1.73 m^2 6 months after the transplant (n=20), and 72.8 (58.6 to 74.4) mL/min/1.73 m^2 12 months after the transplant (n=10) (Reese et al, 2018). At both 6 and 12 months the study patients had significantly higher (better) eGFR than the matched patients who had been transplanted with a HCV-negative kidney with a similar KDPI score (p<0.001 at both 6 months and 12 months). At both 6 and 12 months, the study patients' eGFR was not statistically significantly different from that of the matched patients who had been transplanted with a HCV-negative kidney with a lower (better) KDPI score (p=0.56 at 6 months, p=0.76 at 12 months).

Safety
Serious adverse events (SAEs) attributable to HCV infection or its therapy (four studies, n=20, n=10, n=10, n=9). Reese et al (2018) reported that one patient out of 20 (5%) transplanted with a HCV-infected kidney and treated with elbasvir-grazoprevir experienced a SAE attributable to HCV infection or its therapy. Schlendorf et al (2018) reported that two patients out of nine (22%) transplanted with a HCV-infected heart and treated with ledipasvir-sofosbuvir or sofosbuvir-velpatasvir experienced a SAE which was thought possibly attributable to HCV infection or its therapy. Two studies reported that no patients experienced SAEs attributable to HCV infection or its therapy; one was of ten patients transplanted with a HCV-infected kidney and treated with elbasvir-grazoprevir (Durand et al, 2018), and the other was of ten patients transplanted with a HCV-infected heart and treated with elbasvir-grazoprevir (McLean et al 2019).

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[4] The kidney donor transplant index (KDPI) is a continuous metric (ranging from 1% to 100%, with lower scores being better) that estimates risk for allograft failure based on characteristics of deceased donors. Donor HCV seropositivity substantially increases (worsens) the KDPI score.

[5] The study subjects were compared with two matched groups of recipients of HCV-negative kidneys. One group were matched against the actual KDPI of the study subjects (which is lowered due to the donor kidney being HCV-infected) (the 'allocation KDPI' group), and the second group were matched against a recalculated KDPI as if donors were HCV-negative, which has the effect of assigning the kidney a better KDPI score (the 'optimal KDPI' group).

Implementation

Criteria

All patients with HCV RNA detected should be discussed at a multi-disciplinary meeting (MDT) approved by one of the regional 'Hepatitis C Operational Delivery Networks (ODN)'. The MDT will approve and document the treatment type required and the length of treatment.

Patients to be treated are those who have evidence of newly acquired hepatitis C (i.e. a previous negative HCV test with recent high risk behaviour and current, confirmed presence of HCV RNA in a blood test performed at an appropriately accredited laboratory). Newly diagnosed patients with a single positive test for HCV RNA may also be considered for treatment under this scheme.

In addition those patients with acute HCV infection in all HCV negative adult transplant recipients receiving an HCV positive solid organ during transplantation may be treated for acute HCV under this policy after the detection of HCV RNA and confirmation of active viraemia (detectable virus by standard RNA PCR).

A request for drug funding should then be completed through the prior approval system, and a prescription issued by a treatment provider approved by the local ODN. The patient's viral load will be measured as clinically indicated during treatment. At the end of the 12-week treatment, viral load will be measured to determine whether SVR has been achieved. Patient's viral load will be retested 12 months after the completion of treatment.

Effective from

26 September 2019

Recommendations for data collection

The following information must be entered into the treatment registry database: patient details, documentation of a "probable acute" HCV infection, completion of treatment, follow-up and treatment outcome at 12 weeks.

Mechanism for funding

The funding and commissioning of these drugs will continue to be managed through the relevant local NHS England Specialised Commissioning Team and in line with the treatment criteria included within this policy.

Policy review date

This is an urgent policy statement, which means that the full process of policy production has been abridged: a full independent evidence review has not been conducted and public consultation has not been undertaken. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

The policy will be reviewed regularly by Infectious Disease Clinical Reference Group who will seek advice from relevant subgroups and the Hepatitis C Elimination Programme, and make recommendations to NHS England via the Blood & Infection Programme of Care for any amendments required.

Links to other Policies

Lists of Hepatitis C Operational Delivery Networks in England as at 1 October 2016.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

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