Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Increased uptake and new therapies are needed to avert rising hepatitis C-related end stage liver disease in England: Modelling the predicted impact of treatment under different scenarios

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Background & Aims: Hepatitis C (HCV) related disease in England is predicted to rise, and it is unclear whether treatment at current levels will be able to avert this. The aim of this study was to estimate the number of people with chronic HCV infection in England that are treated and assess the impact and costs of increasing treatment uptake.

Methods: Numbers treated were estimated using national data sources for pegylated interferon supplied, dispensed, or purchased from 2006 to 2011. A back-calculation approach was used to project disease burden over the next 30 years and determine outcomes under various scenarios of treatment uptake.

Results: 5000 patients were estimated to have been treated in 2011 and 28,000 in total from 2006 to 2011; approximately 3.1% and 17% respectively of estimated chronic infections. Without treatment, incident cases of decompensated cirrhosis and hepatocellular carcinoma were predicted to increase until 2035 and reach 2290 cases per year. Treatment at current levels should reduce incidence by 600 cases per year, with a peak around 2030. Large increases in treatment are needed to halt the rise; and with more effective treatment the best case scenario predicts incidence of around 500 cases in 2030, although treatment uptake must still be increased considerably to achieve this.

Conclusions: If the infected population is left untreated, the number of patients with severe HCV-related disease will continue to increase and represent a substantial future burden on healthcare resources. This can be mitigated by increasing treatment uptake, which will have the greatest impact if implemented quickly.

Keywords: Back-calculation; Disease burden; Hepatitis C; Liver disease; Modelling; Treatment.

Received 19 March 2013; received in revised form 28 February 2014; accepted 3 May 2014; available online 10 May 2014

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Abbreviations: HCV, hepatitis C; NHS, National Health Service; NICE, National Institute for Health and Care Excellence (formally National Institute for Health and Clinical Excellence); HPAI, Hospital Pharmacy Audit Index; ESLD, end-stage liver disease; HCC, hepatocellular carcinoma; HES, Hospital episode statistics; SVR, sustained viral response; DAA, direct acting antiviral; QALY, quality adjusted life year; CrI, credible interval.

Introduction

The Health Protection Agency estimated that in 2005, 161,000 adults in England were chronically infected with hepatitis C (HCV) [1]. National data sources show that HCV-related liver disease is increasing, with predictions indicating that this trend will continue for at least the next 10 years [2,3]. This will place a substantial burden on healthcare services and result in a significant reduction in lifespan for many infected individuals.

Treating HCV infected patients presents a considerable challenge for the National Health Service (NHS) as many infections are undiagnosed [3] and treatment is not successful in every case [4–8]. A significant proportion of the infected population, including people who inject drugs and minority ethnic populations, are 'hard to reach' and service provision has been shown to vary geographically and not always be configured to allow easy access to these groups [9]. Despite the availability of NICE recommended therapies for some years [4,5] the treatment of patients with HCV in England remains sub-optimal. Successful treatment increases health and quality of life and reduces premature mortality from liver disease, which is a specific government target for improvement and public health outcome [10,11]. Improving access to hepatitis C treatment services will also help to reduce health inequalities as many of those infected belong to marginalised groups of society [12].

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The Government's 2004 Hepatitis C Action Plan for England [13] called for 'high-quality services for the assessment and treatment of all patients with hepatitis C be co-ordinated and accessible across the country'. However, countrywide assessment of service provision has not been possible over recent years because national surveillance systems do not monitor referral and treatment. Consequently, progress towards achieving the provision required by the 2004 action plan is not easily assessed and it remains difficult to evaluate any impact on the future burden of hepatitis C. This study aims to provide a national estimate of the number of people who have received HCV treatment using a number of alternative data sources, and to assess the impact and associated costs of various treatment strategies on the future burden of HCV-related disease in England. Results from this work are intended to raise awareness of the existing level of treatment coverage in England, the consequent future burden of hepatitis C and the likely impact of increased treatment on this burden. This awareness is crucial to inform commissioning of treatment services and ensure that they are configured in a way that allows easy access to those groups that need them most.

Materials and methods

The analysis consists of three steps: (1) estimating numbers of patients treated in the period 2006–2011 via datasets relating to total volumes of drugs used for hepatitis C treatment; (2) applying a back-calculation approach to estimate the current disease-stage and age distribution of the infected population and progression probabilities within a health-state model; and (3) using the estimated model to predict future burden under different scenarios for the proportion of those with chronic infection treated each year.

Data on drugs used for treatment of hepatitis C

Three data sources representing volumes of drugs used to treat HCV were used to estimate the number of people treated annually for HCV.

(i) Ex-factory sales to NHS hospitals
The use of ex-factory sales data was negotiated with the drug companies who were sole suppliers of the components of anti-HCV combined therapy: (Roche: peginterferon alfa-2a Pegasys and the ribavirin Copegus; Schering Plough (now Merck Sharp & Dohme) peginterferon alfa-2b Viraferon-Peg and the ribavirin Rebetol). The companies provided data for the years 2006–2011 for hospitals and dispensing pharmacies in England.

(ii) Pharmex – National usage by primary buying groups
These data consist of NHS hospital-sector annual usage of the components of combined therapy by primary buying groups in England – largely equivalent to Regions. The estimates are derived from data collected via the DH Commercial Medicines Units' Pharmex system [14] (covering 97% of the constituent NHS Trusts).

(iii) IMS HEALTH Hospital Pharmacy Audit Index (HPAI)
IMS data on the amount of the components of anti-HCV combined therapy dispensed in 2006–2011 were used. These data were supplied via drug companies by arranging third party data sharing agreements. IMS collect information from 97% of English acute hospitals on all medicines dispensed in hospitals.

Data from all three sources were used to calculate the number of weeks of treatment in 2006–2011, based on recommended weekly doses of pegylated interferon for chronically infected patients. Data on ribavirin were also used for validation, although calculations require more assumptions due to weight-specific dosing and adjustment. The NICE template definitions for the length of treatment used by patients with HCV genotypes 1 and 4, or 2 and 3 [5], and the distribution of these genotypes in England [15] were used to calculate the average number of weeks' treatment required for each patient. Briefly, 55% of patients are assumed to have genotypes 1, 4, 5, or 6; of whom 46% discontinue early at 12 weeks, with the remainder receiving 48 weeks of treatment; those with genotypes 2 and 3 receive 24 weeks of treatment [5]. We assessed sensitivity to these assumptions using values of 37% and 55% discontinuations for genotypes 1, 4, 5, or 6; and 20% and 50% discontinuation at 12 weeks for genotypes 2 and 3. The number of weeks dispensed, sold or prescribed divided by the average number of weeks of treatment required was used to give estimates of the number of patients treated in 2006–2011, obtained by averaging estimates from the three different sources. Further details are available in Supplementary data, section "Calculation of the number of doses of pegylated interferon".

Back-calculation model

Analyses were based on previous work [2], which estimated the burden of HCV in England via **back-calculation**, using data on disease end points and information on progression rates [16]. A multistate model was constructed to represent the evolution of HCV infection through disease states: acute infection, infection clearance, mild chronic HCV, moderate chronic HCV, cirrhosis, decompensated cirrhosis (end-stage liver disease; ESLD), hepatocellular carcinoma (HCC), and death. Hospital episode statistics (HES) data on ESLD and HCC; and Office of National Statistics (ONS) data on HCC mortality were used as disease endpoints. Both datasets were grouped into 10-year age bands prior to analysis. The number of hospital episodes for ESLD (defined by ICD10 codes for ascites (R18), bleeding oesophageal varices (I850); hepato-renal syndrome (K767), hepatic encephalopathy or hepatic failure (K704, K720, K721, K729)) and HCC (ICD10 code C22.0) were available from HES for the period April 1995 to March 2009. Multiple episodes for the same individual within a year were identified and excluded using the unique HES ID number. Death entries with any mention or code for primary liver cancer or HCC (ICD9 155.0, ICD10 C22.0) and any mention or code for hepatitis C infection were included for the period 1996–2009; and the observed data were corrected for under-reporting within the model [2].

Information on the probabilities of progressing through the disease states was taken from the literature as in Sweeting *et al.* [2] and combined with the above data to derive estimates of the underlying incidence of infection and the number of individuals in each disease state over time. Moreover, an estimate of the overall adult anti-HCV prevalence was used to constrain the total number of infected individuals in 2005 [1]. Resulting estimates are then consistent with current estimates of the infected population size and observed data on ESLD, HCC, and HCC mortality. Further details are available in Supplementary data, section "back-calculation model".

Burden projection

The numbers of individuals in each health state in 2012 and progression probabilities estimated by the back-calculation model were used to generate future projections, based on the assumption that the progression probabilities remain the same over time. We also assumed continued incidence of 5000 infections (HCV antibody positive) per year, based on the back-calculation estimate for the period 2006–2010. This estimate is imprecise, but broadly consistent with evidence on the population size of injecting drug users [17,18], previous estimates of the proportion susceptible [1] and the force of infection applied to this population [19], from which the bulk of new infections arise. This pragmatic assumption leads to a relatively stable overall prevalence of chronic infections (in the absence of treatment) between 2010 and 2020 that then declines slowly by around 20% by 2040.

During each year, a proportion of those in chronic, moderate, and cirrhotic states are assumed to be treated; and may then achieve sustained viral response (SVR) with age, disease state, and genotype-specific probabilities estimated from an observational cohort of patients in clinical practice, which should broadly reflect the HCV-infected population in the UK [20]. These probabilities are based on intention to treat analysis, and hence discontinuation and adherence issues are assumed to be incorporated in the overall response rate. Briefly, those aged 40 with non-1 genotype have SVR probabilities of 0.82, 0.70, and 0.40 for mild, moderate, and cirrhosis states; while those with genotype 1 have probabilities of 0.57, 0.37, and 0.11. Those 10 years younger/older have probabilities of SVR around 0.05–0.10 higher/lower; and in the absence of information on probabilities in other age groups, we assumed younger/older groups to be the same as the youngest/oldest known group. Upon achieving SVR, patients in mild and moderate states are no longer at risk of progressing further and have comparable mortality to the general population; although higher rates were assessed in sensitivity analyses, with a five-fold increase in those aged 20–59. Those with compensated cirrhosis are assumed to still be at risk of further progression, but at a reduced rate [21]. Those failing to respond to treatment continue to progress through health states as before, and are not treated again. Progression through health states and treatment is shown in Fig. 1. We also assumed some of those with ESLD