Emerging and Re-emerging Infectious Diseases: Hepatitis C

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Article ID: WMC003342
Article Type: Review articles
Submitted on: 08-May-2012, 02:56:26 AM GMT  Published on: 08-May-2012, 08:32:25 PM GMT
Article URL: http://www.webmedcentral.com/article_view/3342
Subject Categories: INFECTIOUS DISEASES
Keywords: Infectious diseases; Hepatitis C

How to cite the article: Shakoor Z, Siddiqui MR. Emerging and Re-emerging Infectious Diseases: Hepatitis C. WebmedCentral INFECTIOUS DISEASES 2012;3(5):WMC003342

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Source(s) of Funding:
None

Competing Interests:
None
Emerging and Re-emerging Infectious Diseases: Hepatitis C

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Abstract

Aim: To explore new developments in anti-viral therapy used to treat hepatitis C.

Background: Hepatitis C is a blood-borne virus currently affecting 175 million people worldwide. Infection with the virus can predispose to chronic infection, cirrhosis and hepatocellular carcinoma. The virus can be contracted through exposure with a hepatitis C infected person’s blood. Intravenous drug use is the most common mode of transmission. Those infected with the virus may experience vague symptoms such as malaise and fatigue, or they may show symptoms of liver disease or any other complications of the infection. As symptoms may be non-specific and are not often detected in the early stages of infection the hepatitis C virus (HCV) is in this sense known as a silent killer, as the liver may be extensively damaged before infection with the virus is detected. Anti-viral therapy for treating chronic hepatitis C currently remains the only option in preventing cases of liver cirrhosis and hepatocellular carcinoma. Currently no vaccines have been developed.

Method: An insight and understanding of HCV was gained by using books, journals and the internet. Electronic databases used were used to conduct a literature search for articles regarding the development of anti-viral drugs; the outcome of this is shown in the results table. An inclusion and exclusion criteria was applied to the articles generated and the most suitable articles were selected for discussion.

Results: The results of almost all of the anti-viral drugs researched were successful in attaining a decrease in the HCV RNA levels and achieving a sustained viral response.

Conclusion: The results of the clinical trials researched show some promise for future developments in anti-viral therapy. A successful treatment regime which can eliminate the hepatitis C virus is in great demand, given the substantial amount of morbidity and mortality caused by the virus.

Introduction

Aim: To investigate new developments in anti-viral therapy used to treat hepatitis C.

Infectious diseases are defined as diseases which are caused by “pathogenic microorganisms, such as bacteria, viruses, parasites or fungi; the diseases can be spread, directly or indirectly, from one person to another”(1). Emerging infections such as hepatitis C may emerge in a new population or area or may be recognized in a changing environment. They may also be caused by changes in the current microorganisms or become identified by the realization that they are a cause of a known chronic disease (2). The burden of infectious diseases is significant with 20% of deaths worldwide and a staggering 50% in Africa due to infectious causes (3).

Hepatitis C emerged in 1989 as non A-non B hepatitis after the virus was identified and cloned as the cause of most cases of post-transfusion of hepatitis (4). Contracting the virus can lead to fibrosis, cirrhosis and hepatocellular carcinoma (HCC) of the liver. Transmission of hepatitis C (HCV) is mostly parenteral as it is a blood borne virus and because of this, 90% of intravenous drug users are at greater risk of contracting the virus (5).

HCC is the sixth most common cause of cancer worldwide, and the third most common cause of cancer death. It is the leading cause of liver disease in the United States of America (6). These studies have also suggested that over the next two decades the number of deaths caused by hepatitis C infection will continue to increase. Therefore it is vital that steps are taken to help reduce transmission of HCV and treatments derived to help treat those who are infected by either clearing the virus or suppressing it to delay the progression of liver disease.

Epidemiology

The WHO estimates that the global disease burden of hepatitis C is 175 million worldwide, this reflects 3% of the world’s population. Each year a staggering 3-4 million people are infected with the virus (5). Recent data shows that 100,000 of 250,000 people affected in the UK are unaware of their infection with HCV (7).
Hepatitis C is a widespread with over 130 countries reporting cases of the infection. There is significant variation of the virus worldwide, thus demonstrating the virus’s high mutation rate and rapid evolution. Less developed countries such as Southern Europe, Africa and Egypt report higher incidence rates, compared to northern European countries with the lowest levels, such as Great Britain, Germany and France (4). The virus has 6 different genotypes classified from one to six, with seventy subtypes (3). The genotypes vary significantly in their geographical prevalence (8). Genotype 1 is most common with 40-50% of all HCV infected patients in the UK with this genotype (9). There may be some overlap in features between genotypes and infection with two strains at the same time or re-infection with the same strain is also possible (10). Differences between genotypes may be present in terms of their replication method. Other differences may be their mutation rate and the type and severity of liver damage that can be detected or caused (4). As the virus mutates easily during replication, any antibodies produced in response to one strain do not provide protection for other strains a person may become infected with because it is an RNA virus with many different serotypes, causing difficulties in developing vaccines (11).

Classification of Hepatitis C

All the hepatitis viruses have an RNA genome, apart from hepatitis B which contains DNA. The hepatitis viruses all belong to different families. Hepatitis C is a member of the Flavivirdae family and the Hepacivirus genus (13).

Virology

Hepatitis C is a small spherical virus. The molecule has a diameter of 50nm, whilst the diameter of the core RNA strand is 30nm3. A single strand of RNA with positive ending polarity is enveloped by the nucleocapsid, which is the virus? protein coat (15). The virus is isohedral and many small surface binding proteins such as the glycoproteins E1 and E2 project from its surface (3).

Signs and Symptoms

Acute hepatitis C is defined as infection within 6 months of contracting the hepatitis c virus. If HCV has persisted for more than 6 months, this is classed as chronic HCV infection (17). Only 10% of those infected will show symptoms in the acute phase (18). An acute symptomatic period is rare, whilst a long asymptomatic period is common (19). In this sense the virus was named the ‘silent epidemic’ as the cause of any symptoms experienced are often not detected until a significant time after contracting the virus, because they are often rare, mild and non-specific and at this point the liver may already have been extensively damaged. Patients may be diagnosed incidentally by routine tests or after investigating any symptoms they may have experienced. 80% of those infected with HCV will develop chronic hepatitis, regardless of the mode of onset (20). Symptoms such as fatigue can complicate chronic infection, although this does not correlate with the extent of liver damage. Symptoms of cirrhosis or liver disease may also complicate HCV infection (18). Extra-hepatic manifestations such as skin rashes, diarrhoea, arthritis and various auto-immune diseases may also be experienced by some patients (21).

Transmission of Hepatitis C

Hepatitis C can be transmitted by various methods as shown in table 1:

Diagnosis

The following diagnostic tests may be performed on individuals at risk or suspected to have contracted hepatitis C.

Immunoblotting and ELISA? tests may be conducted initially to detect the presence of antibodies in infected people with the HCV protein. There is a window period of 6 to 12 weeks following acute infection until these antibodies may be detected although these antibodies may spontaneously persist in the blood stream after the virus has been cleared or following treatment (18). Immunoglobulin M (Ig M) anti HCV antibodies suggests acute infection, whilst Ig G antibodies indicate past exposure or chronic infection (23). Liver function tests (LFTs) may also be conducted. Serum transaminases levels may be normal or fluctuate between 50-200U/L, although they have no correlation with histological changes (18).

The presence of HCV RNA in a patient’s serum indicates that there is on-going infection with hepatitis C. Testing the genome confirms the results of antibody testing or is used to test those suspected to have contracted the virus but who have negative serology (18,19).

A liver biopsy may be performed to more accurately identify the extent of fibrosis and cirrhosis as serum transaminase levels are a poor reflection of the amount of fibrosis. Monitoring liver cirrhosis patients who are at risk of developing hepatocellular carcinoma can also be done (18) The Metavir system is commonly used as a non-invasive method of assessing liver fibrosis (19).

Molecular analysis is used to identify which hepatitis C
genotype a patient is infected with. This is helpful in determining the most suitable treatment as the treatment response depends on the genotype. However it doesn’t predict the effect of infection or the progression of liver disease varies worldwide.

An ultrasound of the liver may also be conducted to assess the extent of cirrhosis and therefore is useful in monitoring patients chronic HCV who are at risk of developing cirrhosis.

Treatment

Current treatment will be discussed later (6). Anti-viral therapy is used to eliminate HCV and clearance of the virus is indicated when HCV RNA levels remain undetectable in an infected person’s serum 6 months after therapy (8). The level of treatment a patient receives depends on the nature of the infection i.e. acute or chronic, and the progression and severity of liver disease. The rate of disease progression depends on the viral load and genotype of HCV, amongst other factors such as alcohol. Early treatment is another factor which can impact the effectiveness of viral clearance or suppression and delay disease progression in those who HCV clearance cannot be achieved (11).

Management for acute HCV infection is mainly focused on patient education, advice and support. Symptoms such as fever which may be experienced will be treated with medication (10).

The treatment of choice currently used and recommended by the National Institute of Clinical Excellence (NICE) is pegylated-interferon in combination with ribavirin, for mild to severe chronic hepatitis C (11).

Interferon molecules are glycoproteins which are considered as the “backbone” of anti-viral therapy (5). They increase the immune response against HCV, and have anti-viral and anti-proliferative effects in cells (23). The pegylated interferon molecule is formed by a covalent bond between a polyethylene glycol and interferon molecule. The addition of polyethylene glycol increases the half-life of the interferon, leading to sustained plasma levels, fewer adverse effects and better efficiency compared to interferon monotherapy (5,8). Once weekly subcutaneous injections are only needed so current therapy is more convenient. Ribavirin is a guanosine analogue which is always used in combination with other anti-viral drugs as it increases the sustained viral response (SVR) of the treatment. It is taken twice a day and the dose is adjusted according to weight.

Patients with the HCV genotype 1, 4, 5 or 6 are advised to take treatment for 48 weeks. Those with genotypes 2 and 3 show better responses to treatment therefore only need therapy for 24 weeks. 50% of HCV genotype 1 patients achieve an SVR of 50%, compared to 80% achieved by those with genotype 2 or 3 (25).

During treatment blood tests may be conducted regularly to ensure the patient is stable whilst on the treatment. Regular monitoring of HCV RNA is done throughout therapy and weekly full blood counts are conducted weekly in the first month of treatment and thyroid function tests are done every 3 months (10).

Over half of the patients taking combination therapy will experience side effects. Doses may need to be reduced so that the efficiency of treatment is not impaired.

Complications

Chronic hepatitis C carriage, liver cirrhosis or HCC are the most common complications of HCV. Hepatic failure in the acute phase affects 0.5% of those infected (18). Other complications which may be experienced are very rare, such as dryness of the mouth and eyes, lichen planus, glomerulonephritis and sensitivity to light. Changes in the thyroid gland activity, insulin resistance, diabetes, gallbladder disease, cryoglobulinaemia and non-Hodgkin’s lymphoma may be experienced (26).

Prognosis

The rate of progression of HCV will depend on numerous factors such as their age, HCV genotype and viral load. The length of infection and the extent of liver damage are other important factors. Their response to treatment and any other health conditions will affect a person’s prognosis (9). Following anti-viral treatment only 15-20% of people eradicate the virus. 20-30% of those who remain infected with the virus will go on to develop cirrhosis over 10-20 years. The development of cirrhosis predisposes to hepatocellular carcinoma in 1-5% of those chronically infected with the virus.

Methods

Initially background reading on infectious diseases that have emerged in the last thirty years was conducted. Having chosen hepatitis C as the infectious disease to be discussed numerous books and websites such as the Health Protection Agency, Centres for Disease Control and Prevention and the World Health Organization were used to gain an understanding of the virus.

A literature search was then carried out using various
The hepatitis C virus has the potential to produce virions at a rate of 10 per day (27,28) and drug resistant mutants. The anti-viral drugs in the more advanced stages of clinical trials, will be discussed (29,30).

Entry inhibitors are currently being investigated to see if they can effectively inhibit the entry of the HCV into permissive cells and achieve reduction or elimination of the virus. It was found that CD81 surface receptors, class B type 1 binding lectins (SCARB1) and the claudin 1 protein (CLDN1) are essential in the entry and fusion of the virus (29). This allowed entry inhibitors to be designed which inhibit one or more of the steps needed in this process, and therefore preventing viral replication.

Monoclonal and polyclonal antibodies which are known to interfere with viral attachment have also been tested. An open label RCT study was undertaken in patients undergoing a liver transplant. The human hepatitis c immunoglobulin (HICG) antibody was taken either at 75mg/kg or 200mg/kg for 14 weeks although following treatment the HCV-RNA levels did not reduce (28). Another antibody, the human anti-E2 monoclonal antibody which acts by neutralising invading antigens was also tested in infected patients receiving a liver transplant. The control group taking the placebo drug achieved a decrease in HCV-RNA levels of 1.5log10 (31). The group receiving the drug were given a dose between 20 and 240mg of HCV-AB68. It was found that the levels of HCV-RNA decreased from the baseline level by a median of 1.8 and 2.4 log10 in the group receiving between 120 and 240mg respectively. However the difference in HCV RNA levels between the control and treatment group was not sustained when all doses taken were reduced after seven days. Polymerase or NS5A inhibitors are another anti-viral drug being developed. They regulate the anti-viral interferon response and are involved in the assembly and replication of the virus. A-832 and BMS-790052 are two STAT-C NS5A compounds with specific anti-viral therapy that are at currently phase 1 and phase 2 of clinical trials respectively. In a double-blinded study a placebo group and single ascending dose method was used (32). The 18 participants in the study were split equally into 3 groups, taking doses of 1, 10 or 100mg of BMS-790052. Successful anti-viral therapy was demonstrated across all HCV genotypes. When tested in vivo following treatment a dramatic decline in the amount of HCV-RNA was observed. No adverse effects reported (33). BMS-790052 was also tested on hepatitis C infected patients of the genotype 1, in a phase 1 RCT. The single doses were tolerated well; no adverse effects were experienced and a level of safety similar to that of the placebo drug was achieved. After forty eight hours in the group taking 100mg, the maximum mean decline in HCV RNA was 3.6log10, and this was sustained for 144 hours. The outcomes of this study therefore support the use of once-daily dosing. Multiple ascending studies are now being conducted on BMS-790052. The encouraging results achieved with NS5A inhibitors in these clinical trials provide scope for further advancement in polymerase inhibitors.

The protease inhibitors telaprevir and boceprevir previously known as VX-950 and SCH503034 respectively have both reached phase 3 of clinical trials. Telaprevir is a STAT-C drug has been extensively researched. It is a specific inhibitor of HCV as it was developed in accordance with the structure of HCV and acts by inhibiting the serine protease HCV NS3.4A. It resembles the HCV polypeptide that needs to be cleaved in viral replication by the viral protease. A 3 dosing arm study (34,16) was conducted with 20 genotype 1 participants. The greatest median decrease in HCV RNA was shown in those taking telaprevir in addition to peg-interferon alpha 2a. A decrease in HCV RNA of 5.5log 10group was achieved compared to telaprevir mono-therapy which attained a decrease of 4log10 in the telaprevir HCV RNA.

Another study conducted used 12 genotype 1 chronic HCV participants. A rapid viral response was shown in all 12 patients as by the 28th day of therapy HCV RNA levels were undetectable. 5 patients experienced a rash although this was resolved during or after telaprevir treatment. Participants received telaprevir 750mg every 8 hours in combination with peg-IFN-alpha 2a 180ug/week and ribavirin 1000 or 1200mg/day. Phase 2 trials were then conducted under the name of ‘PROVE’ (protease inhibition for viral eradication). Two phase 3 studies were then conducted. ‘ADVANCE’ was the first, and was used to assess triple combination lead-in therapy of 8 and 12 weeks, followed by different variations in standards of care in treatment naïve patients. ‘REALIZE’ is the next phase 3 trial to be conducted and is similar to ‘ADVANCE’ although treatment experienced patients were used. Boceprevir is another protease inhibitor which is currently at phase 3 of clinical trials. The
results of a RCTS in its phase 1b trial demonstrate that the greatest decrease in HCV RNA was found when using with boceprevir in combination with pegylated interferon (28,29). A decrease of log10 2.88 was achieved compared to boceprevir mono-therapy and pegylated-interferon alpha 2b mono-therapy which achieved a maximum mean decrease of log 10 1.26 and log 10 1.6 respectively. Phase 2 trials were then conducted with the aim of defining the most effective treatment regime for treatment-naive genotype 1 individuals and to assess their SVR. A 4 week lead in therapy of peginterferon-alpha2b or ribavirin followed by peginterferon-alpha2b, ribavirin or boceprevir showed the greatest SVR (28,29).

The results of phase 2 studies with telaprevir and boceprevir also suggest that the ideal length of treatment with these protease inhibitors is 24 weeks, rather than 48 weeks as a shorter treatment length has the potential to produce higher response rates. However, a significant disadvantage of telaprevir is that viral resistance often occurs quickly and telaprevir is known to produce common adverse effects such as anaemia and rashes. Thrice daily doses of telaprevir and boceprevir must be taken. The toxicity of protease inhibitors is another aspect of treatment to consider especially when used in combination with pegylated interferon and ribavirin as the toxicity will be increased. The results of phase 2 studies with telaprevir found that ribavirin was needed to enhance the SVR and to minimise the breakthrough of viral resistance and relapse.

Phase 3 studies are currently underway with the aim of defining a lead-in strategy for treatment-naïve patients, and to find out if response rates of those who previously showed no response to treatment can be increased.

Conclusion

Having researched current anti-viral therapy developments some promising results were shown, especially in the case of telaprevir and boceprevir. Although the other anti-viral drugs researched demonstrated a decrease in HCV RNA levels and a SVR with treatment, this was not as great as that achieved by these phase 3 protease inhibitors. However the clinical trials which were conducted will be useful in providing a platform for future anti-viral drug developments. Given the significant amounts of morbidity and mortality caused by HCV, there is a need for anti-viral drugs which have the capacity to successfully eliminate HCV across all genotypes, regardless of any previous lack of treatment and without significant adverse effects or any relapses.

References

### Illustrations

#### Illustration 1

### Results

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Illustration 2

Table 1

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<th>Sources of transmission of hepatitis C</th>
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<td><strong>Injection and other illicit drug use</strong></td>
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<td>Most common mode of acquisition in developed countries</td>
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<td>- use of intranasal cocaine has been associated with acquisition</td>
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<tr>
<td><strong>History of blood product transfusion</strong></td>
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<tr>
<td>Screening of blood and blood products introduced in the UK in 1991; patients who received blood products before that date or in other countries may be at risk</td>
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<tr>
<td><strong>History of having surgery abroad</strong></td>
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<tr>
<td>Having had surgery in a country where sterilising of instruments may be suboptimal is a risk factor</td>
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<tr>
<td><strong>Haemodialysis</strong></td>
</tr>
<tr>
<td>Hepatitis C antibody testing was introduced in 1992</td>
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<td><strong>Needle stick injuries</strong></td>
</tr>
<tr>
<td>The Incidence of seroconversion following needle stick injury is 3% to 4%</td>
</tr>
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</table>
### Sexual activity

People in the long term monogamous relationships are at low risk of acquisition (0 to 0.6% per year); those with multiple sexual partners, particularly those engaging in traumatic sexual activity, are at greater risk.

### Tattooing or body piercing

### Vertical Transmission

Incidence of infection is about 5% among infants born to women with the infection (risk increased with HIV co-infection); breast feeding does not seem to transmit infection, and babies may carry maternal antibodies until age 18 months.
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