Introduction

The hepatitis C virus (HCV) is one of six viruses (A, B, C, D, E, G) that account for the majority of cases of viral hepatitis. It is responsible for about 80 to 90% of non-A, non-B hepatitis. Hepatitis C seroprevalence in the South African population is estimated at about 1%.

Natural history of Hepatitis C

The onset of infection is often unrecognised, and in many individuals the early course of the disease is indolent and protracted. The infection does however become persistent (chronic) in the majority of patients.

Acute infection

- After initial exposure, HCV RNA can be detected in blood within 1 to 3 weeks.
- Within an average of 50 days (range: 15 to 150 days), virtually all patients develop liver cell injury, as shown by an elevation of serum aminotransferases (ALT and AST).
- The majority of patients are asymptomatic and non-icteric. Only 25 to 35% develop malaise, weakness or anorexia, and very few become icteric.
- Antibodies to HCV can be detected in 50 to 70% of patients at the onset of symptoms and in approximately 90% of patients 3 months after the onset of infection.
- In 15% of cases HCV is self-limiting, i.e. HCV RNA disappears from the blood and liver enzyme levels return to normal.

Chronic infection

- About 85% of HCV-infected individuals fail to clear the virus by 6 months. These patients will develop chronic hepatitis with persistent or sometimes intermittent viraemia (detection of HCV RNA by PCR).
- The majority of patients with chronic infection have abnormalities in ALT levels which can fluctuate widely. About one-third have persistently normal serum ALT levels.
- Circulating HCV RNA or antibodies to HCV can be demonstrated in virtually all patients.
- Chronic hepatitis C is typically insidious, progressing (if at all) at a slow rate and showing no symptoms or signs in most patients during the first 20 years following infection.
- Less than 20% develop non-specific symptoms, e.g. mild fatigue and malaise. In most cases, symptoms only appear at the time of development of advanced liver disease.

The complications include

- Chronic hepatitis.
- Cirrhosis (20%).
- Hepatocellular carcinoma (1 to 5%).
- Liver failure and/or portal hypertension.
- Jaundice, ascites, variceal haemorrhage, and encephalopathy.
Although patients with HCV infection and normal ALT levels have been referred to as "healthy" HCV carriers, liver biopsies show histological evidence of chronic hepatitis in most of these patients.

**Cirrhosis of the liver**
- Chronic hepatitis C infection leads to cirrhosis in at least 20% of patients within 20 years of the onset of infection.
- In the case of concomitant alcohol use, cirrhosis and end-stage liver disease may develop more rapidly.

**Hepatocellular carcinoma**
- Chronic hepatitis C infection is associated with an increased risk of liver cancer, which usually occurs in the presence of cirrhosis.

**Extrahepatic manifestations HCV**
- Occasionally patients with chronic HCV infection can present with extrahepatic manifestations or syndromes considered to be of immunological origin, e.g. arthritis, keratoconjunctivitis sicca, glomerulonephritis, mixed cryoglobulinaemia.
- Chronic HCV may be a major underlying cause of porphyria cutanea tarda (found in 60 to 80% of cases).

**The most appropriate approach with a view to diagnosing and monitoring patients**

A variety of tests are available for hepatitis C diagnosis and monitoring. All these are offered by our laboratories and include the following:

**Tests that detect antibody to HCV (serology) - screening test indications for testing:**
- Abnormal liver transaminases (ALT and AST, even if only mildly elevated).
- History of transfusions of blood or blood products prior to 1990.
- Chronic haemodialysis.
- Haemophilia.
- Multiple sexual partners.
- Close household contact with hepatitis C patients.
- History of injection drug abuse.

The ELISA tests used in our laboratory (third generation assays) have a sensitivity of 90% and should be used as an initial test for patients with liver disease, especially those with mildly elevated ALT levels. In low-risk populations, for example blood donors who do not report risk factors (such as parenteral drug abuse, multiple sexual partners, history of transfusion), a negative ELISA result is sufficient to rule out infection. Patients with a positive ELISA result should have a qualitative PCR (polymerase chain reaction) performed for detection of HCV RNA. This will indicate whether the patient has ongoing viraemia or not. As viraemia is indicative of chronic infection, this assay also serves as a confirmation test.
HCV RNA detection by qualitative PCR

- The qualitative HCV RNA detection methods by PCR are generally accepted as the most sensitive test to diagnose HCV infection.
- This assay can detect cases who have not yet developed antibodies.
- Repeated testing for HCV RNA during antiviral therapy can be helpful, because loss of HCV RNA with treatment is a strong predictor of a sustained beneficial response.

HCV RNA levels (viral load) - quantitative PCR

- This assay provides accurate information on viral load.
- The likelihood of a response to alpha interferon correlates with a low level of HCV RNA prior to treatment. However, there is no level of HCV RNA that absolutely precludes the possibility of a response.
- There is little correlation between disease severity or disease progression on the one hand and the HCV viral load on the other.

HCV genotyping

- At least 6 genotypes and more than 30 subtypes of HCV RNA have been identified.
- HCV genotype may be an independent predictor of response to alpha interferon. Patients with genotypes 1a, 2, 3 and 5 are more likely to have a sustained treatment response than those with genotypes 1b and 4.
- Genotype 5 is the most common genotype in South Africa.

Liver biopsy

- This determines the extent of liver injury due to HCV and is considered the gold standard for assessing patients with chronic hepatitis. It should be noted that the histological findings are not sufficiently specific to establish a diagnosis.
- Liver biopsy is of value to assess disease severity, and is recommended before antiviral therapy is considered.

Serum ALT levels

- Testing for serum ALT levels is the most inexpensive and non-invasive means of assessing disease activity. There is however a weak association between ALT levels and the severity of the disease as is histopathologically determined by means of liver biopsy. A single ALT determination is therefore not always accurate in reflecting the severity of the underlying liver disease.
- Serial determinations of ALT levels may provide a better means of assessing liver injury over time, and are recommended for monitoring patients with this infection.

Which patients with Hepatitis C should be treated?

All patients with chronic hepatitis C are potential candidates for specific therapy. However, treatment is recommended only for a select group of patients, namely those with chronic hepatitis C infection who are at greatest risk for progression to cirrhosis. These patients are characterised by the following:
1. Positive serology (anti-HCV).
2. Positive HCV RNA (qualitative HCV PCR).
3. Persistently elevated ALT levels.
4. Liver biopsy with either portal or bridging fibrosis and at least moderate degrees of inflammation and necrosis.
5. Age: >18 years and <60 years.

Patients with decompensated cirrhosis should be treated with currently available therapy for hepatitis C and should be considered for liver transplantation.

Current studies suggest that treatment of patients with persistently normal ALT levels is not beneficial and may actually induce liver enzyme abnormalities.

Even though high HCV RNA levels or the presence of genotype Ib or 4 predicts a less favourable response to therapy, treatment should not be withheld on the basis of these parameters only.

The following potential contra-indications to treatment with interferon must be carefully considered:

- History of major depression.
- Excessive alcohol use.
- Cytopenias.
- Hyperthyroidism.
- Renal transplant.
- Autoimmune disease.

**Therapy for Hepatitis C and follow-up monitoring**

**Laboratory tests that should be obtained before starting therapy include**

- Serum anti-HCV confirmed with positive qualitative PCR for HCV.
- LFT (serum ALT, bilirubin, albumin).
- Prothrombin clotting times.
- FBC with platelet and differential count.
- ANF.
- TSH.
- Glucose.

**Additional tests that may be helpful include**

- HCV viral load (quantitative PCR).
- HCV genotyping.

**Efficacy of therapy is defined as follows**

- Biocemically: Normalisation of serum ALT.
- Virologically: Loss of serum HCV RNA (qualitative PCR).
These two markers (i.e. serum ALT and HCV RNA (PCR)) are measured

- at the end of treatment (end-of-treatment response - ETR) and
- 6 months after treatment (sustained response - SR).

**Drugs**

An alpha interferon (either alpha interferon 2a, or 2b). Dosage = 3 million units subcutaneously three times weekly for 6 to 12 months. The following response to treatment can be expected:

a. **Biochemical**
   - i. ETR in 75 to 85% of patients.
   - ii. SR in 30 to 40% of patients.

b. **Virological**
   - i. ETR in 30 to 40% of patients
   - ii. SR in 10 to 20% of patients.

The biochemical and virological improvement is usually accompanied by histological improvement.

**Monitoring during therapy should be done**

- At 2 to 4-week intervals - with ALT and FBC.
- After 3 months - to assess response with ALT and HCV RNA (qualitative PCR).
- After 6 months and after 12 months - to document ETR and SR with ALT and HCV RNA (qualitative PCR).

A follow-up liver biopsy is not necessary.

If a patient does not display a favourable biochemical or virological ETR (non-responder), retreatment is rarely effective. Within three months after starting an initial course of therapy, patients who are unlikely to respond to treatment can be identified by persistent elevations of serum ALT levels and by the presence of serum HCV RNA. In this situation, therapy should be discontinued.

Recently, excellent results were obtained with a combination of alpha interferon and ribavirin. Ribavirin, however, has not been approved or licensed for use in hepatitis C.

**Specimen collection**

**HCV SEROLOGY**

Specimen required: Collect one 6 ml SST (clotted tube).

Request: Hepatitis C serology.

**HCV RNA PCR (QUALITATIVE)**

Specimen required: Collect one 6 ml SST or one 5 ml EDTA (purple top).

Request: Hepatitis C PCR or qualitative hepatitis C PCR.
HCV RNA LEVEL (VIRAL LOAD; QUANTITATIVE)

Specimen required: Collect one 6 ml SST or one 5 ml EDTA.
Request: Hepatitis C viral load or quantitative hepatitis C PCR.

HCV GENOTYPING

Specimen required: Collect one 6 ml SST or one 5 ml EDTA.
Request: Hepatitis C genotyping.

References