Determining fibrosis stage for the treatment of chronic hepatitis C

PharmaCare covers several antiviral therapies to treat chronic hepatitis C as limited coverage benefits for patients that meet coverage criteria.

Effective October 28, 2014, the PharmaCare coverage criteria for eligible medications for the treatment of chronic hepatitis C are changing. In addition to fibrosis stage F2 or greater as established using Metavir scale or equivalent, the previous criteria for antiviral therapies for chronic hepatitis C included a series of elevated alanine transaminase (ALT) levels as an option for coverage eligibility. As a result of a review by PharmaCare—which included input from experts and a recommendation from the Drug Benefit Council (DBC)—ALT levels alone will no longer be accepted because persistent normal levels of ALT do not exclude significant liver disease[20] and derangement of ALT levels does not accurately reflect the degree of liver fibrosis. Instead of ALT alone, there are other simple, non-invasive, and reasonably sensitive methods to determine level of fibrosis.[2,3]

PharmaCare will continue to cover eligible medications for treatment of chronic hepatitis C for patients with fibrosis stage F2 or greater as established using Metavir scale or equivalent. Acceptable methods to determine fibrosis stage include liver biopsy, transient elastography (FibroScan®), and serum biomarker panels (such as AST-to-Platelet Ratio Index [APRI] or Fibrosis-4 [FIB-4] score) either alone or in combination.

Staging of liver fibrosis to determine eligibility for chronic hepatitis C treatment

Including fibrosis stage in the coverage criteria for treatment of chronic hepatitis C is consistent with the existing PharmaCare coverage criteria, was recommended by the national Common Drug Review (CDR) and provincial DBC, and is consistent with international hepatitis C guideline recommendations.[1,2] PharmaCare will also review and adjust its coverage criteria as needed as new information becomes available.

The Metavir score (below) is the most commonly used method of quantifying the degree of liver fibrosis. Fibrosis is considered significant when it reaches stage F2 or greater.

F0 = no fibrosis
F1 = portal fibrosis without septa
F2 = portal fibrosis with few septa
F3 = numerous septa without cirrhosis
F4 = cirrhosis

Liver fibrosis occurs in response to chronic liver injury or disease, such as hepatitis C. Eighty percent (80%) of acutely infected hepatitis C patients will become chronically infected and approximately 16% will further progress to cirrhosis over 20 years, though studies have reported large variances.[4,5] Advanced fibrosis has been found to lead to a 10% annual chance of progressing to cirrhosis, though it may not progress in all patients, and studies have found the mean time to progress to cirrhosis to be 30 years.[5] Short-term liver related morbidity is not generally expected in patients with F0 and F1.[1]

Methods of Assessing Liver Fibrosis

Liver Biopsy

Liver biopsy is considered the gold standard for assessing the severity of liver damage, with the additional benefits of detecting hepatic steatosis and excluding competing causes of liver injury.[2,6,7] However, it is recognized that the

procedure also has a very low risk of severe complications (1 in 4,000-10,000).[2] In addition, there can be sampling variability depending on the portion of the liver assessed as well as inter and intra-observer variability.[6,]

Blood tests in diagnosing fibrosis and cirrhosis in chronic hepatitis C patients

Measuring ALT levels alone is not a validated method of determining fibrosis score.[2,3] A large systematic review has found certain serologic markers are reasonable alternatives to biopsy for identifying significant fibrosis or cirrhosis.[3] Two such tests widely available in BC are APRI and FIB-4.

1. APRI

The Aspartate aminotransferase (AST) to Platelet Ratio Index or APRI test is a validated method based on the patients AST level and platelet count.

- **Accuracy—**In patients with chronic hepatitis C, a large meta-analysis found that at an APRI cut-off of 0.7, there was a sensitivity of 0.77 and specificity of 0.72 for predicting significant fibrosis (F2-F4).[8] The estimated positive predictive value (PPV) and negative predictive value (NPV) is 70% and 79% respectively. This test may be less accurate in patients co-infected with human immunodeficiency virus (HIV).[3,9] The APRI index is a good non-invasive test for use in clinical practice for confirming the presence of significant fibrosis.
- **Calculation -**

$$\text{APRI} = \frac{\text{AST (in IU/L)} / \text{AST}_{\text{ULN}} \text{ (in IU/L)}}{\text{Platelet count } (10^9/\text{L})} \times 100$$

(*ULN= Upper Limit of Normal)

If APRI < 0.7, no significant fibrosis; if APRI > 1.5, significant fibrosis or cirrhosis

2. FIB-4

The FIB-4 index is another serologic marker test which uses AST, platelet count, age and ALT. In addition to patients with chronic hepatitis C, it has been evaluated in patients co-infected with HIV.[10] The FIB-4 has good predictive accuracy in advanced fibrosis.

- **Accuracy—**A Fib-4 index > 3.25 had a PPV to confirm existence of significant fibrosis (F3-F4) of 82%, a specificity of 0.98 and sensitivity of 0.38.[11] Using a cut-off of < 1.45 for a Metavir score of F ≤ 2 (to exclude extensive fibrosis and cirrhosis (F3-F4)), the sensitivity, specificity and NPV for the Fib-4 test was found to be 0.82, 0.69 and 0.79 respectively.[11] A systematic review presented the median sensitivity to be 0.64 (range: 0.62-0.86) and specificity to be 0.68 (0.54-0.75) to detect fibrosis stages F2-F4.[3]
- **Calculation -**

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (IU/L)}}{\text{Platelet count } (10^9/\text{L}) \times \sqrt{\text{ALT (IU/L)}}}$$

If FIB-4 < 1.45, no significant fibrosis; if FIB-4 > 3.25, significant fibrosis or cirrhosis

Note: When ordering laboratory tests, the individual chemistry must be ordered (e.g., AST, ALT, platelets) and calculations performed. Laboratories do not accept abbreviations such as APRI or FIB-4.

Transient Elastography (TE, FibroScan®)

TE measures liver stiffness using ultrasound to differentiate stiff fibrotic tissue from healthy tissue.[6] Ascites, elevated central venous pressure (seen in heart failure) and narrow intercostal spaces reduce the accuracy of TE.[12] TE has limited applicability in overweight and obese patients. A body mass index (BMI) ≥ 25-28kg/m^2 has shown to produce less

reliable results, and obesity (BMI ≥ 30) is the strongest predictor of failed or unreliable results, though a newer XL probe may attenuate this.[12-14]

- **Accuracy**—Several meta-analyses have been performed and found TE to have sensitivity and specificity of 60-90% and 32%-93% respectively for the diagnosis of significant fibrosis (F2-F3).[15-18] However, there is not yet consensus on the best liver elasticity measurement cut-off, expressed in kilopascals (kPa), to use for assessing fibrosis levels using FibroScan.

  A meta-analysis of 40 studies found that sensitivity and specificity was 0.79 and 0.78 for fibrosis stage ≥ F2.[18]

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