

a series of articles written by medical professionals about the management and treatment of hepatitis C

David M. Feldman, M.D.

Director of Hepatitis Research Saint Vincents Catholic Medical Centers- New York City; Assistant Professor of Clinical Medicine, New York Medical College

Neopterin a Novel Marker of Immune Function in Hepatitis C

Introduction

Neopterin is an early and valuable biochemical marker of cellular immunity. This marker is activated upon stimulation of cells by interferon.

Background

The interaction of the hepatitis C virus with the host (patient's) immune system is probably the most important and least understood of the mechanisms of infection in hepatitis C. The host (patients) immunity is carried out by two major types of white blood cells called lymphocytes and classified as B and T cells. The T cell (a type of white blood cell that fights viral infection) response plays an important role in the outcome of the hepatitis C infection because of its ability to recognize and eliminate virus from infected cells. Studies suggest that the strength and quality of both T helper cells (CD4+) and cytotoxic T cells (CD8+) responses differ between patients who recover and those who develop chronic infection. It is this host viral interaction that will determine whether a patient will clear the infection without treatment or have persistence of infection. A majority of people

exposed to hepatitis C will have persistence of infection.

The Immune Response

T cells are important in the control of viral infection, when infection persists, CD4+ and CD8+ cells contribute to the inflammatory infiltrate within the liver and may help mediate ongoing hepatocellular injury. CD8+ cells directly cytolyze (kill) liver cells and also release cytokines. CD4+ cells play the role of helper cells by releasing cytokines upon virus recognition. It has been shown, that those persons with chronic HCV infection who have a strong CTL response have lower viral levels; however such patients also have higher Histologic Activity Index scores (HAI score).¹

The Immune System Causes the Liver Injury in Hepatitis C Infection

In chronic infections T cells compartmentalized in the liver contribute to hepatic damage, which is mainly Th1 mediated. It is these activated T cells in the liver that are responsible

for the liver damage that results.^{2,3}

Where Does Neopterin Fit In?

The early innate nonspecific response of the immune system is activated by gamma interferon which activates monocytes/macrophages producing a chemical called 7,8 dihydro-neopterin and its oxidation product neopterin.⁴

What is Neopterin?

Due to its chemical structure, neopterin belongs to the class of pteridines. It is excreted in an unchanged form via the kidneys. Serum levels above 10 nmol/L are regarded as elevated.

What Do We Know about Neopterin?

Increased concentrations of neopterin were reported in patients with viral infections, suggesting that increased neopterin may originate from the immune response of patients to the infections. In vitro studies revealed that human monocytes/macrophages produce neopterin when stimulated by interferon-gamma. Therefore, measurement of neopterin concentra-

tions in body fluids like serum, cerebrospinal fluid or urine provides information about activation of T helper cell derived cellular immune activation. Neopterin can easily be detected in serum and urine. The most important clinical applications for the determination of neopterin are prognostic indicator and follow-up of chronic infections, monitoring of immunostimulatory therapy, differential diagnosis of acute viral and bacterial infections, and early indications of complications in allograft recipients. As high

ing and prognosis of disease progression.

How Does Interferon Affect the Immune System?

Interferons bind to specific receptors on the cell surface initiating intracellular signaling via a complex cascade of protein-protein interactions leading to rapid activation of gene transcription. Interferon-stimulated genes modulate many biological effects including the inhibition of viral

neopterin in patients with liver cirrhosis.⁷

Other Recent Findings of Neopterin

In recent years new physiological functions of neopterin have been discovered such as inducing or enhancing cytotoxicity, inducing apoptosis (programmed cell death) and the role of a chain breaking antioxidant.⁸

Enhanced neopterin concentrations together with increased degradation of tryptophan and low serum levels of tryptophan

tion of the immune response, but also with immunosuppressive mechanisms. The increased formation of neopterin and degradation of tryptophan may result in a decreased T cell responsiveness and development of "immunodeficiency."¹⁰

Treatment Implications

Host immune responses affect response to treatment. Patients with a high degree of HCV-specific CTL activity in the liver are significantly more likely to achieve a sustained response to interferon monotherapy.¹¹

Cramp et al investigated the role of virus specific T cells in determining response to interferon or combination therapy in 25 patients with chronic HCV. They found that HCV specific T cell reactivity was uncommon at baseline but increased greatly during therapy, peaking at around 4 - 8 weeks. Viral eradication was more likely in patients who developed HCV specific T cell proliferation with increased IFN gamma and decreased IL 10 production. Non-responders exhibited weaker or absent CD4+ T cell activity.¹²

Summary

Current treatments for hepatitis C are interferon based. The mechanism for interferon treatment eradication is currently thought to be through the activation of immune cells with interferon receptors of the hosts (patient's) immune system.

The immune system is responsible for allowing the persistence of hepatitis C infection. It is also the viral host immune interaction that causes the ongoing damage to liver cells. Measures of immune activation by neopterin could potentially be helpful surrogate markers in progression of liver disease, predicting outcome of treatment and response to treatment.

Neopterin measurements not only provide an insight into the present state of cell-mediated immune response but also allow monitoring and prognosis of disease progression.

neopterin production is associated with increased production of reactive oxygen species and with low serum concentrations of antioxidants like alpha-tocopherol, neopterin can also be regarded as a marker of reactive oxygen species formed by the activated cellular immune system. Therefore, by neopterin measurements not only the extent of cellular immune activation but also the extent of oxidative stress can be estimated.

A number of European hospitals measure blood neopterin levels in transplant patients as a way of monitoring degree of activation of a patient's immune system. Longitudinal studies have revealed that neopterin levels in HIV disease correlate strongly with disease progression.⁵

What is Neopterin Good For?

Neopterin measurements not only provide an insight into the present state of cell-mediated immune response but also allow monitor-

ing and prognosis of disease progression. replication in infected cells, inhibition of cell proliferation, and immunomodulation. The clinical relevance of these in vitro activities is not known. Interferon stimulates the production of effector proteins such as serum neopterin and 2', 5'-oligoadenylate synthetase. These protein markers have been used in the interferon studies to demonstrate immune activation by the interferon. Neopterin has been validated in a large number of studies as a marker of interferon activation.

The level of neopterin increases with the dose of interferon.⁶

How Does It Apply to Liver Disease and Hepatitis?

Prior to an available test for hepatitis C, studies have looked at the ability of the marker neopterin to differentiate fatty liver from non A-non B hepatitis, now called hepatitis C. One study found higher levels of

neopterin in patients with liver cirrhosis.⁷ correlate with neuropsychiatric abnormalities like cognitive decline and depressive symptoms, especially in long-lasting and chronic diseases.⁹

What Is the Interaction between Cytokines, Neopterin and Interferon in Chronic Infections?

Neopterin concentrations in humans reflect the degree of Th1-type immune activation. Since IFN-gamma also stimulates the release of reactive oxygen species (ROS) from immunocompetent cells, the amount of neopterin produced also serves as an indirect estimate of oxidative stress. In parallel, IFN-gamma activates the degradation of tryptophan, which appears to limit the growth of intracellular pathogens and the proliferation of cells, including T lymphocytes. Thus, during persisting states of immune activation, the production of IFN-gamma is not only associated with forward regula-

Areas of Potential Uses for Neopterin and Future Studies in Neopterin

- Outcome of treatment in elevated or normal level neopterin.
- Correlation at baseline neopterin with ALT and more advanced liver disease.
- An elevated baseline level of neopterin may respond better to treatment with interferon.
- Higher elevation of neopterin while on treatment may have better sustained virologic response.
- A peak level of neopterin may have to be reached and sustained to achieve an SVR.
- Relapse to treatment may have elevation of neopterin prior to any other manifestation.
- A return to a normal neopterin after stopping interferon is observed.
- An elevated neopterin may be helpful in differentiating the primary source of liver injury in those with both steatohepatitis and hepatitis C.
- Those with low neopterin and chronic hepatitis C may be manifesting an "immune tolerance."

How Can you Have Neopterin Tested in the Doctor's Office?

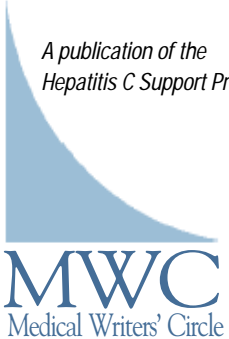
The test is offered by Quest laboratories Teterboro, New Jersey, test number 97402P. Testing requires a blood sample, 0.2 mL serum from a no additive red top tube that must be transferred to an amber vial (protected from light), or wrap tube in aluminum foil and ship frozen. The laboratory will reject tubes that are not protected from light or not frozen. Currently only blood is accepted for testing, although other laboratories accept urine or CSF fluid in addition to

blood. The test is performed by Immunoassay (RIA) and results are equivalent to high-pressure liquid chromatography (HPLC). The cost is approximately \$135 at the current time.¹³

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A publication of the
Hepatitis C Support Project



The Mission of the Hepatitis C Support Project is to offer support to those who are affected by the hepatitis C Virus (HCV), hepatitis B Virus (HBV) and HCV coinfections.

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