Neutralizing Antibody (NAb) Testing Using the Cytopathic Effect (CPE) Assay to Assess Interferon Beta Treatment of Multiple Sclerosis

Policy Number: 2.04.500  Last Review: 03/2014
Origination: 03/2014  Next Review: 03/2015

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for NAb testing to assess interferon beta treatment of multiple sclerosis. This is considered investigational.

When Policy Topic is covered
Not Applicable

When Policy Topic is not covered
Neutralizing antibody (NAb) testing using the cytopathic effect (CPE) assay to assess interferon beta treatment of multiple sclerosis is considered investigational.

Description of Procedure or Service
Multiple sclerosis (MS) is second only to trauma as a cause of acquired neurological disability in young adults. MS is believed to affect approximately 400,000 people in the United States, striking primarily between the ages of 20 and 50 years, and disproportionately affecting women. MS symptoms and deficits vary among those affected, and the symptoms typically change and worsen as the disease evolves. Those that appear most frequently include: fatigue (reported in up to 80%); depression (occurs in up to 50%); motor involvement such as weakness, and spasticity; visual involvement including temporary vision loss and diplopia; sensory symptoms such as numbness and paresthesias; and brainstem symptoms like vertigo. It is likely that in many patients, central nervous system (CNS) inflammation starts many years before the onset of clinical signs and symptoms.

The most common forms of MS are:
- Relapsing-remitting (RRMS): This form occurs in about 85% of those affected and involves periods of neurological deterioration (relapses) interspersed with partial or complete recovery (remission). After 10 to 15 years, the disease enters a chronic progressive phase in 30% to 50% of patients, this being termed secondary-progressive MS.
- Primary progressive (PPMS): This more treatment-resistant form occurs in approximately 10% of those affected and involves gradually increasing neurological disability without discernible relapses. Mean age of onset is a decade later than for RRMS.

Usual care for MS includes drugs that interfere with the overactive immune response such as corticosteroids and other immune-modifying drugs, in particular, interferon beta-1a. In some patients, treatment with interferon stimulates an immune response that generates anti-interferon antibodies that reduce or eliminate the therapeutic effects of interferon.

The cytopathic effect assay detects neutralizing antibodies against interferon beta based on their ability to inhibit the biological activity of interferon beta. For this assay, human cells such as fibroblasts or the A549 or WISH cell line are incubated with interferon beta that has been mixed with serial dilutions of
patient sera. After a sufficient amount of time has passed to enable the interferon to induce an antiviral response, the cells are incubated with a virus such as the vesicular stomatitis virus or encephalomyocarditis virus. If neutralizing antibodies are present, they prevent the antiviral action of interferon beta and the cells are lysed by the virus. Assay results are determined by staining the intact cells and quantifying the intensity of staining.

Measurement of neutralizing antibodies against interferon beta is typically prescribed by a neurologist and performed with a blood sample collected by a nurse or phlebotomist.

Although assays for detection of interferon-binding antibodies have been developed, these antibodies may not have a neutralizing effect since it is possible for an antibody to bind to interferon beta without blocking its biological effect. Other than the cytopathic effect assay, the only assay that is commonly used for detection of neutralizing antibodies against interferon beta is a Myxovirus Resistance A (MxA) gene expression assay. This test involves incubating human cells with a mixture of patient sera and interferon beta. Neutralizing antibodies prevent binding of interferon beta to its receptors, which prevent expression of the MxA gene and production of the MxA protein. Results of this assay are obtained by measuring MxA RNA or protein levels.

**Rationale**

Evidence evaluated in this report was obtained primarily from searches of the MEDLINE and Embase databases. The keyword, subject word, and title word fields were searched using the terms (neutralizing, neutralising, OR nab) AND interferon AND multiple sclerosis AND cytopathic. Studies were selected for detailed review if they were published in the peer-reviewed literature in English-, German-, Dutch-, or French-language journals, evaluated the cytopathic effect assay for detection of neutralizing antibodies to interferon beta in serum samples from at least 50 patients, and determined the statistical significance of correlation between assay findings and clinical response to treatment with interferon beta. Studies were also reviewed if they enrolled at least 20 patients who were known to have neutralizing antibodies and investigated the correlation between changes in antibody status and clinical response over time.

Results of the available studies provide consistent evidence that the cytopathic effect assay can be used to detect neutralizing antibodies that reduce the effectiveness of interferon beta therapy in patients who have MS. All of the reviewed studies found that the presence of neutralizing antibodies was associated with a statistically significant increase in relapses of MS or worsening of disability. A shortcoming of these studies is that there were variations in assay methodology that may affect which patients are considered to have a positive versus negative test result. Another shortcoming of the studies is that they did not determine the sensitivity and specificity of the cytopathic effect assay for detection of MS patients who will respond poorly to interferon beta therapy. In addition, the available studies did not compare the cytopathic effect assay with a symptom-based approach to patient management that relies on response to treatment as the sole criterion for continuation or discontinuation. Overall, the quality of the available evidence is poor. Data presented by Sbardella et al. (2009) suggests that the majority of MS patients who have relapses do not have neutralizing antibodies to interferon beta; therefore, the cytopathic effect assay may have relatively low sensitivity for detection of MS patients who will respond poorly to treatment with interferon beta. Nevertheless, for patients who respond poorly and who have neutralizing antibodies, results of the cytopathic effect assay may be useful in management of interferon beta therapy, by indicating that a higher dosage of interferon may be beneficial or indicating that interferon therapy should be discontinued until neutralizing antibodies are no longer detectable. Additional studies are needed to evaluate the sensitivity and specificity of the cytopathic effect assay for detection of neutralizing antibodies and to determine whether information provided by this assay can be used to improve management of patients undergoing interferon beta therapy for MS.

**References:**


Billing Coding/Physician Documentation Information

86849 Unlisted immunology procedure

Additional Policy Key Words

N/A

Policy Implementation/Update Information

3/1/14 New policy; considered investigational

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