BlueCross BlueShield of Alabama

Name of Policy:

Therapeutic Apheresis, with Extracorporeal Column Immunoadsorption and Plasma Reinfusion

Policy #: 010
Category: Surgical

Latest Review Date: December 2008
Policy Grade: **Effective March 12, 2012: Active policy but no longer scheduled for regular literature reviews and update.**

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Extracorporeal immunoadsorption (ECI) using protein A columns, also referred to as protein immunoadsorption therapy, consists of highly purified protein A (isolated from *Staphylococcus aureus*) that is bonded to a silica Matrix. Plasma is collected from the patient in a pheresis procedure and then is passed over the column. Circulating immune complexes (CICs) and IgG bind to the protein A and are thus selectively removed from the plasma. The plasma can then be returned to the patient, thus eliminating the need for a plasma exchange.

Pathogenic levels of IgG and circulating immune complexes are associated with a number of diseases such as idiopathic thrombocytopenia purpura (ITP), hemolytic uremic syndrome, and red cell aplasia. In the past, plasma exchange was used to remove CICs and IgG. ECI represents a selective removal of the pathogenic substances and thus has been investigated as an alternative to plasma exchange, particularly for patients with ITP. Recently, immunoadsorption columns have been investigated in patients with rheumatoid arthritis. The Prosorba column is a U.S. Food and Drug Administration (FDA)-approved immunoadsorption protein A column. Labeled indications include the following:

- Therapeutic removal of immunoglobulin G and IgG-containing circulation immune complexes from plasma in patients with idiopathic thrombocytopenic purpura (ITP) having platelet counts less than 100,000mm.
- Therapeutic reduction of the signs and symptoms of moderate to severe rheumatoid arthritis in adult patients with long-standing disease who have failed or are intolerant to disease-modifying anti-rheumatic drugs (MPRM 8.02.03)

Policy:

Extracorporeal Immunoadsorption (ECI) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage when:

1. Treatment of patients with idiopathic thrombocytopenic purpura or hemolytic uremic syndrome unresponsive to other therapies with either of the following:
   - A platelet count below 20,000 OR
   - A platelet count below 50,000 with evidence of bleeding

*For treatment of idiopathic thrombocytopenia, patients typically undergo given treatments 6 times over the course of 2 to 3 weeks.

2. Treatment of signs and symptoms of moderate to severe rheumatoid arthritis in adult patients with long-standing disease that has failed or is intolerant to disease-modifying anti-rheumatic drugs (DMARDs).
   - Severe, active disease is defined as greater than five swollen joints, greater than 20 tender joints, and morning stiffness greater than 60 minutes
   - Patients must have failed an adequate course of a minimum of three DMARDs. Disease-modifying antirheumatic drugs include (but not limited to): methotrexate (Rheumatrex), hydroxychloroquine (Plaquenil), sulfasalazine (Azulfidine), gold (Ridaurs, Solganal),

azathioprine (Imuran), D-penicillamine (Depen, Cuprimine), etanercept (Enbrel), and leflunomide (Arava).

For treatment of rheumatoid arthritis, patients typically undergo one treatment per week for 12 weeks.

Extracorporeal Immunoadsorption (ECI) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** when performed for the following purposes:

1. Treatment of cancer.
2. Autoimmune diseases other than rheumatoid arthritis.
3. Renal transplant recipients.
4. Macular Degeneration (Age Related) (AMD)

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Idiopathic thrombocytopenic purpura (ITP) is characterized by rapid platelet destruction and typically appears in young women and also in HIV-positive patients. It is usually a relatively benign disorder in its chronic form, and treatment is not needed if the platelet count remains above 50,000/ml. In cases involving more serious bleeding or with platelet counts less than 20,000/ml, ECI has successfully reversed the immune thrombocytopenia by removal and modulation of platelet-specific IgG and circulating immune complexes. Treatment of ITP was the original FDA-label indication for extracorporeal immunoadsorption.

In 1999, **ECI** received an additional FDA-labeled indication for the treatment of "signs and symptoms of moderate to severe rheumatoid arthritis in adult patients with long-standing disease who have failed or are intolerant to disease modifying anti-rheumatic drugs (DMARDs)" DMARDs include: methotrexate (Rheumatrex), hydroxychloroquine (Plaquenil), sulfasalazine (Azulfidine), gold (Ridaurs, Solganal), azathioprine (Imuran), D-penicillamine (Depen, Cuprimine), etanercept, and leflunomide.

The FDA approval was based in part on a randomized, double-blind sham placebo controlled trial of 91 patients. Trial participants had rheumatoid arthritis for an average of 15 years and had failed an average of 4.2 DMARDs prior to entry. Patients received weekly treatments for each of 12 weeks and were followed for an additional seven to eight weeks. Treatment effect was assessed by the number of tender and swollen joints and pain scores, according to a scoring system developed by the American College of Rheumatology. Improvement was defined as at

least a 20% improvement in the tender joint count, at least 20% improvement in swollen joint count and at least 20% improvement in at least three of the following five: patient pain assessment, patient global assessment of disease activity, physician global assessment of disease activity, patient assessment of physical function, and a health functional status questionnaire. A total of 31.93% of patients in the treatment arm showed improvement compared to 11.4% in the sham placebo group. Among those experiencing improvement during the trial, the median duration of response was 32 weeks. Originally, the investigators had planned to enroll 178, but at an interim analysis the trial was stopped early due to the significant comparative improvement in the treatment group.

ECI has also been used in the treatment of hemolytic uremic syndrome, which is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and progressive renal failure, thought to be related to circulating immune complexes. Patients treated with immunoadsorption columns have achieved a definite increase in platelet count, decrease of hemolysis, and stabilization of renal function. ECI has also been investigated as a technique to reduce the number of antibodies reactive against human lymphocyte antigens in highly sensitized potential kidney transplant recipients. While a number of case series have been reported, there are inadequate data to validate the treatment effectiveness. Similarly, there are scattered reports of using **ECI** to treat other autoimmune diseases, such as systemic lupus erythematosus, but the literature is inadequate to permit conclusions.

Various malignancies have also been treated with **ECI**. The proposed rationale is that cancer patients are known to have depressed immune functions due to various factors in the plasma and that **ECI** might remove these blocking antibodies and immune complexes. Fennelly and colleagues conducted a phase II trial of **ECI** in patients with metastatic breast cancer and reported that **ECI** was not associated with antitumor activity, and that patients with breast cancer did not appear to have higher levels of circulation immune complexes compared to normal controls.

December 2008 Update
A literature review revealed no additional studies that would alter the coverage statement of this policy. A review of plasma exchange in rheumatoid arthritis suggests that despite good results with protein A columns, their use was supplanted by the biologic disease-modifying anti-rheumatic drugs (such as tumor necrosis factor alpha inhibitors) due to efficacy, convenience, and practicality.

Key Words:

Extracorporeal Immunoadsorption, ECI, Protein A Column, Therapeutic Apheresis, Prosorba Column, Protein A Column Pheresis, Extracorporeal Immunoadsorbent Therapy, ITP, Rheumatoid Arthritis, Rheo, Rheopheresis

Approved by Governing Bodies:

FDA approved March 1999

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP contracts Special benefit consideration may apply. Refer to member's benefit plan.
Pre-certification requirements: Not applicable

Current Coding:

Effective for dates service on or after January 1, 2003:

CPT codes:

36515	Therapeutic apheresis; with extracorporeal immunoadsorption and plasma reinfusion
36516	Therapeutic apheresis; with extracorporal selective adsorption or selective filtration and plasma reinfusion

References:

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10. Snyder HW, Mittelman A, Oral A et al. Treatment of cancer chemotherapy-associated thrombotic thrombocytopenic purpura/hemolytic uremic syndrome by protein a immunoadsorption of plasma, Cancer 1993; 71:1882-92.

Policy History:

BCBSA Medical Policy Reference Manual, March 1996
BCBSA Medical Policy Reference Manual, July 1999; 8.02.04
BCBSA Medical Policy Reference Manual, December 1999; 8.02.03
Medical Policy Group, July 2001
Medical Policy Group, July 2005 **(1)**
Medical Policy Administration Committee, July 2005
Available for comment July 28-September 10, 2005
Medical Policy Group, December 2005 **(2)**
Medical Policy Administration Committee, December 2005
Medical Policy Group, December 2008 **(1)**
Medical Policy Group, March 2012: **Effective March 12, 2012 this policy is no longer scheduled for regular literature reviews and updates.**
Medical Policy Group, October 2013 **(1)**: Removed ICD-9 Diagnosis/Procedure codes; no change to policy statement.
